RESEARCH ARTICLE

Effects of *STIP1* and *GLCCI1* 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. One hundred fifty 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 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 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 and *GLCCI1* rs37969 mutant genotypes were associated with 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.

Keywords: Childhood asthma, *STIP1*, *GLCCI1*, Polymorphism, Pulmonary function

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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.
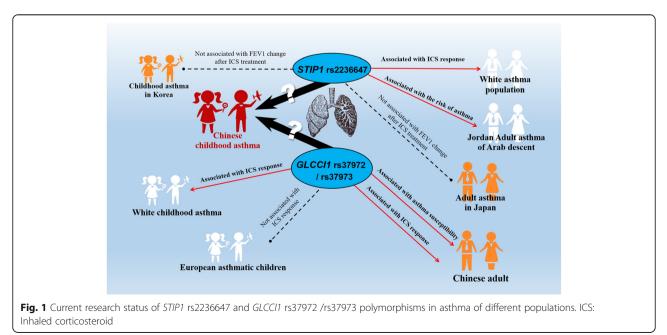
The current perspective is that the drug response of asthma in children and adults are closely associated with genetic factors. Studies have shown that genetic factors contribute about 70% of the variability in inhaled corticosteroid (ICS) response [7, 8]. There are more than 1000 candidate genes had 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

Fig. 1 Current research status of *STIP1* rs2236647 and *GLCCI1* rs37972 /rs37973 polymorphisms in asthma of different populations. ICS: Inhaled corticosteroid

Huang *et al. BMC Pulmonary Medicine*   (2020) 20:303

Page 3 of 8

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
Two hundred sixty-three 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 Table 1). These subjects all come from Hunan, China.

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 s (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 hyperresponsiveness.

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 KitII, Omega, USA). The primers were designed by AssayDesigner3.1 (Details are listed in Additional file 1: Table S1).

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.

Table 1 Inclusion criteria for enrollment in case-control study and the treatment trial

Asthmatics inclusion criteria

1. Meets the 2017 GINA guidelines on the diagnostic criteria for asthma.

2. No history of respiratory infections and systemic infections within 1 month.

3. No history of hospitalization for asthma exacerbation within 1 month.

4. No regular history of using ICS within 1 month.

5. No following diseases: congenital lung malformations; airway obstruction or extraluminal oppression; congenital heart disease; active tuberculosis; bronchiectasis; severe systemic diseases.

Controls inclusion criteria

Without the following diseases: Bronchial asthma; Bronchiolitis; Allergic diseases such as eczema, allergic rhinitis and atopic dermatitis; Severe systemic diseases; Family history of allergic diseases.

Table 2 Baseline demographics of subjects involved in the study

Characteristics	N (%)		P-value
	Asthma patients	Controls	
Total	263	150	
Age (year)			
< 6	54(20.53)	33(22.00)	0.725
≥ 6	209(79.47)	117(78.00)	
Gender			
Boys	188(71.48)	97(64.67)	0.150
Girls	75(28.52)	53(35.33)	
Smoking exposure			
Yes	154(58.56)	99(66.00)	0.135
No	109(41.44)	51(34.00)	
Allergies			
Yes	172(65.40)	0(0.00)	
No	91(34.60)	150(100.00)	
Family history of asthma			
Yes	89(33.84)	0(0.00)	
No	174(66.16)	150(100.00)	

Huang *et al. BMC Pulmonary Medicine*   (2020) 20:303

Page 4 of 8

Table 3 The allele and genotype frequency of 4 SNPs in asthmatics and controls

Gene	SNP	Genotype / Allele	Cases (n = 263)	Controls (n = 150)	P-value/Corrected p-value[a]	REC[b] model p-value/Corrected p-value[a]	DOM[c] model p-value/Corrected p-value[a]
STIP1	rs2236647	TT	38(14.44%)	29(19.33%)	**0.018**/0.072	0.195/0.780	**0.005**/**0.020**
		TC	113(42.97%)	78(52.00%)			
		CC	112(42.59%)	43(28.67%)			
		T	189(35.93%)	136(45.33%)	**0.008**/**0.032**		
		C	337(64.07%)	164(54.67%)			
GLCCI1	rs37969	TT	53(20.15%)	34(22.67%)	0.820/1.000	0.547/1.000	0.708/1.000
		GT	130(49.43%)	73(48.67%)			
		GG	80(30.42%)	43(28.67%)			
		T	236(44.87%)	141(47.00%)	0.554/1.000		
		G	290(55.13%)	159(53.00%)			
	rs37972	TT	47(17.88%)	28(18.67%)			
		TC	121(46.01%)	70(46.67%)	0.952/1.000	0.840/1.000	0.766/1.000
		CC	95(36.12%)	52(34.67%)			
		T	215(40.87%)	126(42.00%)	0.752/1.000		
		C	311(59.13%)	174(58.00%)			
	rs37973	GG	54(20.53%)	36(24.00%)	0.675/1.000	0.412/1.000	0.550/1.000
		GA	128(48.67%)	72(48.00%)			
		AA	81(30.80%)	42(28.00%)			
		G	236(44.87%)	144(48.00%)	0.385/1.000		
		A	290(55.13%)	156(52.00%)			

The values $p \leq 0.05$ were in bold
[a]Corrected by Bonferroni multiple adjustment; [b]REC means (AA + Aa) vs aa; [c]DOM means AA vs (Aa + aa); "A" is the major allele and "a" is the minor allele

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. Two hundred nine 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 baseline demographics of subjects are listed in Table 2.

