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GLCCI1 rs37973 is associated with the response of adrenal hormone to inhaled corticosteroids in asthma

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ABSTRACT

Background: Previous studies have demonstrated that glucocorticoid-induced transcript 1 gene (*GLCCI1)* rs37973 mutant genotype is associated with poor inhaled corticosteroid (ICS) response in asthmatics. As human airway relaxation is regulated by circulation epinephrine, which can be enhanced by corticosteroid. It is unknown whether or not *GLCCI1* rs37973 is associated with circulation epinephrine and cortisol concentrations in asthma. The aim of this study is to evaluate these relationships.

Methods: A total of 182 asthmatics and 180 healthy controls were recruited for the study. 30 mild-to-moderate asthmatics received fluticasone propionate (125 μg, bid) treatment for 12 weeks. *GLCCI1* rs37973 genotyping was performed with the iPlex MassARRAY genotyping platform. The plasma concentrations of cortisol and epinephrine of each participant were detected by enzyme linked immunosorbent assay (ELISA) kits.

Results: GLCCI1 rs37973 homozygotes mutant genotype GG had a higher plasma epinephrine concentration (median concentration 27.032 pg/ml, $n_{GG} = 36$; median concentration 23.149 pg/ml, $n_{AA+AG} = 146$; $P = 0.015$) and cortisol concentration (median concentration 1.141 ng/ml, $n_{GG} = 36$; median concentration 0.921 ng/ml, $n_{AA+AG} = 146$; $P = 0.013$). Both epinephrine concentration and cortisol concentration in plasma were positively correlated with FEV_1 ($r = 0.889$ and $r = 0.821$, respectively. $n_{asthma} = 182$). For asthmatics treated with ICS, rs37973 was associated with change in plasma epinephrine and cortisol concentration in a recessive model (AA + AG vs GG), with GG had less improvement in epinephrine concentration [$\Delta EPI_{AA+AG} = 6.843$ (9.26) pg/ml, $n_{AA+AG} = 26$; $\Delta EPI_{GG} = -1.666$ (6.52) pg/ml, $n_{GG} = 4$; $P = 0.018$] and cortisol concentration [$\Delta COR_{AA+AG} = 0.3040$ (0.21) ng/ml, $n_{AA+AG} = 26$; $\Delta COR_{GG} = -0.066$ (0.24) ng/ml, $n_{GG} = 4$; $P = 0.009$].

Conclusions: Our study suggested that the poor ICS response in *GLCCI1* rs37973 mutant genotype might be related to the less increased amplitudes of plasma epinephrine and cortisol in asthmatic patients.

Trial registration: ChiCTR-RCC-13003634 www.chictr.org.cn. Active since September 27, 2013.

Background

Inhaled corticosteroids (ICS) are the first-line drugs for the control and management of asthma. However, the response to ICS is characterized by high intra-individual repeatability and high inter-individual variability in asthmatic patients.[1,2] Glucocorticoid resistance or insensitivity is a major barrier to the treatment of asthma.[3] A study by Tantisira et al. indicated that the functional polymorphism of glucocorticoid-induced transcript 1 gene (*GLCCI1*), rs37973, was associated with response to ICS in non-Hispanic white subjects with asthma.[4] The data showed that the mean increase of forced expiratory volume in 1 s (FEV_1) in the treated asthmatic subjects who were homozygous for the mutant rs37973 genotype (GG) was only about one third of that in similarly treated subjects who were homozygous for the wild-type allele.[4] Izuhara et al. even demonstrated that *GLCCI1* variant accelerated pulmonary function decline in patients with asthma receiving ICS.[5] Recently, we also found a similar phenomenon in a Chinese Han population.[6]

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As adrenergic nerves are absent in human airway smooth muscles, the relaxation of airways is mainly regulated by endogenous epinephrine (EPI), which binds to the adrenergic receptors in airway smooth muscles. Studies have indicated that plasma epinephrine levels were decreased in asthmatic patients,[7,8] which may be the major reason for supplementing exogenous epinephrine and other β_2-adrenergic receptor agonists in relieving asthma attack.

Epinephrine regulates airway relaxation in human beings; as a result, is it related to lung function? Furthermore, it is well known that glucocorticoids can enhance the effects of epinephrine and β_2-adrenergic receptor agonists. Studies also have shown that glucocorticoids could promote the expression of epinephrine.[9–11] Therefore, is the poor response to ICS in asthmatic patients with rs37973 GG genotype related to the change of plasma epinephrine concentration? It is necessary to elucidate the association among *GLCCI1* rs37973 genotype and plasma epinephrine and cortisol concentration in asthmatic patients.

