# Genetic association analysis of CIITA variations with nasal polyp pathogenesis in asthmatic patients 

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#### Abstract

Nasal polyps are abnormal lesions arising mainly from the nasal mucosa and paranasal sinuses. Since the human class II, major histocompatibility complex, transactivator (CIITA) is a positive regulator of class II, major histocompatibility complex gene transcription, the CIITA gene is thought to be involved in the presence of nasal polyps in asthma and aspirin hypersensitive patients. To investigate the association between CIITA and nasal polyposis, 18 single nucleotide polymorphisms (SNPs) were genotyped in 467 asthmatics who were classified into 158 aspirin-exacerbated respiratory disease (AERD) and 309 aspirin-tolerant asthma (ATA) subgroups. Differences in the frequency distribution of CIITA variations between polyp-positive cases and polyp-negative controls were determined using logistic analyses. Initially, a total of 9 CIITA variants were significantly associated with the presence of nasal polyps in the overall asthma, AERD and ATA groups $[\mathrm{P}=0.001-0.05$, odds ratio $(\mathrm{OR})=0.53-2.35$ in the overall asthma group; $\mathrm{P}=0.01-0.02, \mathrm{OR}=2.45-2.66$ in the AERD group; $\mathrm{P}=0.001-0.05, \mathrm{OR}=0.45-2.61$ in the ATA group using various modes of genetic inheritance]. One the variations (rs12932187) retained this association after multiple testing corrections $\left(\mathrm{P}^{\text {corr }}=0.01\right)$ in the overall asthma group. In


[^0]Key words: aspirin-exacerbated respiratory disease, asthma, class II, major histocompatibility complex, transactivator, nasal polyp, single nucleotide polymorphism, genetic variation, genetic epidemiology, allergy, association, haplotype
addition, two variations (rs12932187 and rs11074938) were associated with the presence of nasal polyps following multiple testing corrections ( $\mathrm{P}^{\text {corr }}=0.02$ and 0.04 , respectively) in the ATA group. These novel findings suggest that $r s 12932187$ and rsl1074938 may constitute susceptibility markers of inflammation of the nasal passages in asthma patients.

## Introduction

Nasal polyps are small abnormal lesions or bags that protrude from the nasal cavity, and are characterized by edematous stroma following progression of dense eosinophilia to a thickened basement membrane in epithelium (1). Although usually harmless, nasal polyposis may cause significant airway obstruction including infection of nose or sinuses, and is known to be associated with bronchial asthma by occurring more frequently in asthma and aspirin-hypersensitive patients $(2,3)$. Although the exact mechanism for the origin of nasal polyps remains unknown, allergies, infections, inflammation and genetic factors are considered to contribute to the onset of this condition (4-6).

The human class II, major histocompatibility complex, transactivator (CIITA) encodes a major histocompatibility complex (MHC) class II transactivator and is essential for MHC class II molecules (7). The full length of the human CIITA gene is $\sim 48 \mathrm{~kb}$ and is located on chromosome 16 p 13 . The gene contains 20 exons and 4 alternative promoters with tissue-specific transcription (8). CIITA is often referred to as the master control factor of MHC II molecules due to its regulating activity at the transcriptional level (9). Since abnormal immune responses and immunodeficiency are associated with lack of expression of MHC II genes, the function of CIITA, which interacts other transcription factors in the MHC II promoter region, is considered to be a master factor in immune response $(8,10,11)$. Wang et al (12) reported that MHC class II antigens were more frequently detected in polyps in atopic and cystic fibrosis patients, suggesting that the MHC class II antigens in airway epithelial cells of nasal polyps are able to be regulated by interferon $\gamma$ at the transcriptional level.

Polymorphisms in CIITA are reportedly associated with several immune diseases such as multiple sclerosis, Addison's

Table I. Clinical profile of asthmatic patients ( $\mathrm{n}=467$ ).

