

Effects of *STIP1* and *GLCC11* polymorphisms on the risk of childhood asthma and inhaled corticosteroid response in Chinese asthmatic children

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Abstract

Background: Asthma is a common chronic lung disease in children. We aimed to determine the associations between stress-induced phosphoprotein 1 (STIP1) and glucocorticoid-induced transcript 1 (GLCCI1) polymorphisms and susceptibility of childhood asthma and inhaled corticosteroid (ICS) response in children.

Methods: A total of 263 Chinese Han asthmatic children were recruited from the Xiangya Hospital, Central South University. Pulmonary function tests were performed before the treatment and 3 months after the treatment. 150 non-asthmatic children were recruited. Each participant's DNA was extracted from the peripheral blood and Method of MassARRAY was used to genotype the single-nucleotide polymorphisms (SNPs).

Results: STIP1 rs2236647 wild-type homozygote (CC) was associated with increased asthma risk of children (OR=1.858, 95% CI=1.205-2.864), but not associated with the onset age of asthma and ICS response. GLCCI1 rs37969, rs37972 and rs37973 polymorphisms were not associated with the risk of childhood asthma. However, rs37969 mutant genotypes (TT/GT) were significantly associated with increased risk of early onset asthma (OR=2.254, 95% CI: 1.068-4.757) and less improvement in PD20 ($p = 0.028$). We also found significant associations between rs37969, rs37972 and rs37973 mutant genotypes and less improvement in maximal midexpiratory flow (MMEF) after ICS treatment for 3 months ($p=0.036$, $p=0.010$ and $p=0.003$, respectively).

Conclusions: STIP1 rs2236647 was associated with asthma risk of children. GLCCI1 rs37969 mutant genotypes were associated with increased asthma risk of early onset and less improvement in airway hyper-responsiveness. GLCCI1 rs37969, rs37972 and rs37973 polymorphisms might be associated with pulmonary function in childhood asthma patients after ICS treatment.

Background

Asthma is one of the most common chronic lung diseases in children and adults. Approximately 358 million individuals suffer from asthma in the world [1]. The average global prevalence of adult asthma is 4.3%, up to 21.0% in Australia [2]. Simultaneously, the global prevalence of asthma in children aged 6 to 7 years and in those aged 13 to 14 years are respectively 11.6% and 13.7% [3]. In developed countries, the prevalence increased more obviously in the past few years. Meanwhile, the clinical control of asthma is not promising. Uncontrolled asthma accounts for 53.4% in Asian pediatric asthma and 45% in European adult asthma [4, 5]. In China, only 28.7% of patients achieved complete asthma control [6]. Asthma is an important contributor to the burden of families and society around the world. Therefore, reducing the prevalence of asthma and improving asthma control will significantly decrease the global medical burden and meaningfully promote the development of global health care.

The current perspective is that the onset and drug response of asthma in children and adults are closely associated with genetic factors. Studies have shown that genetic factors contribute about 70% of the

variability in inhaled corticosteroid (ICS) response [7, 8]. There are more than 1,000 candidate genes had been discovered in the genome-wide association studies (GWAS) [9], and approximately 50 genes have been replicated identified [10].

Many of the replicated genes were involved in the steroid molecular pathway and one of the important genes in the steroid molecular pathway is stress-induced phosphoprotein 1 (STIP1). STIP1 contains 14 exons and encodes heat shock organizing proteins (hops) that participate in the activation of glucocorticoid receptor (GR). GR is usually inactive and activated with the help of hop-hsp90 complex [11, 12]. Then, the GR-glucocorticoid complex can suppress airway inflammation, inhibit the activation of inflammatory genes, and regulate the activity and transcription of airway remodeling genes. In short, the STIP1 gene can affect the binding process of glucocorticoid (GC) and GR, thereby affecting the efficacy of GC. 3 STIP1 single-nucleotide polymorphisms (SNPs; rs4980524, rs6591838 and rs2236647) were found to be associated with ICS response in a white adult population [13] and another study found STIP1 rs2236647 polymorphism was also associated with the risk of asthma in adult population of Arab descent [14]. Besides, no association was found between STIP1 SNPs and change in FEV1 after ICS treatment in the study of childhood asthma in Korea and adult asthma in Japan [15].