Materials and methods

Study population

From March 2013 to March 2014, 182 unrelated asthmatic patients were recruited from the outpatient clinic of respiratory medicine of Xiangya Hospital in Changsha, Hunan, China. One hundred eighty unrelated, random-sampled healthy controls who underwent comprehensive medical screening at Xiangya Hospital were recruited. Asthma diagnosis was established according to the Global Initiative for Asthma (GINA) recommendations,[12] based on clinical asthma symptoms and pulmonary function test. The level of asthma severity was determined on the basis of GINA report guidelines.[12] Inclusion criteria for the study were: 1) a history of episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning; 2) either a positive bronchial hyper-responsiveness or a positive bronchodilator test. Exclusion criteria included: 1) the occurrence of acute exacerbated asthma within the previous 4 weeks; 2) being a smoker or an ex-smoker with a history of at least 10 packs per year; 3) use of inhaled or systemic steroids within the previous 4 weeks and maintenance therapy with theophylline, a leukotriene antagonist, or other add-on asthma therapies; 4) suffering from diseases of digestive system, endocrine system, circulatory system, blood system, etc; and 5) history of other lung diseases except asthma.

Two study series were performed: case-control study and treatment trial. The 182 asthmatics and 180 healthy controls were included in the case-control study. Plasma epinephrine and cortisol concentration were analyzed. In the treatment trial, 36 asthmatics selected from the case-control study who were in mild-to-moderate stage received fluticasone propionate treatment (125 μg, inhalation, twice a day, Glaxo Wellcome. SA) for 12 weeks after an acceptable two-week run-in period. These patients also received salbutamol (100 μg, inhalation, Glaxo Wellcome. SA) as needed throughout the run-in and treatment period. No other medications were permitted. All patients received spirometry and plasma epinephrine and cortisol tests at the 0 and 12th week. The blood samples were all collected at about 8:00 am.

All participants provided informed written consent to participate in the study. The study was approved by the Chinese Ethics Committee of Registering Clinical Trials (Registry ID: ChiCTR-RCC-13–3634) and was carried out in accordance with the Helsinki declaration of the World Medical Association.

Genotyping

GLCCI1 rs37973 genotyping was performed with the iPlex MassARRAY genotyping platform (*Sequenom, Inc, San Diego, Calif*). Controls and blanks were included for quality and error checking. The DNA was extracted from 0.2 ml of the collected blood using a DNA extraction kit as recommended by the manufacturer (*Qiagen, Hiden, Germany*). The primers for genotyping were designed by AssayDesigner 3.1 (Forward: 5′-ACGTTGGATGAAGAACTTCTGGTGATCAGG-3′, Reverse: 5′-ACGTTGGATGCAAATGTTAGGCTGTAAGAG-3′).

Pulmonary function test

Pulmonary function was performed using the Jaeger Masterscope® spirometry system (*Jaeger, Wuerzburg, Germany*) according to the American Thoracic Society (ATS) guideline.[13] Before measuring, we explained the test procedure to all patients and gathered their age, sex, height and weight. Each subject took a full inspiration and then breathed out quickly with maximum effort. Each test was repeated at least 3 times. The baseline was defined as the best of three recordings. All the asthmatic patients had their pulmonary function measured. Bronchial dilation test or methacholine bronchial provocation test were performed to confirm airway obstruction and airway hyper-reactivity, respectively.

Enzyme linked immunosorbent assay (ELISA)

Plasma epinephrine and cortisol concentration were quantified using a commercial ELISA kit (*Cusabio*) according to the manufacturer's instructions. Each sample was run in duplicate and compared with a standard curve. The mean concentration was determined for each sample.