| Clinical profile | Polyp-positive | Polyp-negative | P-value |
| :---: | :---: | :---: | :---: |
| No. of subjects | 158 | 309 |  |
| Age (years), mean (range) | 46.24 (17.93-76.86) | 47.00 (15.40-77.88) | 0.56 |
| Gender (male/female), n | 55/103 | 100/209 | 0.60 |
| Total smoker (current smoker; ex-smoker) (\%) | 27.21 (11.39; 15.82) | 27.83 (11.33; 16.50) | 0.93 |
| Body mass index ( $\mathrm{kg} / \mathrm{m}^{2}$ ) | $23.95 \pm 3.00$ | $24.53 \pm 3.51$ | 0.06 |
| Percentage decrease of $\mathrm{FEV}_{1}$ by aspirin provocation | $12.22 \pm 14.39$ | $6.78 \pm 11.46$ | <0.0001 |
| Positive rate of aspirin intolerance (\%) | 41.77 | 15.53 | <0.0001 |
| Positive rate of the history of aspirin hypersensitivity (\%) | 30.52 | 8.55 | <0.0001 |
| Blood eosinophil (\%) | $6.92 \pm 6.23$ | $5.98 \pm 6.00$ | 0.12 |
| PC20 methacholine ( $\mathrm{mg} / \mathrm{ml}$ ) | $5.83 \pm 8.87$ | $6.88 \pm 8.62$ | 0.23 |
| Total IgE (IU/ml) | $298.35 \pm 469.67$ | $368.39 \pm 654.01$ | 0.19 |
| $\mathrm{FEV}_{1}$ (\% predicted) | $89.67 \pm 15.76$ | $91.79 \pm 17.33$ | 0.18 |
| FVC (\% predicted) | $89.02 \pm 12.65$ | $87.68 \pm 14.56$ | 0.30 |
| Positive rate of skin test (\%) | 51.90 | 57.61 | 0.24 |

Values are the means $\pm$ standard error (SE). BMI, body mass index; $\mathrm{FEV}_{1}$, forced expiratory volume in 1 sec; FVC, forced vital capacity. Bold values indicate significant differences between polyp-positive and polyp-negative groups ( $\mathrm{P}<0.0001$ ).
disease, and systemic lupus erythematosus $(7,13,14)$. CIITA and MHC II genes are involved in immune responses. Subsequently, we hypothesized that the CIITA gene is a marker for the development of nasal polyps in asthmatic patients. The aim of this case-control study was to investigate the association between CIITA polymorphisms and the presence of nasal polyps in asthmatic patients.

## Materials and methods

Subjects. A total of 467 asthmatics were recruited from the Soonchunhyang University hospitals in Seoul and Bucheon (Korea), both of which are under the Asthma Genome Research. The participants provided written informed consent, and the study protocols were approved by the Institutional Review Board of the Hospital. Following the guidelines of Global Initiative for Asthma (GINA), asthma was diagnosed as previously described (15). Twenty-four common inhalant allergens were used in a skin-prick test (Bencard Co. Ltd., Brentford, UK ), and atopy was defined as at least a $3-\mathrm{mm}$ wheal reaction to any of the allergens. Furthermore, total immunoglobulin E (IgE) was measured using the CAP system (Pharmacia Diagnostics, Uppsala, Sweden). Asthmatics with endoscopically visible polyps present in the middle nasal meatus were classified as polyp-positive cases, while the remaining individuals were identified as polyp-negative controls.

To distinguish aspirin-exacerbated respiratory disease (AERD) from aspirin-tolerant asthma (ATA) patients, all the asthma patients underwent oral aspirin challenge (OAC) that was performed according to previously described methods (15). Asthmatics exhibiting $\geq 20 \%$ decrease in forced expiratory volume in $1 \sec \left(\mathrm{FEV}_{1}\right)$ or a $15-19 \%$ decrease in $\mathrm{FEV}_{1}$ with naso-ocular or cutaneous reactions comprised the AERD group, whereas those demonstrating $<15 \%$ decrease in $\mathrm{FEV}_{1}$ without naso-ocular or cutaneous reactions comprised the ATA group. The clinical profile of the patients included
in this study is summarized in Table I. Results from the aspirin-provocation test demonstrated significant differences in the mean score of aspirin-induced the reduced rate of $\mathrm{FEV}_{1}$ between polyp-positive asthma patients and polyp-negative controls ( 12.22 vs. $6.78 \%, \mathrm{P}<0.0001$ ). Additionally, the positive rate of aspirin intolerance and the history of aspirin hypersensitivity were also found to be significantly prevalent in the two groups (Table I).