Glucocorticoid-induced transcript 1 (GLCCI1) also plays a key role in steroid biology and involved essentially in asthma signaling [16]. GLCCI1 contains 8 exons and encodes glucocorticoid-induced transcript 1 that promotes the anti-inflammatory effects of glucocorticoids [17]. A GWAS study indicated that GLCCI1 rs37972 polymorphism was associated with ICS response in white childhood asthma patients and replicated their findings in three adult clinical trials and a Network childhood asthma trial (Data from the database of Genotypes and Phenotypes, dbGaP) [16]. However, the result was not repeated in north European asthmatic children [18]. Hu C et al. found that GLCCI1 variations (rs37972, rs37973 and rs11976862 polymorphisms) were associated with ICS response and asthma susceptibility in Chinese adult [19]. A recent study indicated that GLCCI1 variants (rs37972 and rs37973 polymorphisms) could serve as asthma risk biomarkers in a Tunisian adult population [20].

Figure 1 summarizes the advances of STIP1 rs2236647 and GLCCI1 rs37972 /rs37973 polymorphisms in asthma researches. And currently, the studies on the above two genes (STIP1 and GLCCI1) and Chinese childhood asthma are still rarely reported. The aim of our study is to investigate the effects of STIP1 and GLCCI1 polymorphisms on the risk of childhood asthma and ICS response in Chinese asthmatic children.

Methods

Subjects

263 Chinese Han asthmatic children and 150 controls were recruited from the Xiangya Hospital of Central South University. All the asthmatic patients received ICS treatment for 3 months (inclusion and exclusion criteria of all cases are listed in Additional file 1: Table S1).

Pulmonary function test

Pulmonary function was performed using the Jaeger Masterscope spirometry system (Jaeger, Wuerzburg, Germany). All asthmatic children over 6 years of age had pulmonary function measured at their first visit and after 3 months of ICS treatment. Forced expiratory volume in 1 second (FEV1)/pre, FEV1/Forced vital capacity (FVC), Peak expiratory flow (PEF)/pre, Forced expiratory flow (FEF) 25/pre, FEF 75/pre and Maximal midexpiratory flow (MMEF)/pre were used to evaluate the pulmonary function. The provocative dose of methacholine causing a 20% drop in FEV1 (PD20) was used to represent airway hyper-responsiveness.

Selection of SNPs

In this study, 4 SNPs in two genes (rs2236647 in STIP1; rs37969, rs37972, and rs37973 in GLCCI1) were investigated for their associations with asthma in children of China. The studied genes were selected based on their known biological functions in lung and their role in ICS response. These SNPs were selected from previous studies and database information (NCBI, <https://www.ncbi.nlm.nih.gov/pubmed>).

Genotyping

Genotyping was performed using the iPLEX MassARRAY genotyping platform (Sequenom, Inc., San Diego, CA). DNA was extracted from 1 mL of the collected blood using a DNA extraction kit (SQ Blood DNA Kit, Omega, USA). The primers were designed by AssayDesigner3.1 (Details are listed in Additional file 1: Table S2).

Statistical methods

Statistical analyses were performed using PLINK 1.07 and SPSS v.18.0 (SPSS Inc., Tokyo, Japan). $p > 0.05$ was considered to be consistent with Hardy-Weinberg equilibrium (HWE). The chi-squared test was used to calculate significant differences in allele and genotype frequencies between asthmatics and controls. Odds ratios (OR) and 95% confidence intervals (CI) for asthma susceptibility in relation to the SNPs were performed by logistic regression analysis. Multivariate logistic regression analysis was used to adjust for age and gender. Analysis of variance (ANOVA) test and t-test were used to determine the influence of genotype on spirometry. $p \leq 0.05$ were considered significant.

Results

Subject characteristics

We recruited 263 asthmatics (188 males, 75 females, mean age 8.18 ± 2.73 years) and 150 non-asthmatic controls (97 males, 53 females; mean age 8.20 ± 2.28 years) in our study. There was no difference between 2 groups in age, gender and smoking exposure (p -value: 0.725, 0.150 and 0.135, respectively). All patients received ICS treatment. 209 patients were over 6 years of age and 54 were under 6 years of age. In the patients over 6 years of age, 134 completed the 3-months follow-up. Other patients did not have follow-up or substandard treatment. The detailed data are listed in Additional file 1: Table S3.

***STIP1* rs2236647 was associated with the risk of childhood asthma**

All the SNPs involved in our study were in HWE (Additional file 1: Table S4). The allele and genotype frequencies of the 4 SNPs in asthmatics and controls were listed in Table 1. We found allele frequencies and genotype frequencies of *STIP1* rs2236647 in asthmatics and controls were significantly different ($p = 0.008$ and $p = 0.018$, respectively; Table 1). Children with *STIP1* rs2236647 CC genotype showed increased risk of asthma compared with the other two genotypes ($p = 0.005$, Table 1). After adjusting for age and gender, we found that rs2236647 CC genotype was still associated with increased the risk of childhood asthma (OR = 1.840 and 1.929 in two different model; Table 2). However, similar associations were not found in rs37969, rs37972, and rs37973 polymorphisms (Table 1).

