Pharmacogenetic study of the effects of NK2R G231E G>A and TBX21 H33Q C>G polymorphisms on asthma control with inhaled corticosteroid treatment

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SUMMARY

Background and Objective: Inhaled corticosteroids (ICS) are widely used as maintenance regimens for asthma patients. However, response to ICS shows marked inter-individual variability. Genetic factors have been shown to be potential predictors of responsiveness to ICS. We aimed to evaluate those pharmacogenetic effects on asthma control in further detail.

Methods: Fifty-three mild-to-moderate asthmatics were genotyped for four genetic polymorphisms of four genes: β2-adrenergic receptor (ADRB2), adenylate cyclase 9 (ADCY9), neurokinin receptor 2 (NK2R) and T-box 21 (TBX21). The principal clinical outcome was the achievement of asthma control, as assessed using the Global Initiative for Asthma (GINA) guidelines. During treatment with ICS, the forced expiratory volume in 1 second (FEV1), maximal mid-expiratory flow (MMEF) and peak expiratory flow rate (PEFR) were monitored every 4 weeks and twice daily.

Results: Forty-eight of the 53 patients with asthma were in a controlled or partly controlled state after 12 weeks of treatment with ICS, whereas five asthmatics were in an uncontrolled state even after active treatment. Of the four genetic polymorphisms examined, NK2R G231E G>A and TBX21 H33Q C>G were significantly associated with asthma control status (P = 0.041 and P = 0.006). The subjects with wild-type alleles at each polymorphism showed a significant association with the well-controlled or partly controlled state, as compared to those with mutant alleles. At 5–12 weeks after ICS treatment, the NK2R G231E G>A was associated with therapeutic response to ICS, as reflected by improvement in predicted FEV1%.

Conclusion: Our results suggest that NK2R G231E G>A and TBX21 H33Q C>G are genetic predictors of response to ICS, at least with respect to asthma control status and changes in FEV1%, in Korean patients with asthma. Further prospective validation of those associations is necessary.

Keywords: asthma control, genetic polymorphism, Inhaled corticosteroid, NK2R, T-box 21

INTRODUCTION

Inhaled corticosteroids (ICS) are the most commonly used controller medications for asthma, being the most effective anti-inflammatory agents for persistent asthma (1). Many clinical studies have demonstrated the efficacy of ICS in reducing asthma symptoms, improving lung function (2–4), decreasing bronchial hyperresponsiveness (4–6), and reducing asthma exacerbations and mortality (7). However, the between-patient variability in responses to ICS is wide. In the treatment of persistent asthma, 20–30% of patients show no improvement in forced expiratory volume in...
1 second (FEV$_1$) or airway hyperresponsiveness (8–10). It has been estimated that 60–80% of this between-patient variability is attributable to genetic variation (10).

The development of individualized medication regimens based on genetic polymorphisms should reduce patient exposure to agents that are unlikely to be effective or that increase the risk of adverse events, thereby maximizing patient benefits and minimizing risks. Observations of individual responses to ICS support the importance of genetic contribution to ICS response variability. There is accumulating evidence of an association between differences in responses to anti-asthmatic drugs, including ICS, β2-receptor agonists and leukotriene receptor antagonists (LTRA), and individual genetic variants (11). In particular, a functional variant of T-box 21 (TBX21) (12) and sequence variants of the corticotrophin-releasing hormone receptor 1 gene (CRHR1) (13) have been associated with responses to ICS. However, these genetic associations have not been replicated in other studies (14). Dijkstra et al. reported contradictory findings, i.e. CRHR1 polymorphisms were not related to immediate or long-term improvement in FEV$_1$ by ICS or to the prevention of accelerated FEV$_1$ decrease in adult asthma (14). Significant variations in the allele and haplotype frequencies of asthma-related genes have been noted among different racial and ethnic groups (15–18). Adenylyl cyclase type 9 (ADCY9) is considered to be a candidate locus for predicting beta-agonist efficacy in the absence and presence of corticosteroid treatment (19). In the Korean population, neurokinin receptor 2 (NK2R) G231E has been shown to be significantly associated with isocyanate-induced asthma (20) and chronic cough (21). However, there has been no report related to therapeutic response according to these single nucleotide polymorphisms (SNPs).