Selection and genotyping of single nucleotide polymorphisms (SNPs). Eighteen common SNPs with minor allele frequencies (MAF) $>0.05$ were selected for genotyping in the Asian population (Chinese and Japanese) from the International HapMap database (http://hapmap.ncbi.nlm.nih.gov/index.html.en). Genomic DNA was isolated from the blood of patients using the Wizard ${ }^{\circledR}$ Genomic DNA Purification kit (Promega, Madison, WI, USA). Genotyping was performed using TaqMan assay on the ABI PRISM ${ }^{\circledR} 7900 \mathrm{HT}$ sequence detection system (Applied Biosystems, Foster City, CA, USA). Genotyped data quality was assessed by duplicate DNA checking ( $\mathrm{n}=10$; rate of concordance in duplicates $>99 \%$ ).

Statistical analysis. Differences in the genotype distributions of CIITA variations in polyp-positive asthma cases and polyp-negative asthma controls were analyzed using logistic models adjusted for the age of initial diagnosis (continuous value), gender (male, 0 ; female, 1 ), smoking status (non-smoker, 0 ; ex-smoker, 1 ; smoker, 2 ) and atopy (absence, 0 ; presence, 1 ) to eliminate confounding variables that might influence findings. AERD status was also controlled for the logistic analysis of the overall asthmatic patients. Data were managed on the Statistical Analysis System (SAS) version 9.1 (SAS Institute, Inc., Cary, NC, USA).

Statistical power of single associations was determined using the Power for Genetic Association Analyses (PGA) software (16), and multiple testing corrections were calculated


B


Figure 1. (A) Physical map of the CIITA gene. Schematic gene map and SNPs in the CIITA gene on chromosome 16. The black blocks represent the coding exons and the white block represents $5^{\prime}$ and $3^{\prime}$ UTR. The first base of the translation site is indicated as nucleotide +1 . (B-D) Two linkage disequilibrium blocks were inferred from the pairwise comparison of the genotype polymorphisms, and 11 major haplotypes (frequency $>0.05$ ) were examined for association with the presence of nasal polyps among asthmatic patients.
using the effective number of independent marker loci (Meff) that accounts for the eigenvalue spectral decomposition (SpD) of all the genotypes represented in the correlation matrix (17) that was extracted from the SNPSpD program (Meff value $=16.5417$ ).

## Results

Characteristics of study subjects. The clinical profile of the included patients showed that the positive rate of aspirin intolerance and of the history of aspirin hypersensitivity were significantly higher in the nasal polyp-positive asthmatic patients compared to the polyp-negative controls. In addition,
the reduced rate of $\mathrm{FEV}_{1}$ decreased by aspirin provocation was 2-fold higher in the nasal polyp-positive patients compared to the polyp-negative controls ( $\mathrm{P}<0.0001$, Table I). These findings indicate that nasal polyposis is associated with aspirin hypersensitivity in asthma.

Distribution of CIITA polymorphisms. A total of 18 SNPs in the CIITA gene were successfully genotyped. Most of the polymorphisms were localized in the non-coding regions of the gene (introns). Notably, 3 SNPs were located in coding regions (exons), and 2 SNPs (rs4774 and rs7201430) were nonsynonymous variations that induced amino acid change by base substitution. Fig. 1A shows the position and MAF of each
Table II. Association of significant CIITA variants with nasal polyps in all the asthmatic patients ( $\mathrm{n}=467$ )