STIP1 rs2236647 was associated with the risk of childhood asthma

All the SNPs involved in our study were in HWE (Additional file 1: Table S2). The allele and genotype frequencies of the 4 SNPs in asthmatics and controls were listed in Table 3. 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 3). Children with *STIP1* rs2236647

CC genotype showed increased risk of asthma compared with the other two genotypes ($p = 0.005$, Table 3). After adjusting for age and gender, we found that rs2236647 CC genotype was still associated with increased the risk of childhood asthma (OR = 1.929; Table 4). However, similar associations were not found in rs37969, rs37972, and rs37973 polymorphisms (Table 3).

4 candidate SNPs were not associated with baseline lung function measures

Baseline lung function of different genotypes is shown in Table 5 and 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; Table 5). We

Table 4 Association (OR, 95% CI) between gene SNPs and childhood asthma susceptibility[a]

SNP		OR	OR corr [b]
rs2236647	CC vs (TC + TT)	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]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)
* $p \leq 0.05$; ** $p \leq 0.01$

Huang *et al. BMC Pulmonary Medicine*   (2020) 20:303

Page 5 of 8

Table 5 Baseline lung function of different genotypes

Gene	SNP	Allele	FEV1/pre (%)	FEV1/FVC	PEF/pre (%)	FEF 25/pre (%)	FEF 75/pre (%)	MMEF/pre (%)	PD20 (mg)
STIP1	rs2236647	CT + TT	93.18 ± 11.74	94.69 ± 9.64	88.73 ± 13.24	80.36 ± 17.67	56.78 ± 20.53	66.32 ± 18.95	0.76 ± 0.76
		CC	93.80 ± 14.78	95.27 ± 9.30	86.89 ± 16.33	83.25 ± 22.70	55.48 ± 21.67	66.18 ± 21.96	0.83 ± 0.86
GLCCI1	rs37969	GT + TT	93.93 ± 12.90	95.10 ± 10.15	88.07 ± 15.25	82.36 ± 20.82	57.3 ± 22.32	67.06 ± 20.89	0.84 ± 0.84
		GG	92.24 ± 12.86	94.44 ± 7.94	88.07 ± 12.47	79.29 ± 16.59	54.16 ± 17.32	64.53 ± 18.01	0.66 ± 0.69
	rs37972	CT + TT	92.97 ± 12.84	94.69 ± 10.46	87.33 ± 14.57	80.63 ± 20.28	56.17 ± 22.65	65.79 ± 21.01	0.74 ± 0.77
		CC	94.09 ± 13.00	95.23 ± 7.74	89.29 ± 14.15	82.65 ± 18.51	56.55 ± 17.81	67.05 ± 18.40	0.84 ± 0.84
	rs37973	AG + GG	93.82 ± 12.75	95.00 ± 10.01	87.53 ± 14.52	81.09 ± 19.6	57.38 ± 22.09	66.68 ± 20.35	0.79 ± 0.80
		AA	92.41 ± 13.24	94.66 ± 8.24	89.34 ± 14.19	82.13 ± 19.77	53.81 ± 17.68	65.29 ± 19.36	0.75 ± 0.80

also did not observe significant associations between baseline PD20 and the 4 SNPs (Table 5).

3 SNPs in *GLCCI1* 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 more percentage change in subjects who were rs37969 wild-type homozygote (GG) as compared with those who were mutant genotype (TT/GT) (20.79 ± 20.65%, 13.23 ± 18.39%, p = 0.036; Table 6, Fig. 2). Similar results were found in rs37972 (21.08 ± 21.03%, 12.23 ± 17.58%, p = 0.010; Table 6, Fig. 2) and rs37973 (23.22 ± 21.52%, 12.36 ± 17.52%, p = 0.003; Table 6, 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.