We investigated several genetic polymorphisms that have been reported as being associated with susceptibility to and progression of asthma in Asian subjects, as well as TBX21 and CRHR1, to assess the potential impact of genetic variants on ICS responses in a Korean population. SNPs of four genes related to asthma development, airway inflammation and symptoms, i.e. β2-adrenergic receptor (ADRB2) (R16G A>G), ADCY9 (I772M T>C), NK2R (G231E G>A) and TBX21 (H33Q C>G) were analyzed in the present study.

The major clinical outcome of this study was asthma control, assessed according to the Global Initiative for Asthma (GINA) guidelines (1), which reflect our understanding that the severity of asthma comprises not only of the severity of the underlying disease, but also of its responsiveness to treatment. As we were interested in developing a comprehensive approach to asthma treatment, we adopted more integrative outcome measures of asthma control status, as well as FEV$_1$, asthma symptoms and asthma-related quality of life, in the present study.

To investigate the influences of genetic or ethnic differences on the effects of ICS maintenance therapy, we compared the clinical outcomes from a 12-week trial of budesonide 400 μg in mild-to-moderate asthma to four candidate genotypes, including the NK2R G231E G>A and TBX21 H33Q C>G polymorphisms.

**METHODS**

**Subjects and study design**

Fifty-three South Korean patients (30 males, 23 females) with a documented history of mild-to-moderate asthma for at least 6 months were enrolled in the study. All patients provided written informed consent, as approved by the local committee on human research. The study group had a mean age of 37.09 ± 13.26 years and had predicted FEV$_1$% of at least 60% of the predicted value. At the first visit, basic demographic information was collected, including age, sex, weight, height, smoking history, family and history of allergic disease.

The main outcome was the achievement of asthma control. We determined asthma control status using daytime symptoms, night symptoms/awakening, need for reliever/rescue medication and lung function (predicted FEV$_1$%). To gain an understanding of the variability of responses to ICS, subjects were evaluated at Weeks 1–4 (the initial period) and at Weeks 5–12 (the maintenance period).

The levels of asthma control were classified as well-controlled, partly controlled and uncontrolled according to the GINA guidelines (1). We recorded
the asthma control status at Week 4 and Week 12 of treatment.

During the 2-week baseline period, eligible patients stopped their usual prescribed ICS and all other anti-asthma medications (with the exception of salbutamol). Morning and evening peak expiratory flow rate (PEFR), use of rescue-medication and asthma-related symptoms were recorded twice daily in a diary. Upon completion of the baseline period, eligible patients received ICS therapy with budesonide at a dose of 400 µg daily for 12 weeks.

During the 12-week treatment period, patients measured their morning and evening PEFR values with a peak flow meter (Mini-Wright; Clement Clarke International, Harlow, Essex, UK) and recorded their daytime and night-time symptoms of asthma and use of rescue medication. At baseline and at Weeks 4, 8 and 12 of treatment, patients underwent calibrated spirometry. The FEV₁, maximal mid-expiratory flow (MMEF) and PEFR are presented as percentage predicted values adjusted for height and weight. In addition, the Asthma Quality of Life Questionnaire (AQLQ), which ranges in scale from 1 (severe impairment) to 7 (no impairment), as validated by the Korean Society of Allergology (22) was conducted at Week 0 and Week 12.

### Statistical analysis

Hardy–Weinberg equilibrium (HWE) is a basic assumption in many genetic studies, which asserts independent allelic associations under ideal genetic and environmental conditions (23). Therefore, we initially examined the allele frequencies and genotype distributions of the studied genetic polymorphisms by HWE using Pearson’s χ² test.

Asthma control status was tested using a permutation based exact analysis for linear association using Monte Carlo simulation and 99% confidence interval (SPSS software version 12.0.1; SPSS Inc., Chicago, IL, USA). We applied the Monte Carlo exact test, as it can be used when the sample size is not sufficiently large for asymptotic approximation (23). Changes in lung function parameters (predicted FEV₁%, MMEF%) and changes in AQLQ and PEFR (percentage predicted values) of the genotypic groups for each polymorphism were assessed by repeated measures analysis of variance (RMANOVA) with adjustment for sex and age.

Mauchly’s sphericity test was used for repeated measurements. The Student’s t-test and the χ² test were used to compare demographic data among the groups. P < 0.05 was taken to indicate significance, and we performed power analysis using PASS, 2005 program.