| SNP/haplotype | MAF |  | Co-dominant |  |  | Dominant |  |  | Recessive |  |  | Statistical power |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | Polyp-positive ( $\mathrm{n}=158$ ) | Polyp-negative ( $\mathrm{n}=309$ ) | OR (95\% CI) | $\mathrm{P}^{\text {a }}$ | $\mathrm{P}^{\text {corb }}$ | OR (95\% CI) | $\mathrm{P}^{\text {a }}$ | $\mathrm{P}^{\text {corrb }}$ | OR (95\% CI) | $\mathrm{P}^{\text {a }}$ | $\mathrm{P}^{\text {corb }}$ |  |
| rs12932187 | 0.456 | 0.359 | 1.42 (1.08-1.88) | 0.01 | NS | 1.25 (0.83-1.90) | 0.29 | - | 2.35 (1.41-3.90) | 0.001 | 0.02 | 82.0 |
| rs4781011 | 0.127 | 0.129 | 0.93 (0.61-1.42) | 0.73 | - | 0.95 (0.59-1.52) | 0.83 | - | 0.63 (0.12-3.43) | 0.60 | - | 57.5 |
| rs11074934 | 0.285 | 0.309 | 0.88 (0.65-1.19) | 0.40 | - | 0.93 (0.62-1.39) | 0.71 | - | 0.64 (0.31-1.30) | 0.22 | - | 80.2 |
| rs8043545 | 0.449 | 0.494 | 0.85 (0.64-1.12) | 0.24 | - | 0.71 (0.46-1.11) | 0.13 | - | 0.91 (0.56-1.47) | 0.69 | - | 82.3 |
| rs8063850 | 0.085 | 0.097 | 0.84 (0.50-1.40) | 0.50 | - | 0.86 (0.51-1.46) | 0.58 | - | - | - | - | 48.3 |
| rs6498119 | 0.320 | 0.280 | 1.14 (0.85-1.54) | 0.38 | - | 1.00 (0.67-1.50) | 0.99 | - | 1.83 (0.98-3.41) | 0.06 | - | 78.6 |
| rs7189406 | 0.443 | 0.468 | 0.95 (0.71-1.27) | 0.72 | - | 0.95 (0.61-1.48) | 0.82 | - | 0.91 (0.55-1.51) | 0.71 | - | 82.7 |
| CIITA_BL1_htl | 0.237 | 0.299 | 0.77 (0.56-1.07) | 0.12 | - | 0.75 (0.50-1.12) | 0.16 | - | 0.64 (0.28-1.43) | 0.27 | - | 79.7 |
| CIITA_BL1_ht2 | 0.288 | 0.244 | 1.19 (0.88-1.62) | 0.26 | - | 1.07 (0.71-1.60) | 0.75 | - | 2.03 (1.03-3.99) | 0.04 | NS | 75.9 |
| CIITA_BLI_ht 3 | 0.136 | 0.155 | 0.85 (0.58-1.26) | 0.43 | - | 0.89 (0.57-1.41) | 0.63 | - | 0.46 (0.12-1.75) | 0.25 | - | 63.4 |
| CIITA_BL1_ht4 | 0.082 | 0.092 | 0.86 (0.51-1.44) | 0.56 | - | 0.88 (0.51-1.51) | 0.64 | - | - | - | - | 46.7 |
| CIITA_BL1_ht5 | 0.082 | 0.055 | 1.71 (0.99-2.95) | 0.05 | NS | 1.67 (0.92-3.02) | 0.09 | - | 6.32 (0.56-71.23) | 0.14 | - | 32.2 |
| rs6498124 | 0.440 | 0.450 | 1.09 (0.81-1.45) | 0.58 | - | 1.05 (0.68-1.62) | 0.83 | - | 1.21 (0.73-2.01) | 0.46 | - | 82.9 |
| rs4781016 | 0.180 | 0.212 | 0.80 (0.56-1.15) | 0.24 | - | 0.86 (0.57-1.31) | 0.49 | - | 0.34 (0.09-1.23) | 0.10 | - | 72.5 |
| rs4774 | 0.184 | 0.214 | 0.81 (0.57-1.17) | 0.26 | - | 0.83 (0.54-1.26) | 0.38 | - | 0.53 (0.17-1.69) | 0.28 | - | 72.7 |
| rs4781019 | 0.342 | 0.327 | 1.11 (0.81-1.52) | 0.52 | - | 1.04 (0.69-1.56) | 0.86 | - | 1.46 (0.75-2.85) | 0.26 | - | 81.0 |
| rs6498126 | 0.269 | 0.285 | 0.93 (0.66-1.30) | 0.66 | - | 0.78 (0.52-1.18) | 0.24 | - | 1.77 (0.78-3.99) | 0.17 | - | 78.9 |
| rs11074938 | 0.446 | 0.503 | 0.76 (0.56-1.02) | 0.07 | - | 0.53 (0.33-0.83) | 0.006 | NS | 0.97 (0.59-1.59) | 0.90 | - | 82.2 |
| rs11074939 | 0.377 | 0.341 | 1.23 (0.90-1.67) | 0.19 | - | 1.19 (0.79-1.80) | 0.40 | - | 1.57 (0.85-2.90) | 0.15 | - | 81.5 |
| rs7404786 | 0.199 | 0.186 | 1.02 (0.71-1.48) | 0.90 | - | 1.03 (0.67-1.57) | 0.90 | - | 1.03 (0.35-3.10) | 0.95 | - | 68.9 |
| rs7201430 | 0.161 | 0.147 | 1.00 (0.67-1.50) | 1.00 | - | 0.98 (0.63-1.54) | 0.94 | - | 1.18 (0.30-4.59) | 0.81 | - | 61.8 |
| rs4781024 | 0.358 | 0.322 | 1.22 (0.89-1.66) | 0.21 | - | 1.22 (0.81-1.84) | 0.34 | - | 1.45 (0.76-2.77) | 0.26 | - | 80.8 |
| rs1139564 | 0.241 | 0.227 | 1.07 (0.77-1.50) | 0.69 | - | 1.12 (0.74-1.68) | 0.59 | - | 0.94 (0.38-2.32) | 0.90 | - | 74.2 |
| CIITA_BL2_ht1 | 0.285 | 0.269 | 1.22 (0.88-1.69) | 0.24 | - | 1.36 (0.91-2.04) | 0.14 | - | 0.96 (0.41-2.22) | 0.92 | - | 77.9 |
| CIITA_BL2_ht2 | 0.152 | 0.183 | 0.81 (0.55-1.19) | 0.28 | - | 0.82 (0.53-1.28) | 0.39 | - | 0.51 (0.13-1.90) | 0.31 | - | 68.4 |
| CIITA_BL2_ht3 | 0.127 | 0.121 | 0.97 (0.63-1.50) | 0.89 | - | 0.97 (0.60-1.57) | 0.90 | - | 0.90 (0.16-4.96) | 0.90 | - | 55.5 |
| CIITA_BL2_ht4 | 0.111 | 0.086 | 1.22 (0.75-1.97) | 0.42 | - | 1.25 (0.74-2.12) | 0.40 | - | 1.10 (0.16-7.55) | 0.93 | - | 44.6 |
| CIITA_BL2_ht5 | 0.057 | 0.079 | 0.77 (0.43-1.38) | 0.38 | - | 0.80 (0.44-1.47) | 0.48 | - | - | - | - | 42.0 |
| CIITA_BL2_ht6 | 0.054 | 0.058 | 1.01 (0.54-1.87) | 0.98 | - | 0.88 (0.45-1.72) | 0.71 | - | - | - | - | 33.5 |