Table 1

The allele and genotype frequency of 4 SNPs in asthmatics and controls.

Gene	SNP	Genotype / Allele	Cases (n = 263)	Controls (n = 150)	p-value	REC ^a model p-value	DOM ^b model p-value	
STIP1	rs2236647	TT	38(14.44%)	29(19.33%)	0.018	0.195	0.005	
		TC	113(42.97%)	78(52.00%)				
		CC	112(42.59%)	43(28.67%)				
		T	189(35.93%)	136(45.33%)	0.008			
		C	337(64.07%)	164(54.67%)				
GLCCI1	rs37969	TT	53(20.15%)	34(22.67%)	0.820	0.547	0.708	
		GT	130(49.43%)	73(48.67%)				
		GG	80(30.42%)	43(28.67%)				
			T	236(44.87%)	141(47.00%)	0.554		
			G	290(55.13%)	159(53.00%)			
	rs37972	TT	47(17.88%)	28(18.67%)	0.952	0.840	0.766	
		TC	121(46.01%)	70(46.67%)				
		CC	95(36.12%)	52(34.67%)				
		T	215(40.87%)	126(42.00%)				
		C	311(59.13%)	174(58.00%)				
	rs37973	GG	54(20.53%)	36(24.00%)	0.675	0.412	0.550	
		GA	128(48.67%)	72(48.00%)				
		AA	81(30.80%)	42(28.00%)				
		G	236(44.87%)	144(48.00%)				
		A	290(55.13%)	156(52.00%)				
The values $p \leq 0.05$ were in bold.								
^a REC means (AA + Aa) vs aa;								
^b DOM means AA vs (Aa + aa); "A" is the major allele and "a" is the minor allele.								

Table 2
Association (OR, 95% CI) between gene SNPs and childhood asthma susceptibility.^a

SNP	Model ^b	OR	OR corr ^c
rs2236647	DOMDEV	1.798(1.141–2.833) ☒	1.840(1.162–2.914) ☒☒
rs2236647	DOM	1.846(1.201–2.838) ☒☒	1.929(1.247–2.986) ☒☒
^a Table only shows SNPs that are associated with asthma susceptibility through logistic regression analysis of alleles and different genotypes.			
^b Model: DOMDEV means using the wild-type homozygote as dummy variable, the logistic regression analysis of heterozygotes. If A is the major allele and a is the minor allele, DOM means AA vs (Aa + aa).			
^c OR corr: the p value after adjusting age, gender and smoking exposure as covariates; OR: Odds ratio (reference group designated with an OR of 1.0).			
☒ p ≤ 0.05; ☒☒ p ≤ 0.01.			

***GLCCI1* rs37969 was associated with onset age of asthma**

The allele and genotype frequency of 4 SNPs in different age groups are listed in Table 3. The genotype frequencies of rs37969 in the group over 6 years of age and the group under 6 years of age were significantly different in dominant model (p = 0.033, Table 3). There were no differences in the other 3 SNPs (Table 3). After adjusting for gender, the dominant model revealed that the rs37969 TT/TC genotypes were significantly associated with increased risk of asthma in the children under 6 years old (OR = 2.254, 95% CI: 1.068–4.757, Tables 3 and 4). There was no association between rs2236647, rs37972, and rs37973 and onset age of asthma (Table 3).

Table 3

The allele and genotype frequency of 4 SNPs in group above / under 6 years.

Gene	SNP	Genotype / Allele	Age ≥ 6 years group(n = 209)	Age < 6 years group(n = 54)	p-value	REC ^a model p-value	DOM ^b model p-value	
STIP1	rs2236647	TT	32(15.31%)	6(11.11%)	0.435	0.434	0.216	
		TC	92(44.02%)	21(38.89%)				
		CC	85(40.67%)	27(50.00%)				
		T	156(37.32%)	33(30.56%)	0.191			
		C	262(62.68%)	75(69.44%)				
GLCCI1	rs37969	TT	40(19.14%)	13(24.07%)	0.102	0.420	0.033	
		GT	99(47.37%)	31(57.41%)				
		GG	70(33.49%)	10(18.52%)				
		T	179(42.82%)	57(52.78%)	0.064			
		G	239(57.18%)	51(47.22%)				
	rs37972	TT	37(17.70%)	10(18.52%)	0.333	0.889	0.152	
		TC	92(44.02%)	29(53.70%)				
		CC	80(38.28%)	15(27.78%)				
			T	166(39.71%)	49(45.37%)	0.286		
			C	252(60.29%)	59(54.63%)			
rs37973	GG	40(19.14%)	14(25.93%)	0.156	0.271	0.063		
		GA	99(47.37%)				29(53.70%)	
		AA	70(33.49%)				11(20.37%)	
		G	179(42.82%)	57(52.78%)	0.064			
		A	239(57.18%)	51(47.22%)				
The values $p \leq 0.05$ were in bold.								
^a If "A" is the major allele and "a" is the minor allele, REC means (AA + Aa) vs aa;								
^b If "A" is the major allele and "a" is the minor allele, DOM means AA vs. (Aa + aa);								