### SNP genotyping

Four genetic polymorphisms in four genes were genotyped using the SNaPshot ddNTP primer extension kit (Applied Biosystems, Foster City, CA, USA) in accordance with the manufacturer’s protocol.

### RESULTS

#### Demographics and asthma control status of the study subjects

The clinical characteristics of the 53 patients enrolled in the present study are shown in Table 1. The prevalence of atopy and family history of allergic diseases were 57.4% and 14.8%, respectively. The baseline FEV₁%, MMEF%, methacholine PC₂₀ (mg/mL) and serum total IgE (IU/mL) values were 72.5 ± 5.14, 59.4 ± 18.97, 5.63 ± 6.99

<table>
<thead>
<tr>
<th>Variable</th>
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<tbody>
<tr>
<td>Sex (male/female)</td>
<td>30/23</td>
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<tr>
<td>Age (years)</td>
<td>37.09 ± 13.26</td>
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<tr>
<td>Family history (presence, %)</td>
<td>8 (14.8%)</td>
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<tr>
<td>Atopy (positive, %)</td>
<td>31 (57.4%)</td>
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<tr>
<td>Total IgE (IU/mL)</td>
<td>386.68 ± 380.56</td>
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<tr>
<td>Methacholine PC₂₀ (mg/mL)</td>
<td>5.63 ± 6.99</td>
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<tr>
<td>Baseline predicted FEV₁%</td>
<td>72.52 ± 5.14</td>
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<tr>
<td>Baseline predicted MMEF%</td>
<td>59.44 ± 18.97</td>
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<tr>
<td>Asthma control status over Weeks 1–4</td>
<td>0/48/5</td>
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<tr>
<td>(well/partly/uncontrolled)</td>
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<tr>
<td>Asthma control status over Weeks 5–12</td>
<td>10/38/5</td>
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<tr>
<td>(well/partly/uncontrolled)</td>
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Well/partly/uncontrolled indicates well-controlled, partly controlled, and uncontrolled asthma status according to the classification in the GINA guidelines (2006). To investigate the variability in responses to ICS, the evaluation was divided into two periods: initial (Weeks 1–4) and maintenance (Weeks 5–12).
and 386.68 ± 380.56, respectively. None of the patients had well-controlled asthma during the initial 4 weeks of treatment with ICS. Forty-eight of the 53 asthmatic patients (90.6%) had partly controlled status, whereas the remaining five (9%) showed poor control from Weeks 1 to 4. Ten (18.9%) of the 53 patients progressed to the well-controlled status from Weeks 5 to 12, whereas five patients (9%) still showed poor control of their asthma (Table 1).

The baseline FEV1% values and PC20 methacholine dosages of patients with well-controlled and partly controlled statuses during Weeks 5–12 of ICS treatment were significantly higher than those of patients with poorly controlled status (73.1% vs. 66.8%, P < 0.001 for mean FEV1%, 6.1 mg/mL vs. 1.2 mg/mL, P = 0.001 for mean PC20). There were no significant differences in baseline serum total IgE between the patients with well-controlled or partly controlled asthma and those with poorly controlled asthma.

**Allele and genotype frequencies of four candidate genetic polymorphisms**

As shown in Table 2, the minor allele frequencies (MAF) of the four selected genetic polymorphisms [ADRB2 (G16R A>G), ADCY9 (I772M T>C), NK2R (G231E G>A) and TBX21 (H33Q C>G)] were >5%. The ADRB2 46 A>G polymorphism was excluded, as it did not show HWE. There were no significant differences in baseline spirometry findings between the two allelic groups of the NK2R G231E G>A and TBX21 H33Q C>G polymorphisms, with the wild-type allele group having a mean predicted FEV1% of 72.4% (59.5%) and MMEF% of 72.5% (61.4%), and the mutant allele group having a mean predicted FEV1% of 72.6% (60.5%) and MMEF% of 73.4% (52.2%). There were no significant differences in the demographic parameters, such as age and sex, between the two allelic groups of the NK2R G231E G>A and TBX21 H33Q C>G polymorphisms. There were no significant differences in PC20 methacholine, asthma duration, family history of asthma, smoking status, atopy or serum total IgE in relation to allele type (P > 0.05).