Statistical analysis

The *t*-test was used to identify the difference of epinephrine and cortisol concentrations between cases and controls. The Mann-Whitney *U* test and the Kruskal-Wallis H test were used to identify the association between rs37973 genotype and plasma epinephrine and cortisol concentration. Multivariate linear regression analysis was used to identify the association among plasma epinephrine and cortisol concentration and lung function (FEV_1), adjusting for age as covariate. The statistical analyses were carried out using SPSS™ version 19.0 (*SPSS Inc., IBM*). In all tests, $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

In the case-control study, 182 asthmatics (female: 95, male: 87; mean age: 42.86 ± 10.72) and 180 healthy controls (female: 89, male: 91; mean age: 40.92 ± 11.06) were recruited. The case and control populations were well matched in terms of gender (p = 0.600) and age (p = 0.091) distributions. The basic characteristics of the participants are shown in Table 1. Of the 182 asthmatic patients in the case-control study, 119 were in mild-to-moderate stage, 36 received fluticasone propionate treatment. As a result, 30 completed the 12 weeks follow-up, 3 did not complete the 12-week follow-up, 2 withdrew consent and 1 was withdrawn by clinician for his poor compliance. The 30 asthmatics who completed the 12-week treatment were included in the analyses. The characteristics of these asthmatics are listed in Table 2. The consort diagram of this study is shown in Fig. 1.

Analyses for the basic plasma epinephrine and cortisol concentration

The plasma epinephrine and cortisol concentrations of each participant were detected by ELISA kits. The results indicated that the plasma epinephrine concentration was lower in asthmatic patients than that in healthy controls ($P = 0.003$, $n_{asthma} = 182$, $n_{control} = 180$). So did the plasma cortisol concentration ($P = 0.000$, $n_{asthma} = 182$, $n_{control} = 180$). Data are shown in Table 1.

The results showed that in asthmatic patients, the plasma epinephrine concentration in rs37973 mutant homozygotes was higher than that in wild-type homozygotes and heterozygotes (median concentration

Table 1
Basic characteristics of the cases and controls.

Characteristics[a]	Asthma	Control	P value
Number	182	180	–
Age(y)	42.86 ± 10.72	40.92 ± 11.06	0.091
Gender:male/female	87/95	91/89	0.600
FEV_1 (L)	2.00 ± 0.72	2.68 ± 0.64	0.000
FEV_1 (% predicted)	69.49% ± 20.00%	87.35% ± 16.47%	0.000
FVC (L)	3.25 ± 0.89	3.27 ± 0.63	0.791
FEV_1/FVC (%)	61.06% ± 12.48%	84.40% ± 11.26%	0.000
Plasma cortisol (ng/ml)	0.932 (0.832)	1.3012 (0.333)	0.000
Plasma epinephrine (pg/ml)	24.073 (13.180)	26.863 (7.113)	0.003

[a] Data are expressed as means ± SEM, except plasma cortisol and epinephrine concentration, which are descripted as median (inter-quartile range, IQR). FEV_1, forced expiratory volume in one second; FVC, forced vital capacity.

27.032 pg/ml, n_{GG} = 36; median concentration 23.149 pg/ml, n_{AA+AG} = 146; P = 0.015). The same as plasma cortisol concentration (median concentration 1.141 ng/ml, n_{GG} = 36; median concentration 0.921 ng/ml, n_{AA+AG} = 146; P = 0.013). The comparison was also evaluated among normal healthy controls and the entire study population. The results were consistent with asthmatics patients. That is, the serum levels of epinephrine and cortisol was significantly higher in GLCCI1 rs37973 GG genotype group than those in AA + GG gentotype group (P = 0.000 both in healthy controls and in all participants). Data are shown in Fig. 2.

The association among FEV_1 and plasma epinephrine and cortisol concentration in asthmatic patients

Correlation analyses showed that the plasma cortisol, epinephrine concentration and FEV_1 were well correlated (r = 0.889 between epinephrine and FEV_1, r = 0.821 between cortisol and FEV_1, r = 0.799 between epinephrine and cortisol; n_{asthma} = 182). Data are shown in Fig. 3. Multivariate linear regression analysis showed that FEV_1 (Y) was affected by plasma epinephrine (X_1) and cortisol (X_2) concentration. The regression equation is $Y = 0.614 + 0.052 \cdot X_1 + 0.384 \cdot X_2 - 0.006 \times \text{age}$.

The concentration changes of plasma epinephrine and cortisol after ICS treatment

As mentioned above in the present study, FEV_1 was well correlated with plasma epinephrine and cortisol concentration. We analyzed the correlation among the changes in FEV_1 (ΔFEV_1) and the changes in plasma epinephrine (ΔEPI) and cortisol (ΔCOR) concentration after treated with ICS for 12 weeks. Correlation analyses revealed that ΔFEV_1, ΔEPI and ΔCOR were well correlated, as we expected (r = 0.925 between ΔFEV_1 and ΔEPI, r = 0.794 between ΔFEV_1 and ΔCOR, r = 0.830 between ΔEPI and ΔCOR; n_{asthma} = 30). Data are shown in Fig. 4.