[^1]Table III. Association of significant CIITA variants with nasal polyps in AERD patients (n=114).

| SNP/haplotype | MAF |  | Co-dominant |  |  | Dominant |  |  | Recessive |  |  | Statistical power |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | Polyp-positive ( $\mathrm{n}=66$ ) | Polyp-negative ( $\mathrm{n}=48$ ) | OR ( $95 \% \mathrm{CI}$ ) | $\mathrm{P}^{\text {a }}$ | $\mathrm{P}^{\text {corb }}$ | OR ( $95 \% \mathrm{CI}$ ) | $\mathrm{P}^{\text {a }}$ | $\mathrm{P}^{\text {corb }}$ | OR (95\% CI) | $\mathrm{P}^{\text {a }}$ | $\mathrm{P}^{\text {corb }}$ |  |
| rs12932187 | 0.455 | 0.396 | 1.29 (0.75-2.23) | 0.36 | - | 1.21 (0.53-2.73) | 0.65 | - | 1.76 (0.64-4.82) | 0.27 | - | 31.7 |
| rs4781011 | 0.144 | 0.135 | 1.03 (0.47-2.29) | 0.93 | - | 1.08 (0.44-2.60) | 0.87 | - | 0.72 (0.04-12.94) | 0.82 | - | 19.3 |
| rs11074934 | 0.303 | 0.313 | 0.95 (0.56-1.63) | 0.86 | - | 0.87 (0.40-1.85) | 0.71 | - | 1.12 (0.36-3.47) | 0.85 | - | 29.7 |
| rs8043545 | 0.462 | 0.458 | 1.00 (0.55-1.82) | 1.00 | - | 1.00 (0.41-2.44) | 0.99 | - | 1.00 (0.36-2.77) | 1.00 | - | 32.1 |
| rs8063850 | 0.098 | 0.094 | 0.94 (0.35-2.55) | 0.91 | - | 0.94 (0.35-2.55) | 0.91 | - | - | - | - | 15.5 |
| rs6498119 | 0.311 | 0.365 | 0.80 (0.46-1.40) | 0.43 | - | 0.66 (0.30-1.42) | 0.28 | - | 0.99 (0.31-3.17) | 0.99 | - | 31.1 |
| rs7189406 | 0.439 | 0.385 | 1.34 (0.74-2.43) | 0.34 | - | 1.23 (0.53-2.84) | 0.64 | - | 2.01 (0.62-6.48) | 0.24 | - | 31.5 |
| CIITA_BL1_ht1 | 0.220 | 0.250 | 0.88 (0.47-1.65) | 0.68 | - | 0.81 (0.37-1.78) | 0.59 | - | 1.05 (0.22-5.07) | 0.96 | - | 27.1 |
| CIITA_BL1_ht 2 | 0.280 | 0.302 | 0.91 (0.50-1.66) | 0.76 | - | 0.77 (0.36-1.65) | 0.50 | - | 1.50 (0.35-6.48) | 0.59 | - | 29.3 |
| CIITA_BL1_ht 3 | 0.136 | 0.167 | 0.81 (0.39-1.69) | 0.58 | - | 0.77 (0.32-1.89) | 0.57 | - | 0.77 (0.10-6.03) | 0.80 | - | 21.8 |
| CIITA_BL1_ht 4 | 0.091 | 0.094 | 0.88 (0.32-2.39) | 0.80 | - | 0.88 (0.32-2.39) | 0.80 | - | - | - | - | 15.5 |
| CIITA_BL1_ht5 | 0.061 | 0.031 | 2.23 (0.54-9.21) | 0.27 | - | 2.23 (0.54-9.21) | 0.27 | - | - | - | - | 8.7 |