**Effects of genetic polymorphisms on asthma control during 12 weeks of ICS treatment**

Before Week 4 of ICS treatment, there were no significant genetic predictors of changes in asthma control status among these four genetic polymorphisms. However, Weeks 5–12 of treatment with ICS, the NK2R G231E G>A and TBX21 H33Q C>G polymorphisms were significantly associated with asthma control status (P = 0.041, power = 81.419% and P = 0.006, power = 98.564%, respectively). Significance of two genetic polymorphisms (NK2R G231E G>A and TBX21 H33Q C>G) was maintained with multiple regression and adjustment for sex, age, smoking status and baseline FEV1% (P < 0.05). We described the levels of asthma control in relation to the NK2R G231E G>A and TBX21 H33Q C>G polymorphisms in a stack plot (Fig. 1). The frequencies of the wild-type alleles of both the NK2R G231E G>A (25%, 68.3% and 67% for well-controlled, partly controlled and uncontrolled asthma, respectively) and the TBX21 H33Q C>G genotype (22%, 71.6% and 57%, respectively) were significantly higher in the well-controlled or partly controlled asthma group than in the uncontrolled asthma group after 4 weeks of treatment with ICS (P = 0.041 for NK2R G231E, and P = 0.006 for TBX21 H33Q). During Weeks 5–12 of treatment with ICS, 10 patients with the G allele of the NK2R G231E polymorphism were included in the well-controlled group, whereas only five of those with the A allele were included in this group [GG (n = 5) and AG (n = 5) genotypes]. The statistical significance of this finding was analyzed for a linear association using the Monte Carlo exact test (P = 0.041). The TBX21 H33Q C>G polymorphism was associated with asthma control status from Weeks 5 to 12 (P = 0.006). The proportion of patients with well-controlled asthma was

<table>
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<tr>
<th>Table 2. Genotype distributions of candidate genetic polymorphisms and Hardy–Weinberg equilibrium</th>
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<tbody>
<tr>
<td>Genetic polymorphism</td>
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<tr>
<td>----------------------</td>
</tr>
<tr>
<td>ADCY9 I772M T&gt;C</td>
</tr>
<tr>
<td>ADRB2 46 A&gt;G</td>
</tr>
<tr>
<td>NK2R G231E G&gt;A</td>
</tr>
<tr>
<td>TBX21 H33Q C&gt;G</td>
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M, major allele; m, minor allele; HWE, Hardy–Weinberg equilibrium.
significantly higher among C allele carriers of the TBX21 H33Q C>G polymorphism than in those carrying the G allele (100% vs. 0%, P = 0.006). The improved FEV1% and MMEF% values and the higher PC20 methacholine at baseline were significantly related to well-controlled or partly controlled asthma (P < 0.05 by ANOVA).

**Associations between genetic polymorphisms and individual clinical parameters during 12 weeks of ICS treatment**

We examined the results of pulmonary function testing, including predicted FEV1%, MMEF% and PEFR%, and the asthma-related quality of life questionnaire in relation to each genetic polymorphism. The NK2R G231E G>A polymorphism showed significant associations with the mean changes in predicted FEV1% during the 12 weeks of ICS treatment (P < 0.05). Improvements in predicted FEV1% and MMEF%, were superior in patients with the wild-type (G) allele of the NK2R G231E polymorphism than in those with the A allele. The mean changes in predicted FEV1% and MMEF% were 19.33% and 19.53%, respectively, for the G allele carriers, and 15.75% and 13.92%, respectively, for the A allele carriers. These changes were significant in a RMANOVA analysis with adjustments for sex and age, during the 12 weeks of treatment (P = 0.033 and P = 0.051, Fig. 2). For the TBX21 H33Q C>G polymorphism, C allele carriers showed a trend toward a greater increase in FEV1% compared with G allele carriers, although the difference was not statistically significant.

The four genetic polymorphisms were not significantly associated with changes in predicted PEFR%. However, predicted PEFR% tended to show greater improvement in patients with the G allele of the NK2R 231 G>A polymorphism compared with carriers of the A allele (Fig. 3).

Other candidate genetic polymorphisms were not significantly associated with the predicted FEV1%, MMEF% and PEFR% values or with the AQLQ results (all P > 0.05).

**DISCUSSION**

Our study shows that NK2R G231E G>A and TBX21 H33Q C>G polymorphisms were associated with the achievement of asthma control during ICS treatment in Korean asthmatic patients.