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) (0.44 ± 0.82 mg, 0.77 ± 0.74 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.
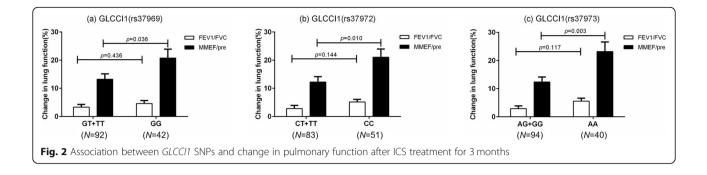
An Arab study has indicated that the *STIP1* rs2236647 C allele can be used as an asthma marker for adult [14]. However, according to the currently reported GWAS, the *STIP1* gene has not been found to be associated with asthma sensitivity, whether in African American, Asian, Caucasian or Latino [21, 22]. 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 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. 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

Table 6 Changes in lung function after treatment with different genotypes[a]

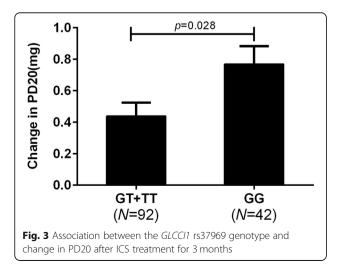| SNP	Biomarker	Major genotype/other genotypes	Biomarker changes in major genotype (min, max)	Biomarker changes in other genotypes (min, max)
rs37969	MMEF	GG/(GT + TT)	20.79(−19.2, 75.2)	13.23(−25.8, 64.8) *
rs37969	PD20	GG/(GT + TT)	0.77(−0.93, 2.19)	0.44(−2.19,2.19) *
rs37972	MMEF	CC/(CT + TT)	21.08(−19.2, 75.2)	12.23(−25.8, 64.8) *
rs37973	MMEF	AA/(AG + GG)	23.22(−19.2, 75.2)	12.36(−25.8, 64.8) **

[a]Table only shows the SNPs that are associated with asthma susceptibility through logistic regression analysis of alleles and different genotypes
* $p \leq 0.05$; ** $p \leq 0.01$

Huang *et al. BMC Pulmonary Medicine*   (2020) 20:303

Page 6 of 8

Fig. 2 Association between *GLCCI1* SNPs and change in pulmonary function after ICS treatment for 3 months

months in Chinese children. We suspected that the differences between childhood asthma and adult asthma were probably due to the age and different underlying pathophysiological basis [23, 24]. Besides, racial differences might also play important roles in these differences. However, the underlying mechanism for these differences is still unclear, and more studies are urgently needed to further explain the reasons.
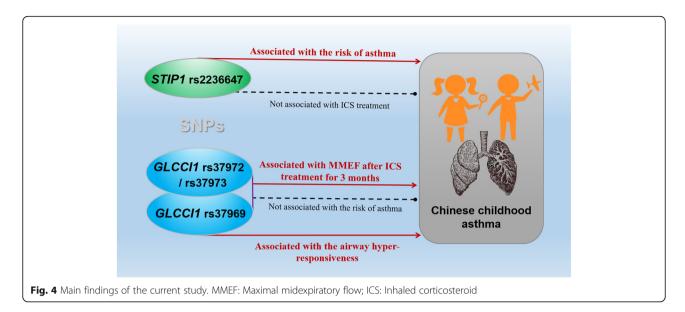
In a Saudi Arabian study, 2 *GLCCI1* SNPs, (rs37972 and rs37973), were found to be unrelated to adult asthma susceptibility [25]. Similarly, we found *GLCCI1* rs37969, rs37972, and rs37973 polymorphisms were all irrelevant to the risk of childhood asthma in the current study. In 2011, *Tantisira* et al. discovered that the *GLCCI1* SNPs, (rs37972 and rs37973), was associated with change in lung function after ICS treatment in 1053 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 [26]. Associations also were found between *GLCCI1* rs37973 and ICS response in Japanese adult asthmatics [27]. However, a non-Hispanic white study

discovered that rs37973 was not associated with the change in FEV1 after treatment with ICS [28]. Negative results were showed in a Saudi Arabian study and a recent GWAS study [25, 29]. Most of the above studies were conducted on adult asthma and there are fewer studies on these SNPs in children with 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 associated with less improvement of the MMEF after ICS treatment. MMEF may be more sensitive than FEV1 when assessing the lung function of asthmatics [30, 31]. Therefore, our study in Chinese Han childhood asthma population support the perspective that *GLCCI1* might be considered as a predictor of ICS response to a certain extent. However, there are fewer studies on these SNPs in children with asthma compared with adults. More studies on childhood asthma are urgently needed to enrich the current theories, and studies of larger sample size and different populations are also needed to reproduce these results.

It is especially noticed that asthmatic children with *GLCCI1* rs37969 mutant genotypes have 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 [32, 33].

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

Huang *et al. BMC Pulmonary Medicine*   (2020) 20:303

Page 7 of 8

Fig. 4 Main findings of the current study. MMEF: Maximal midexpiratory flow; ICS: Inhaled corticosteroid

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 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 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.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12890-020-01332-2.

Additional file 1: Table S1. Primers used in genes genotyping. **Table S2.** Hardy-Weinberg equilibrium test. **Table S3.** Interaction between SNPs of our candidate genes and corticosteroid response in patients with asthma.

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 s; 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

Acknowledgments

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.

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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