Mann-Whitney U test showed that the change of plasma epinephrine concentration was higher in rs37973 wild-type homozygotes and heterozygotes than that in mutant homozygotes [ΔEPI_{AA+AG} = 6.843 (9.26) pg/ml, n_{AA+AG} = 26; ΔEPI_{GG} = −1.666 (6.52) pg/ml, n_{GG} = 4; P = 0.018]. So did the change of plasma cortisol concentration [ΔCOR_{AA+AG} = 0.3040 (0.21) ng/ml, n_{AA+AG} = 26; ΔCOR_{GG} = −0.066 (0.24) ng/ml, n_{GG} = 4; P = 0.009]. Data are shown in Table 2 and Fig. 5.

Discussion

Asthma is characterized by variable symptoms of wheeze, shortness of breath, chest tightness, and/or cough, and by variable expiratory airflow limitation.[14] Owing to lack of adrenergic nerves innervating human airway smooth muscles, the relaxation and constriction of airways are mainly regulated by epinephrine which binds to the adrenergic receptors of airway smooth muscles. Early in 1859, Henry Salter first described circulating endogenous epinephrine as the therapeutics in asthmatics to activate adrenergic receptors.[15] Afterward, some studies found that circulating epinephrine concentration failed to increase effectively in acute asthma or in exercise and hyperventilation induced asthma.[7,8] Recently, we also found that the circulating epinephrine concentration was decreased in asthmatic rats compared to the controls.[16]

In this case-control study, the data showed that the plasma epinephrine concentration was lower in asthmatics than that in healthy controls, which indicated that asthmatics have relatively lower endogenous plasma epinephrine level. Moreover, plasma epinephrine concentration was well positively correlated with basal FEV_1 in asthmatics (r = 0.889), and the multivariate linear regression revealed that FEV_1 was affected by plasma epinephrine concentration.

In this Chinese Han adult population, we have found that *GLCCI1* rs37973 was associated with both lung function and ICS response in a recessive model, which revealed that asthmatics with rs37973 homozygotes mutant genotype GG had better basal FEV_1 but poor ICS response, i.e. less improvement in FEV_1 after ICS treatment, compared to asthmatics with AA and AG genotype.[6] Accordingly, we analyzed the plasma epinephrine concentration in asthmatics with different rs37973 genotype in present study. Interestingly, we found that the mutant genotype GG had higher basal plasma epinephrine than that in wild-type homozygotes and heterozygotes (Fig. 2). However, the following results showed that the increased amplitude of epinephrine concentrations after treated with

Table 2
Characteristics of asthmatics received ICS treatment.

Description	GLCCI1 rs37973 genotype			P value (AA + AG vs GG)
	AA	AG	GG	
N	13	13	4	–
Age [mean (range), year]	41.62 (24–58)	40.69 (25–58)	37.75 (26–48)	0.532
Onset of asthma, Age [mean (range), year]	39.00 (18–58)	32.23 (8–56)	34.50 (24–48)	0.875
Sex (male/female)	6/7	7/6	2/2	–
BMI(mean ± SD, Kg/m^2)	22.547 ± 2.86	23.133 ± 2.437	24.238 ± 1.917	0.317
Blood eosinophils ($\times 10^9$/L)	0.269 ± 0.138	0.385 ± 0.215	0.45 ± 0.15	0.574
Rhinitis (n)	3/13	4/13	1/4	–
AQLQ (mean, range)	4.034 (2.69–4.80)	3.931 (2.83–4.37)	4.110 (3.77–4.34)	0.632
ACT (mean, range)	16.08 (10–20)	14.92 (8–23)	17.75 (16–20)	0.248
Basal FEV_1 (mean ± SD, L)	2.195 ± 0.550	2.098 ± 0.692	2.510 ± 0.383	0.264
FEV_1 at 12 weeks' treatment	2.433 ± 0.520	2.289 ± 0.697	2.428 ± 0.455	0.793
Basal GLCCI1 expression (mean ± SEM)	0.0292 ± 0.0165	0.0310 ± 0.0145	0.0298 ± 0.0114	0.973
GLCCI1expression at 12 weeks (mean ± SEM)	0.0737 ± 0.0364	0.0674 ± 0.0294	0.0486 ± 0.0151	0.201
Basal cortisol [median (IQR),ng/ml]	0.847 (0.528)	0.715 (0.495)	1.568 (0.629)	0.024
Cortisol at 12 weeks [median (IQR),ng/ml]	1.242 (0.539)	0.928 (0.372)	1.612 (0.640)	0.127
Basal epinephrine [median (IQR),pg/ml]	23.049 (8.794)	26.180 (0.513)	33.361 (13.423)	0.222
Epinephrine at 12 weeks [median (IQR),pg/ml]	33.420 (12.983)	30.216 (8.626)	30.851 (18.251)	0.760