Table 4

Association (OR, 95% CI) between gene SNPs and the onset age of asthma.^a

SNP	Model ^b	OR	OR corr ^c
rs37969	DOM	2.216(1.053–4.664) \boxtimes	2.254(1.068–4.757) \boxtimes
^a Table only shows SNPs that are associated with onset age of asthma through logistic regression analysis of alleles and different genotypes.			
^b Model: DOM means AA vs. (Aa + aa)			
^c OR corr: the p value after adjusting gender and smoking exposure as covariates; OR: Odds ratio (reference group designated with an OR of 1.0).			
\boxtimes p \leq 0.05.			

4 candidate SNPs were not associated with baseline lung function measures

We found four SNPs (rs2236647, rs37969, rs37972, and rs37973) were not associated with baseline lung function measures (FEV1/pre, FEV1/FVC, PEF/pre, FEF 25/pre FEF 75/pre and MMEF/pre; Data were not shown). We also did not observe significant associations between baseline PD20 and the 4 SNPs (Data were not shown).

3 SNPs in *GLCC1* were associated with the change in MMEF after ICS treatment

Significant associations were identified between rs37969, rs37972, and rs37973 and the change in MMEF after 3 months of ICS treatment compared with baseline. MMEF improved by a less percentage change in subjects who were rs37969 wild-type homozygotes (GG) as compared with those who were mutant genotype (TT/GT) ($20.79 \pm 20.65\%$, $13.23 \pm 18.39\%$, $p = 0.036$; Table 5, Fig. 2). Similar results were found in rs37972 ($21.08 \pm 21.03\%$, $12.23 \pm 17.58\%$, $p = 0.010$; Table 5, Fig. 2) and rs37973 ($23.22 \pm 21.52\%$, $12.36 \pm 17.52\%$, $p = 0.003$; Table 5, Fig. 2). However, this phenomenon was not repeated in rs2236647. Besides, there was also no associations between the change in FEV1/FVC and the 4 SNPs.

Table 5
Changes in lung function after treatment with different genotypes.^a

SNP	Biomarker	Model ^b	Biomarker changes in major genotype (min, max)	Biomarker changes in other genotypes (min, max)
rs37969	MMEF	DOM	20.79(-19.2, 75.2)	13.23(-25.8, 64.8) ☒
rs37969	PD20	DOM	0.77(-0.93, 2.19)	0.44(-2.19, 2.19) ☒
rs37972	MMEF	DOM	21.08(-19.2, 75.2)	17.58(-25.8, 64.8) ☒
rs37972	MMEF	DOMDEV	21.08(-19.2, 75.2)	13.12(-25.8, 64.8) ☒
rs37972	MMEF	ADD	21.08(-19.2, 75.2)	9.01(-23.9, 38.8) ☒
rs37973	MMEF	DOM	23.22(-19.2, 75.2)	12.36(-25.8, 64.8) ☒☒
rs37973	MMEF	DOMDEV	23.22(-19.2, 75.2)	13.81(-19.6, 64.8) ☒
rs37973	MMEF	ADD	23.22(-19.2, 75.2)	7.58(-25.8, 38.8) ☒☒
rs37973	FEV1	DOM	12.8(-11.7, 39.6)	7.96(-15.3, 56.3) ☒
^a Table only shows the SNPs that are associated with asthma susceptibility through logistic regression analysis of alleles and different genotypes.				
^b Model: ADD and DOMDEV mean using the wild-type homozygote as dummy variable, the logistic regression analysis of the mutant-type homozygote and heterozygotes respectively. If A is the major allele and a is the minor allele, DOM means AA vs (Aa + aa).				
☒ p ≤ 0.05; ☒☒ p ≤ 0.01.				

***GLCCI1* rs37969 was associated with the change in airway hyper-responsiveness**

In our study, we found the mutant genotypes (TT/GT) for the *GLCCI1* rs37969 had less improvement in PD20 compared with wild-type homozygotes (GG) (0.77 ± 0.74 mg, 0.44 ± 0.82 mg; $p = 0.028$) (Fig. 3). However, we did not find the associations between the other 3 SNPs (rs2236647, rs37972, and rs37973) and the improvement in airway hyper-responsiveness.