The principal goal of asthma management is to achieve and maintain control of the disease with minimal or no symptoms (1). The recently revised international guidelines define asthma control in terms of a set of treatment goals based on asthma symptoms, use of rescue β2-agonist, exacerbations,
objective measures of lung function, activity limitation and adverse effects of medication (1). However, the degree and rate of response to anti-asthmatic medications have been reported to show substantial variability (8, 9, 24). Malmström et al. first reported a wide distribution for FEV\textsubscript{1} response to beclomethasone. 50\% of their patients showed improvement in FEV\textsubscript{1} of at least 11\% from baseline, whereas 22\% showed no improvement (8). Moreover, the time courses of different measures of response to treatment appear to be different, with night-time symptoms and lung-function improving relatively quickly, and airway hyperresponsiveness continuing to improve over several months (24). These results suggest that the evaluation of asthma control using any of the individual criteria of control in isolation does not capture accurately the level of control in an individual

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**Fig. 2** Changes in mean values of predicted FEV\textsubscript{1}\% (i) and MMEF\% (ii) over the study period (Weeks 1–12 of active treatment). The changes in predicted FEV\textsubscript{1}\% and MMEF\% in relation to the NK2R G231E G>A (\(P = 0.033\) and \(P = 0.051\), respectively) and TBX21 H33Q C>G polymorphisms (\(P = 0.340\) and \(P = 0.264\), respectively) are shown in (a) and (b), respectively. The \(P\)-value was adjusted for sex and age using RMANOVA.

**Fig. 3** Changes in the morning (a) and evening (b) predicted PEFR\% for the NK2R G231E G>A polymorphism with the G allele are greater than those with the A allele, although the difference is not statistically significant.
patient. Therefore, an array of asthma control measures, which included asthma symptoms, use of rescue-medication, exacerbation and lung function measures, was related to candidate genetic polymorphisms in the present study. The evaluation of ICS effects was conducted over the initial (Weeks 1–4) and maintenance (Weeks 5–12) periods of treatment. None of our patients achieved the well-controlled status during the first 4 weeks of ICS treatment. According to the international guidelines, a period of 3 months of maintenance with controller medications is generally recommended before evaluation of asthma severity and control status, to inform decisions on subsequent treatment (1). Evaluation of asthma control after 4–8 weeks of ICS treatment has been suggested as being useful for identifying asthma patients who genuinely require subsequent medication (25).

There is increasing evidence of individual differences in drug responses being related to genetic variants. Pharmacogenetic studies of ICS have revealed several candidate genes that may help explain the variability in steroid responses (12-13, A). The TBX21 33Gln variant, which increases Th1 and decreases Th2 cytokine expression, is associated with increased ICS response, as defined by PC20 (12). Both pediatric and adult asthmatic patients who are homozygous for the CRHR1 gene GAT haplotype also show increased FEV1 values in patients who are homozygous for the CRHR1 gene (2009 The Authors. Journal compilation 2009 Blackwell Publishing Ltd, Journal of Clinical Pharmacy and Therapeutics). Both peadiatric and adult asthmatic patients who are homozygous for the CRHR1 gene GAT haplotype also show increased FEV1 values with ICS treatment (13). Adenylyl cyclase type 9 (ADCY9) is considered to be a candidate locus for the effects of ICS on airway responsiveness in asthmatic children (11, 12). In the present study, the TBX21 H33Q C>G polymorphism wild-type allele substantially enhanced asthma control during the 12 weeks of ICS treatment. More patients with the C allele of TBX21 H33Q had well-controlled asthma, when compared with G allele carriers. Although not statistically significant, the predicted FEV1% showed greater improvement in the C allele carriers than in the G allele carriers in the present study. These findings suggest that the TBX21 H33Q C>G polymorphism wild-type allele carriers showed better asthma control during the 12 weeks of treatment with ICS. More patients with the C allele of TBX21 H33Q had well-controlled asthma, when compared with G allele carriers. Although not statistically significant, the predicted FEV1% showed greater improvement in the C allele carriers than in the G allele carriers in the present study. These findings suggest that the TBX21 H33Q C>G polymorphism wild-type allele carriers showed better asthma control during the 12 weeks of treatment with ICS. More patients with the C allele of TBX21 H33Q had well-controlled asthma, when compared with G allele carriers.