BMI, body mass index; AQLQ, Asthma Quality of Life Questionnaire; ACT, Asthma Control Test; FEV_1, forced expiratory volume in one second.

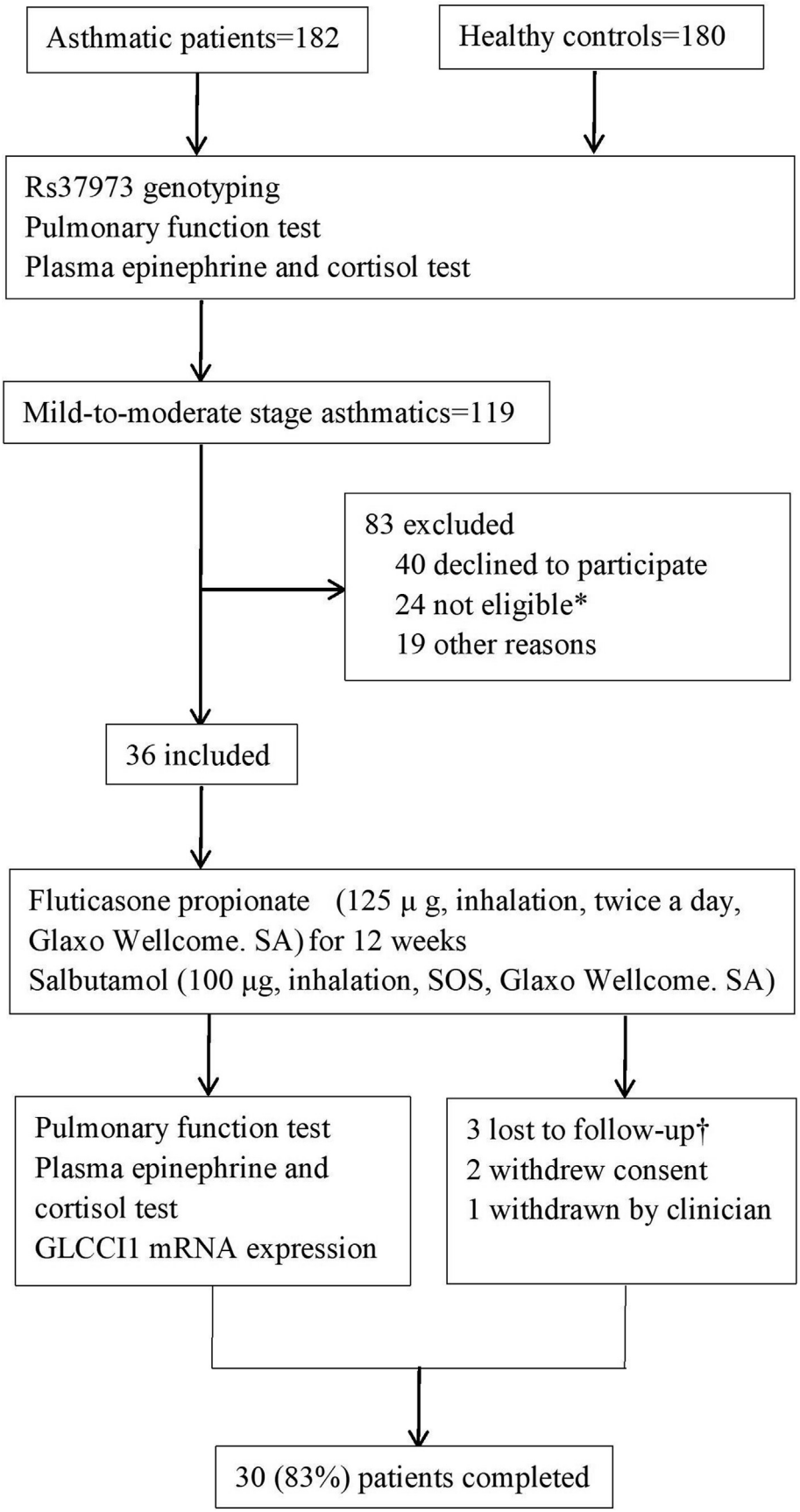

Fig. 1. Study profile. Of the 182 asthmatics in case-control study, 119 were in mild-to-moderate stage. *did not complete the run-in period or could not complete the spirometry. †did not complete the 12-week follow-up.