Discussion

Currently, the association studies between genetic variations and asthma susceptibility in population of Chinese children are still limited. To the best of our knowledge, this is the first study that confirmed the rs2236674 SNP in *STIP1* gene is significantly associated with the risk of Chinese asthmatic children. We

also report here that GLCCI1 rs37969, rs37972, and rs37973 were associated with the response to ICS treatment in Chinese children with asthma.

An Arab study has indicated that the STIP1 rs2236647 C allele can be used as an asthma marker for adult [14]. In our study, C is the major allele of rs2236647 polymorphism and the frequency of wild-type homozygote (CC) in asthmatics was lower than controls. After adjusting the gender and age, we found CC homozygote children had an increased risk of asthma compared with CT/TT genotype. The previous studies were focused on adult asthma and there were no similar results have been reported in childhood asthma. Our finding demonstrated that CC homozygotes of STIP1 rs2236647 polymorphism might be an asthma susceptibility marker in Chinese childhood asthma. However, no relationship was found between rs2236647 polymorphism and onset age of asthma.

Moreover, a white adult asthma study identified that STIP1 rs2236647 was associated with change in lung function after ICS treatment for 4 weeks [13]. But in our study, there was no association between STIP1 rs2236647 and the change of lung function after ICS treatment for 3 months in Chinese children. Therefore, we speculate that the difference may be related to regions and ages and more studies are needed to explore the reasons.

In a Saudi Arabian study, 2 GLCCI1 SNPs, (rs37972 and rs37973), were found to be unrelated to adult asthma susceptibility [21]. Similarly, we found GLCCI1 rs37969, rs37972, and rs37973 polymorphisms were all irrelevant to the risk of childhood asthma in the current study. However, GLCCI1 rs37969 was found to be associated with onset age of asthma. Compared with wild-type homozygote (GG), TT/GT genotypes in asthmatic children were related to the increased risk of early onset asthma. This result indicated that GLCCI1 rs37969 polymorphism might be used to predict the onset age of asthma. And it is necessary that combining rs37969 and the SNPs that are associated with the risk of childhood asthma to predict the occurrence and development of asthma in children.

In 2011, Tantisira et al. discovered that the GLCCI1 SNPs, (rs37972 and rs37973), was associated with change in lung function after ICS treatment in 1,053 asthmatic patients [16]. Then, GLCCI1 rs37972 and rs37973 variant genotypes were found to be related to less improvement in the FEV1 after ICS treatment for 12 weeks in Chinese patients [19]. Similar results were replicated in another Chinese study [22]. Associations also were found between GLCCI1 rs37973 and ICS response in Japanese adult asthmatics [23]. However, a non-Hispanic white study discovered that rs37973 was not associated with the change in FEV1 after treatment with ICS [24]. Negative results were showed in a Saudi Arabian study and a recent GWAS study [21, 25]. Most of the above studies were conducted on adult asthma. In our study, we found there were no associations between GLCCI1 polymorphisms and the improvement in FEV1/pre and FEV1/FVC after ICS treatment in childhood asthma. However, GLCCI1 rs37969, rs37972, and rs37973 mutant genotypes were found to be related to less improvement of the MMEF after ICS treatment. MMEF may be more sensitive than FEV1 when assessing the lung function of asthmatics [26, 27]. Therefore, we support that GLCCI1 can be considered as a predictor of ICS response in Chinese Han childhood asthma, and MMEF deserves more attention after ICS treatment.

It is especially noticed that asthmatic children with GLCCI1 rs37969 mutant genotypes have increased risk of early onset asthma and lower ICS response compared with the wild-gene homozygote in our study. Rs37969 is located in the intron region of GLCCI1 (<https://www.ncbi.nlm.nih.gov/snp/>). The current data on GLCCI1 rs37969 is extremely lacking, especially in childhood asthma. More basic experimental studies are needed to confirm whether the mutation affects the expression of GLCCI1.

There are still several limitations in this study. First, the follow-up for asthmatic children in this study was only 3 months. The follow-up period could be extended in the future. Second, the number of participants was small for a genetic study, especially in the follow-up group. Third, this study focuses on the effect of single SNPs on childhood asthma. Gene-gene interaction, epigenetics, and environment need to be considered in the future [28, 29].

Conclusions

In conclusion, we found significant associations between the STIP1 rs2236647 polymorphism and the risk of childhood asthma, and GLCCI1 SNPs are related to the onset age of asthma and improvement of lung function in Chinese Han childhood asthma patients who received ICS for 3 months. Our results indicated that STIP1 might be considered as an asthma marker in children, while GLCCI1 might be used to predict the onset age of asthma and ICS response in childhood asthma. And Fig. 4 summarizes the main findings of the current study. It is worth mentioning that we are the first to report the function of STIP1 rs2236647 and GLCCI1 rs37969 in childhood asthma patients and more studies are required to repeat our findings.