| rs6498124 | 0.379 | 0.354 | 1.15 (0.63-2.11) | 0.64 | - | 0.92 (0.42-2.03) | 0.83 | - | 2.54 (0.62-10.49) | 0.20 | - | 30.9 |
| rs4781016 | 0.205 | 0.198 | 1.06 (0.53-2.10) | 0.87 | - | 1.12 (0.50-2.50) | 0.78 | - | 0.77 (0.10-6.09) | 0.81 | - | 24.0 |
| rs4774 | 0.205 | 0.198 | 1.04 (0.53-2.06) | 0.91 | - | 0.93 (0.42-2.06) | 0.86 | - | 2.56 (0.24-26.95) | 0.44 | - | 24.0 |
| rs4781019 | 0.326 | 0.292 | 1.12 (0.64-1.99) | 0.69 | - | 0.92 (0.43-1.98) | 0.83 | - | 2.31 (0.58-9.15) | 0.23 | - | 29.0 |
| rs6498126 | 0.265 | 0.260 | 1.09 (0.55-2.13) | 0.81 | - | 0.93 (0.43-2.03) | 0.85 | - | 3.49 (0.36-34.28) | 0.28 | - | 27.6 |
| rs11074938 | 0.485 | 0.469 | 1.10 (0.61-1.97) | 0.75 | - | 0.88 (0.36-2.17) | 0.78 | - | 1.52 (0.56-4.16) | 0.41 | - | 32.1 |
| rs11074939 | 0.326 | 0.365 | 0.81 (0.43-1.52) | 0.51 | - | 0.63 (0.28-1.40) | 0.26 | - | 1.53 (0.35-6.71) | 0.58 | - | 31.1 |
| rs7404786 | 0.220 | 0.198 | 1.10 (0.55-2.23) | 0.78 | - | 1.42 (0.61-3.28) | 0.42 | - | 0.35 (0.05-2.35) | 0.28 | - | 24.0 |
| rs7201430 | 0.189 | 0.177 | 1.08 (0.51-2.29) | 0.84 | - | 1.27 (0.54-2.99) | 0.58 | - | 0.34 (0.03-3.98) | 0.39 | - | 22.6 |
| rs4781024 | 0.318 | 0.344 | 0.83 (0.44-1.58) | 0.57 | - | 0.69 (0.31-1.54) | 0.37 | - | 1.34 (0.29-6.18) | 0.71 | - | 30.7 |
| rs1139564 | 0.303 | 0.156 | 2.45 (1.21-4.93) | 0.01 | NS | 2.66 (1.19-5.94) | 0.02 | NS | 4.97 (0.53-46.20) | 0.16 | - | 21.0 |
| CIITA_BL2_ht1 | 0.242 | 0.219 | 1.20 (0.61-2.36) | 0.60 | - | 1.07 (0.49-2.36) | 0.87 | - | 3.26 (0.33-32.01) | 0.31 | - | 25.4 |
| CIITA_BL2_ht 2 | 0.167 | 0.156 | 1.09 (0.52-2.27) | 0.82 | - | 1.04 (0.45-2.40) | 0.93 | - | 1.90 (0.16-23.15) | 0.61 | - | 21.0 |
| CIITA_BL2_ht 3 | 0.136 | 0.156 | 0.86 (0.38-1.95) | 0.71 | - | 0.96 (0.40-2.29) | 0.92 | - | - | - | - | 21.0 |
| CIITA_BL2_ht 4 | 0.136 | 0.115 | 1.23 (0.54-2.81) | 0.63 | - | 1.11 (0.45-2.73) | 0.83 | - | - | - | - | 17.5 |
| CIITA_BL2_ht5 | 0.045 | 0.052 | 0.92 (0.25-3.39) | 0.90 | - | 0.92 (0.25-3.39) | 0.90 | - | - | - | - | 11.1 |
| CIITA_BL2_ht6 | 0.045 | 0.042 | 1.16 (0.34-3.93) | 0.81 | - | 0.95 (0.23-3.83) | 0.94 | - | - | - | - | 10.0 |