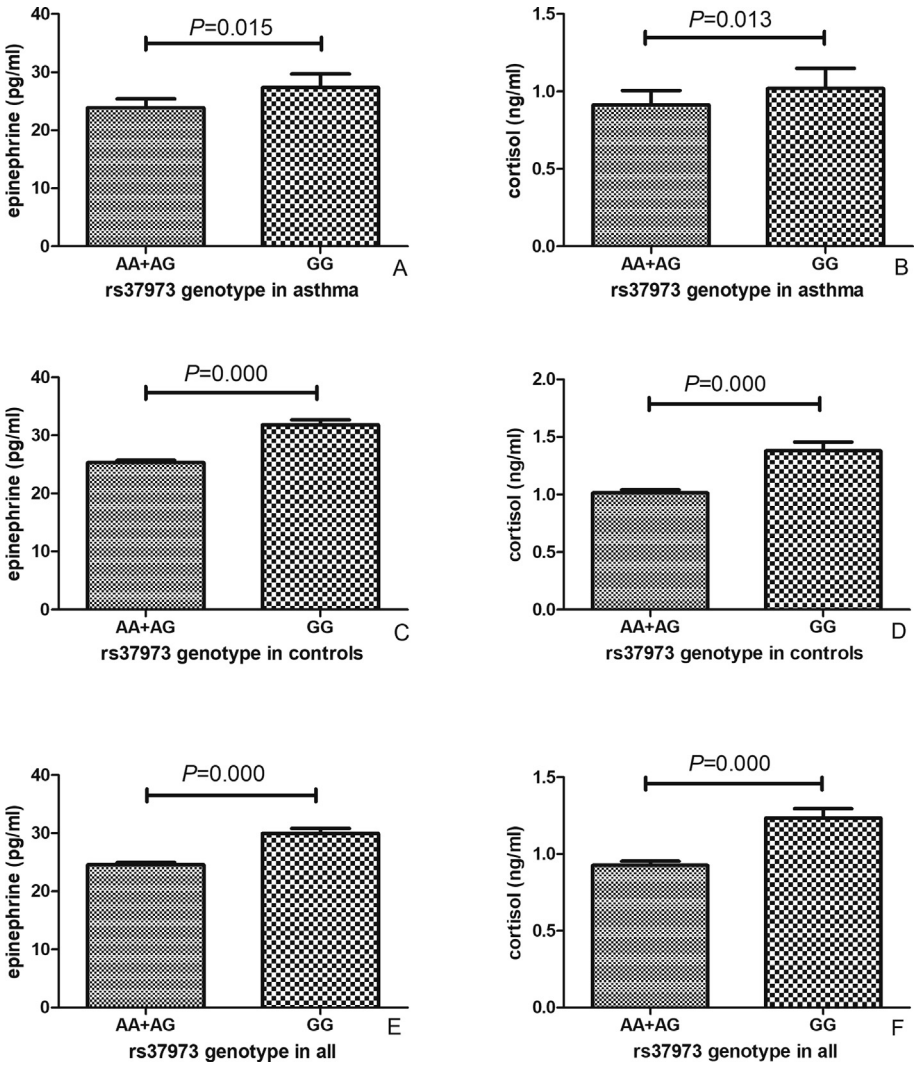

Fig. 2. Association between *GLCCI1* rs37973 genotype and basic concentration of plasma epinephrine and cortisol. A and B showed that in asthmatic patients, plasma epinephrine and cortisol concentration were associated with GLCCI1 rs37973 in a recessive model (AA + AG versus GG), both of which were higher in homozygotes mutant genotype GG ($P = 0.015$ and $P = 0.013$, respectively. $n_{AA+AG} = 146$, $n_{GG} = 36$). The result was consistent in healthy controls ($P = 0.000$, $n_{AA+AG} = 138$, $n_{GG} = 42$. See in C and D) and in all participants ($P = 0.000$, nAA + AG = 284, nGG = 78. See in E and F).