Abbreviations

ICS: Inhaled corticosteroid; STIP1: Stress-induced phosphoprotein 1; GLCCI1: Glucocorticoid-induced transcript 1; GR: Glucocorticoid receptor; GC: Glucocorticoid; FEV1: Forced expiratory volume in 1 second; PEF: Peak expiratory flow; FEF: Forced expiratory flow; FVC: Forced vital capacity; MMEF: Maximal midexpiratory flow; PD20: Provocative dose of methacholine causing a 20% drop in FEV1.

Declarations

Acknowledgment

Not applicable.

Authors' contributions

Conceptualization: HJ and ZXR; Data curation, HJ and TYJ; Formal analysis, LCT; Investigation, KJ; Methodology, WX; Supervision, ZXR and HXL; Writing – original draft, HJ; Review & editing, ZXR and HXL. All authors read and approved the manuscript.

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Availability of data and materials

The data generated or analyzed during this study are included in this article and its supplementary information files.

Ethics approval and consent to participate:

This study was approved by the ethics committee of Xiangya Hospital Central South University and all patients and their parent or guardian provided written informed consent. The study was also registered in the Chinese Clinical Trial Registry (Registry ID: ChiCTR-ROC-17013216).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

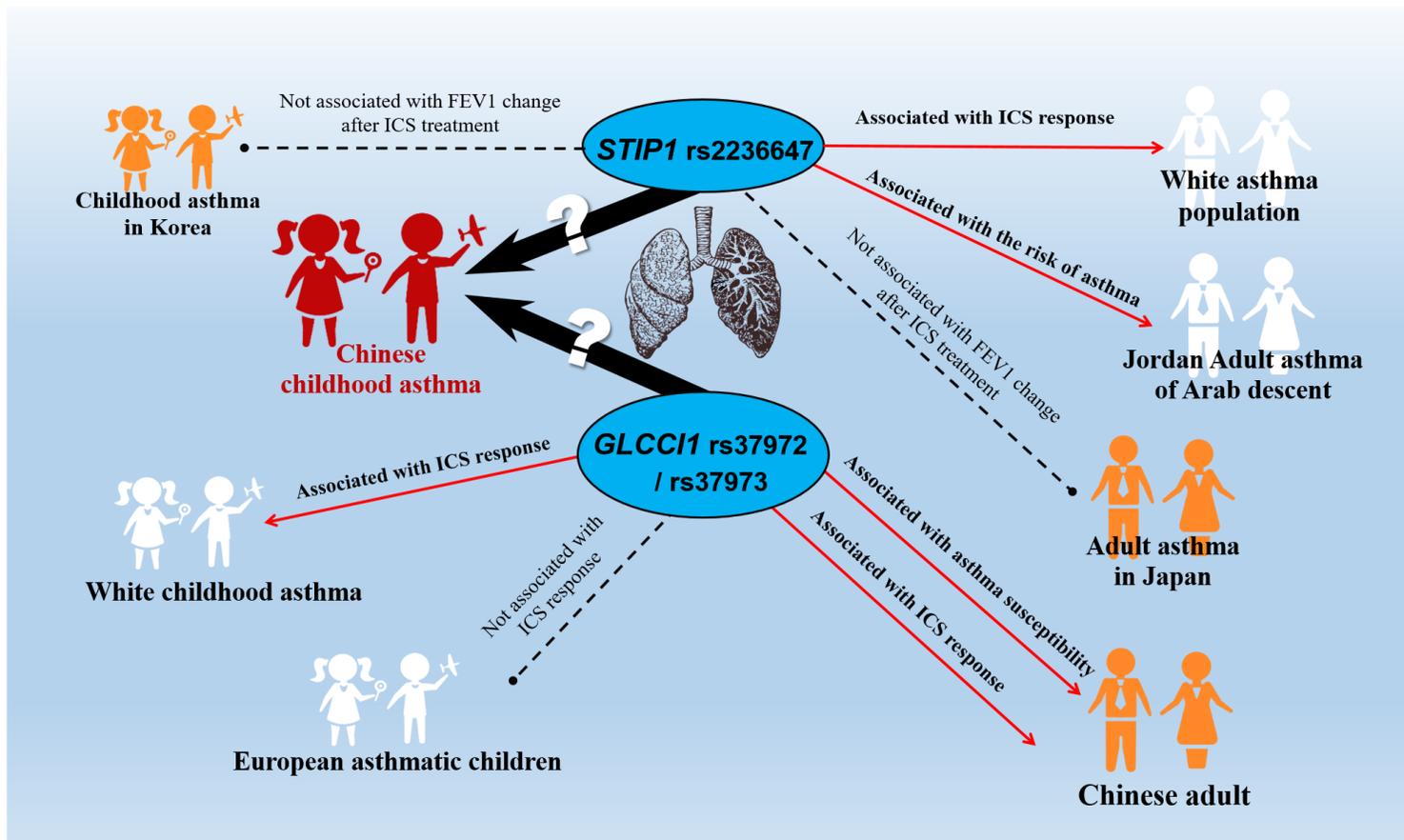


Figure 1

Current research status of STIP1 rs2236647 and GLCCI1 rs37972 /rs37973 polymorphisms in asthma of different populations. ICS: Inhaled corticosteroid.

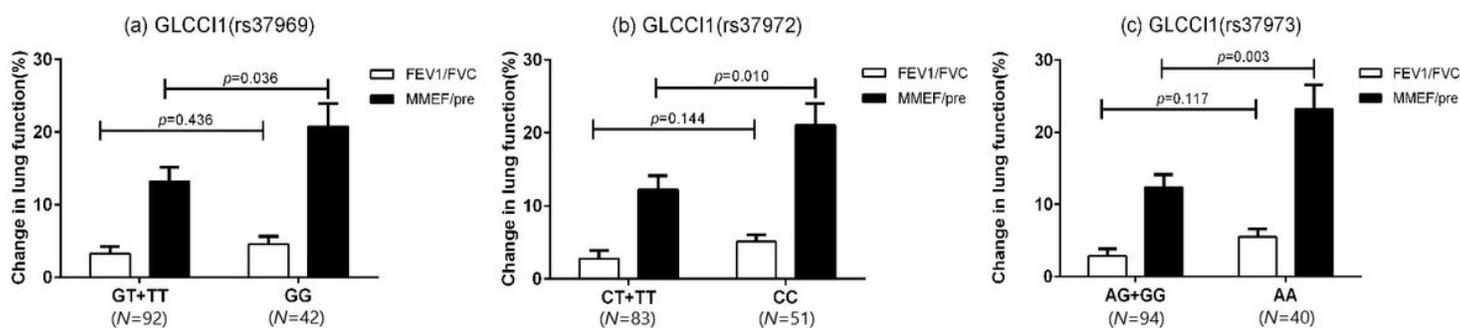


Figure 2

Association between GLCCI1 SNPs and change in pulmonary function after ICS treatment for 3 months.

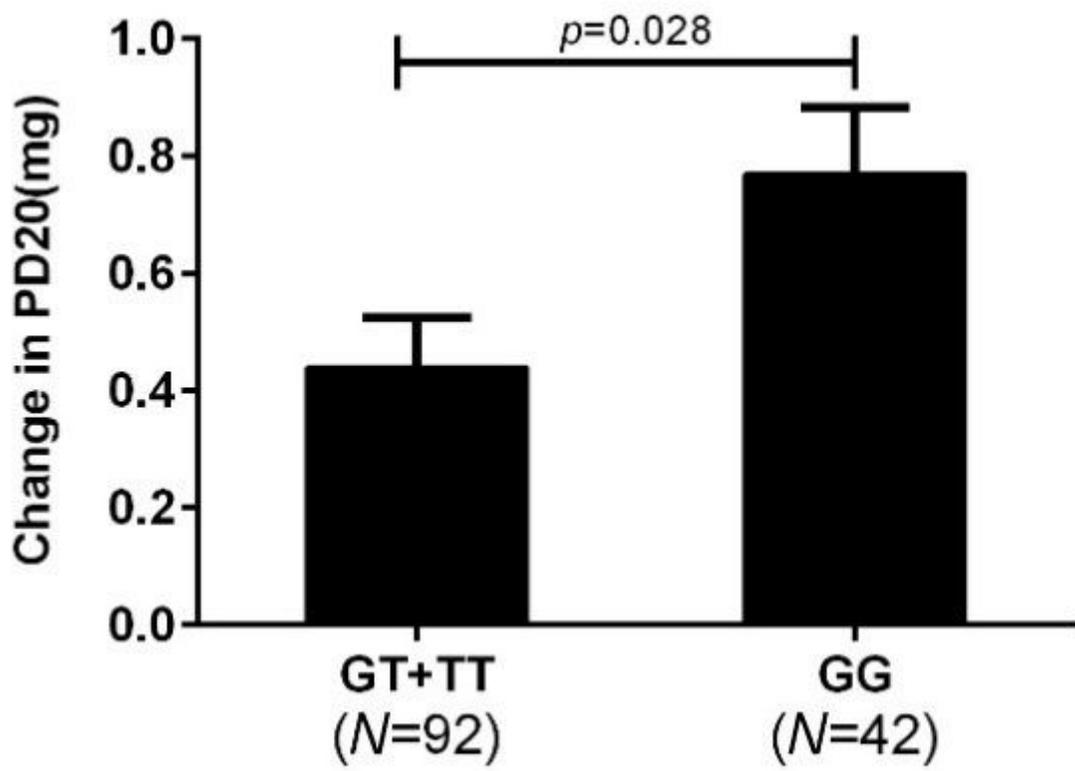


Figure 3

Association between the GLCCI1 rs37969 genotype and change in PD20 after ICS treatment for 3 months.