In the present study, the G allele of the NK2R G231E polymorphism was significantly associated with enhanced improvement of FEV1% as well as asthma control during the 12 weeks of ICS treatment. Several studies have suggested close relationships between NK2R and airway inflammation. NK A induces bronchoconstriction mediated by NK2 receptors in humans, the expression of which may be up-regulated in asthmatic patients (26, 27). The modulation of NK receptor gene expression may augment or diminish the inflammatory, secretory or bronchoconstrictor effects of released tachykinins. Up-regulation of NK2 receptors can be prevented by corticosteroids (27). Codon 231 of NK2R corresponds to the third intracellular loop of the receptor, which has been shown to be an important determinant for NK2R agonist-stimulated second messenger responses and agonist-induced desensitization (28, 29). Recently, we demonstrated that that the NK2R G231E G>A polymorphism was associated with the degree of airway inflammation in patients with isocyanate-induced occupational asthma (20). Enhanced cough sensitivity to capsaicin was noted in chronic cough patients with the mutant (19) allele of the NK2R G231E G>A polymorphism in the Korean population (21). Based on these findings, we speculate that ICS reduce the expression of NK2 receptors in the airway and attenuate the bronchoconstriction and airway inflammation induced by NK A. If changes in the function of NK2 receptors result from NK2R genetic polymorphisms, the responses to ICS should differ according to the NK2R genetic polymorphism. To our knowledge, this is the first study to suggest that the NK2R G231E polymorphism is a genetic marker for predicting ICS responses in patients with mild-to-moderate asthma. Further investigations using a larger cohort and in other ethnic populations are required to confirm these results.

T-box 21 encodes the transcription factor T-bet, which is responsible for the induction of Th1 cell and suppression of Th2 cell development from naïve T lymphocytes (30). T-bet has been implicated in the pathogenesis of asthma (12). The TBX21 H33Q C>G polymorphism substantially enhanced the effects of ICS on airway responsiveness in asthmatic children (11, 12). In the present study, the TBX21 H33Q C>G polymorphism wild-type allele carriers showed better asthma control during the 12 weeks of treatment with ICS. More patients with the C allele of TBX21 H33Q had well-controlled asthma, when compared with G allele carriers. Although not statistically significant, the predicted FEV1% showed greater improvement in the C allele carriers than in the G allele carriers in the present study. These findings suggest that the TBX21 H33Q C>G polymorphism affects steroid responsiveness in asthmatic airways; therefore, it may be useful as a genetic marker for predicting drug responses. We performed multiple testing and estimated the False Discovery Rate (FDR) (31). The FDR of NK2R G231E G>A and TBX21 H33Q C>G were 0.082 and 0.024. The NK2R G231E G>A association with asthma control status became insignificant after adjustment for multiple testing. Further replication studies are necessary to confirm our findings.

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We did not find any significant differences in the measures of asthma control or individual parameters related to the ADCY9 genetic polymorphisms. In addition to genetic polymorphisms, baseline values for several clinical parameters have been demonstrated to predict enhanced responses to ICS, including higher eNO, eosinophil cationic protein levels, serum IgE, lower provocative dosages of methacholine producing a 20% decline in FEV1 (PC20), lower prebronchodilator predicted FEV1%, and lower prebronchodilator FEV1/FVC ratio (9, 22). We found that FEV1%, MMEF% and PC20 methacholine dose at baseline may predict the variability in ICS responses. Improved FEV1% and MMEF% and higher PC20 methacholine values at baseline were associated with well-controlled or partly-controlled asthma status in our present series of patients. This discrepancy may be due to differences in asthma severity of the study subjects and differences in study duration. However, in the present study, there were no differences in baseline FEV1, PC20 methacholine or serum total IgE in relation to the NK2R G231E and TBX21 H33Q genetic polymorphisms.

In conclusion, NK2R G231E G>A and TBX21 H33Q C>G polymorphisms are possible genetic predictors of responses to ICS in relation to changes in FEV1%, and asthma control status, of adult Korean asthmatic patients. These findings should be investigated in further prospective studies in other subgroups of Koreans and in other ethnic groups.

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ROLE OF EACH AUTHOR IN THIS STUDY


sequence variants in CRHR1 with improved lung function in asthmatics treated with inhaled corticosteroids. Human Molecular Genetics, 13, 1353–1359.