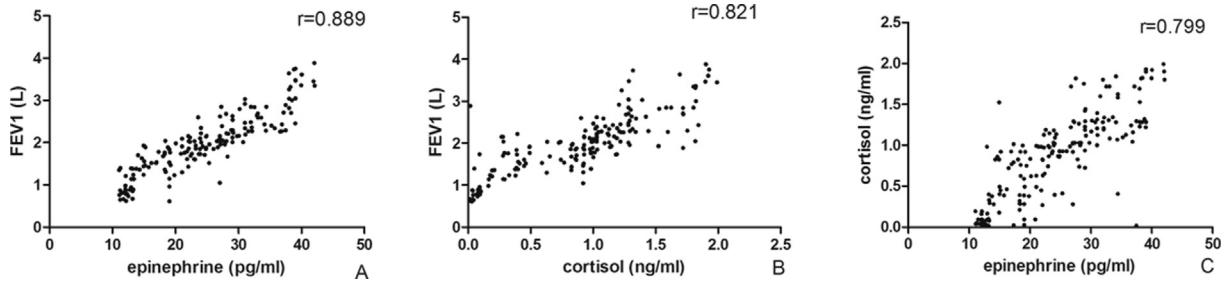

Fig. 3. The associations among FEV_1, plasma epinephrine, and plasma cortisol in asthmatic patients (n=182). (A), (B) and (C) showed that epinephrine, cortisol and FEV_1 were well correlated. r = 0.889 between epinephrine and FEV_1, r = 0.821 between cortisol and FEV_1, r = 0.799 between epinephrine and cortisol. FEV_1, forced expiratory volume in one second.

ICS was less in rs37973 mutant homozygotes than that in wild-type homozygotes and heterozygotes, which was consistent with the ICS response to FEV_1 above mentioned. It indicated that the improvement of lung function to ICS in asthmatic patients might be related with the increased amplitude of epinephrine, but not related with the basic level of epinephrine in asthmatic patients.

ICS are the most commonly used controller medications prescribed for asthma. Similar to epinephrine, the present study showed that asthmatics with rs37973 GG genotype had less improvement in plasma cortisol concentration after 12 weeks' treatment of ICS, too. Glucocorticoids are mainly secreted from the adrenal cortex, while epinephrine is produced by adrenal medulla. Glucocorticoids and epinephrine regulate many physiological processes and have an essential role in the systemic response to stress.[17] Studies have shown that glucocorticoids can enhance the effect and production of epinephrine.[9–11] In this study, asthmatics with rs37973 mutant genotype GG had less changes in both plasma epinephrine and cortisol concentration after ICS treatment, which indicated that *GLCCI1* rs37973 mutation might be related to the poor secretion response of adrenal to ICS in asthmatic patients. Multivariate linear regression analysis in our study showed that FEV_1 was affected by plasma epinephrine and cortisol concentration. Furthermore, the improvement of FEV_1 after ICS treatment was well positively correlated with changes of epinephrine and cortisol

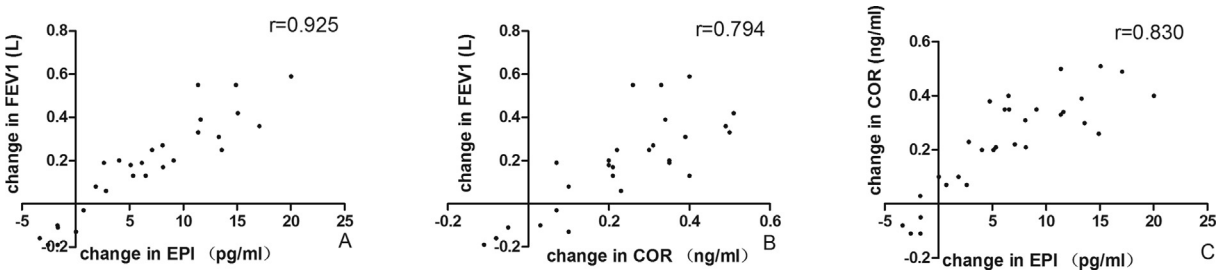

Fig. 4. The associations between change in FEV_1 and epinephrine (cortisol) concentration in asthmatic patients (n=30). Correlation analyses revealed that ΔFEV_1, ΔCOR and ΔEPI were well correlated. r = 0.794 between ΔFEV_1 and ΔCOR in (A), r = 0.925 between ΔFEV_1 and ΔEPI in (B), r = 0.830 between ΔEPI and ΔCOR in (C); $n_{asthma} = 30$. FEV_1, forced expiratory volume in one second; COR, cortisol; EPI, epinephrine.