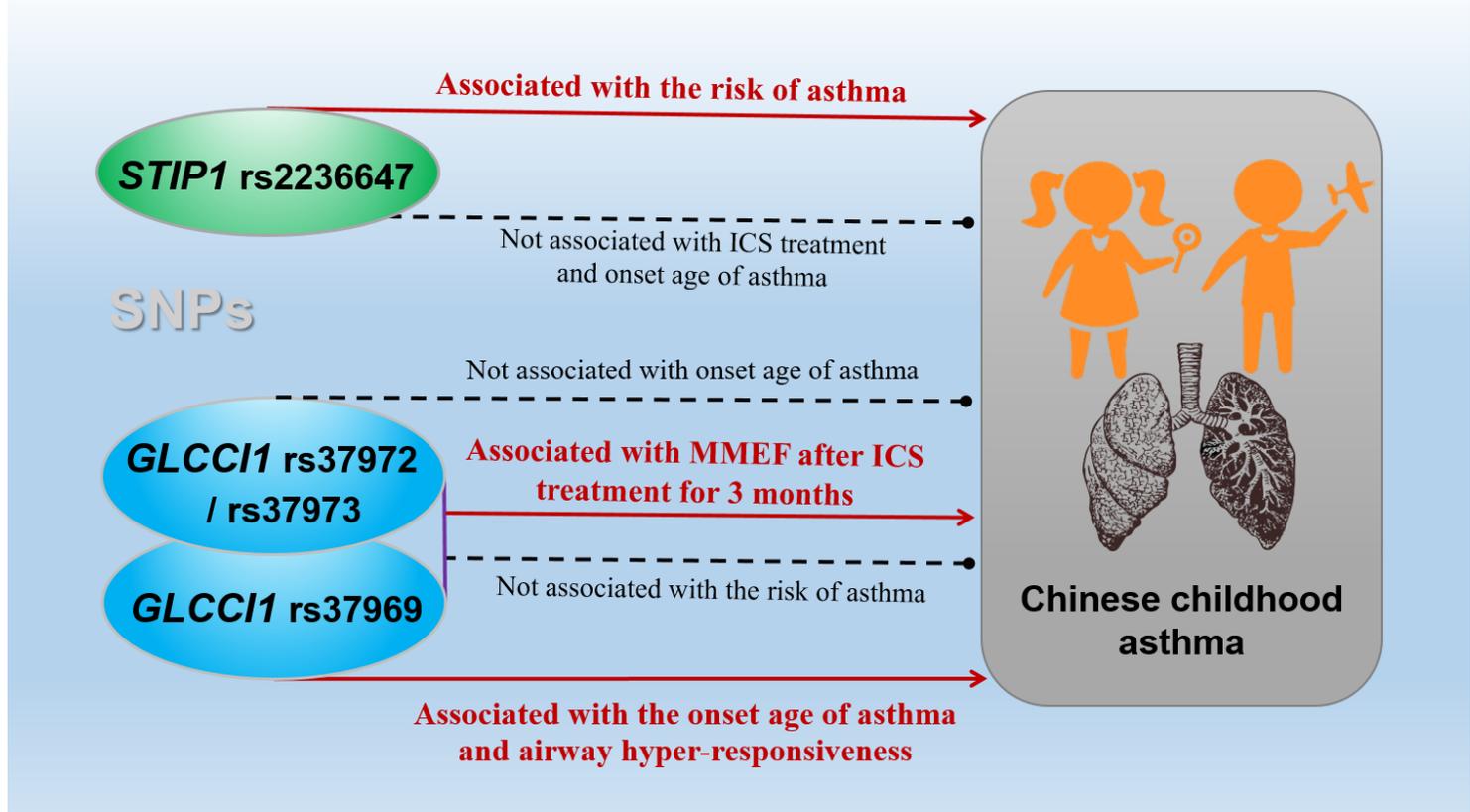


Figure 4

Main findings of the current study. MMEF: Maximal midexpiratory flow; ICS: Inhaled corticosteroid.

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