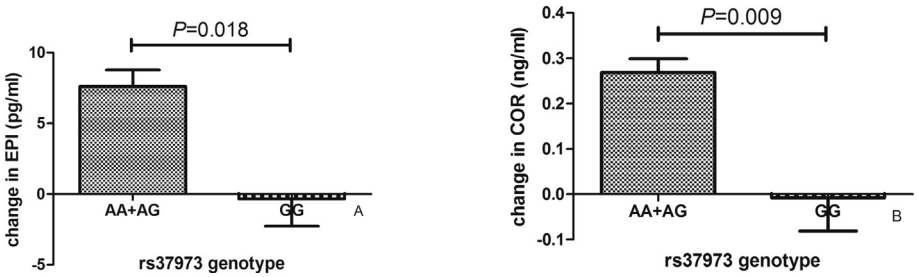

Fig. 5. The changes of plasma epinephrine and cortisol concentration in different rs37973 genotype (n_{AA+AG}=26, n_{GG}=4). (A) showed the change of plasma epinephrine concentration (pg/ml) after 12 weeks' ICS treatment. (B) showed the change of plasma cortisol concentration (ng/ml) after 12 weeks' ICS treatment. Mann-Whiteny *U* test showed that patients with rs37973 GG genotype has poor improvement in both epinephrine concentration and cortisol concentration ($P = 0.018$ and $P = 0.009$, respectively). COR, cortisol; EPI, epinephrine.

concentration. Those suggested that the response to ICS in asthmatic patients might be consistent with the changes of epinephrine and cortisol concentration after treated with ICS. To some extent, the present study indicated that poor response to ICS in asthmatic patients with rs37973 GG genotype might be related to the faint upregulation of epinephrine and cortisol under ICS. It is difficult to deny there was no interaction between epinephrine and cortisol and *GLCCI1* variation in asthma. *GLCCI1* is a protein-coding gene expressed in both lung cells and immune cells. However, the function of *GLCCI1* is still unknown. Chapman et al. indicated that *GLCCI1* might be an early marker of glucocorticoid-induced apoptosis,[18] a key mechanism through which glucocorticoids resolve inflammation in asthma. *GLCCI1* rs37973 mutation might impair some vital elements involved in the mechanism of cortisol acting as anti-inflammation in asthma. As the morphology and function research are limited in human adrenal gland, the mechanism how the rs37973 mutation affects the function of adrenal hormone needs further study.

Conclusions

Our study demonstrated that *GLCCI1* rs37973 was associated with plasma epinephrine and cortisol in Chinese Han adult asthmatics. The poor ICS response in rs37973 mutant genotype might be related to the less increased amplitudes of epinephrine and cortisol in asthmatic patients. However, the exact mechanism for how rs37973 affects the secretion of adrenal gland still needs more in-depth research.

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Conflicts of interest

The authors declare that they have no competing interests.

Availability of data and materials

The datasets generated during the current study are available from the corresponding author on the reasonable request.

Ethics approval and consent to participate

The study was approved by Chinese Ethics Committee of Registering Clinical Trials (Registry ID: ChiCTR-RCC-13–3634) and was carried out in accordance with the Helsinki declaration of the World Medical Association. All participants provided informed written consent to participate in the study.

Consent for publication

Not applicable.

Authors' contribution

Juntao Feng provided major contribution in conception and design of the study as well as involved in analysis and interpretation of the data and writing the manuscript. Qiufen Xun had a major role in acquisition and analysis of data and writing of the manuscript. Chengping Hu contributed important intellectual content, critically revised the manuscript in addition to contribution in data interpretation. Xiaozhao Li provided major contribution in conception and design of the study. Xinyue Hu and Ling Qin had a major role in collection of the participants. Ruoxi He provided major contribution in *GLCCI1* genotyping and ELISA test. Rongli Lu contributed to the pulmonary function test. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

Abbreviations

GLCCI1	glucocorticoid-induced transcript 1 gene
ICS	inhaled corticosteroid
ELISA	enzyme linked immunosorbent assay
FEV_1	forced expiratory volume in 1 s
EPI	epinephrine
COR	cortisol
GINA	Global Initiative for Asthma
ATS	American Thoracic Society

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