[^2] disease; MAF, minor allele frequency; OR, odds ratio; CI, confidence interval; NS, not significant. Significant values are shown in bold.
Table IV. Association of significant CIITA variants with nasal polyps in ATA patients ( $\mathrm{n}=353$ ).

| SNP/haplotype | MAF |  | Co-dominant |  |  | Dominant |  |  | Recessive |  |  | Statistical power |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | Polyp-positive ( $\mathrm{n}=92$ ) | Polyp-negative ( $\mathrm{n}=261$ ) | OR (95\% CI) | $\mathrm{P}^{\text {a }}$ | $\mathrm{P}^{\text {corb }}$ | OR (95\% CI) | $\mathrm{P}^{\text {a }}$ | $\mathrm{P}^{\text {corrb }}$ | OR (95\% CI) | $\mathrm{P}^{\text {a }}$ | $\mathrm{P}^{\text {corrb }}$ |  |
| rs12932187 | 0.457 | 0.352 | 1.49 (1.07-2.07) | 0.02 | NS | 1.29 (0.79-2.11) | 0.31 | - | 2.61 (1.46-4.67) | 0.001 | 0.02 | 64.2 |
| rs4781011 | 0.114 | 0.128 | 0.88 (0.52-1.48) | 0.62 | - | 0.89 (0.50-1.58) | 0.70 | - | 0.57 (0.07-4.96) | 0.61 | - | 41.7 |
| rs11074934 | 0.272 | 0.308 | 0.83 (0.57-1.22) | 0.34 | - | 0.93 (0.58-1.50) | 0.78 | - | 0.41 (0.14-1.20) | 0.10 | - | 62.4 |
| rs8043545 | 0.440 | 0.500 | 0.80 (0.58-1.11) | 0.18 | - | 0.65 (0.39-1.08) | 0.09 | - | 0.86 (0.49-1.50) | 0.59 | - | 64.3 |
| rs8063850 | 0.076 | 0.098 | 0.76 (0.40-1.42) | 0.38 | - | 0.78 (0.41-1.50) | 0.45 | - | - | - | - | 35.0 |
| rs6498119 | 0.326 | 0.264 | 1.31 (0.93-1.86) | 0.13 | - | 1.18 (0.73-1.90) | 0.50 | - | 2.28 (1.12-4.67) | 0.02 | NS | 59.7 |
| rs7189406 | 0.446 | 0.483 | 0.86 (0.62-1.21) | 0.39 | - | 0.87 (0.51-1.46) | 0.59 | - | 0.77 (0.43-1.39) | 0.39 | - | 64.6 |
| CIITA_BL1_htl | 0.250 | 0.308 | 0.74 (0.50-1.09) | 0.12 | - | 0.73 (0.45-1.18) | 0.20 | - | 0.54 (0.20-1.45) | 0.22 | - | 62.4 |
| CIITA_BL1_ht2 | 0.293 | 0.234 | 1.31 (0.92-1.87) | 0.13 | - | 1.23 (0.76-1.99) | 0.40 | - | 2.16 (1.02-4.60) | 0.05 | NS | 57.1 |
| CIITA_BL1_ht3 | 0.136 | 0.153 | 0.87 (0.54-1.40) | 0.57 | - | 0.94 (0.55-1.62) | 0.82 | - | 0.31 (0.04-2.46) | 0.27 | - | 46.4 |
| CIITA_BL1_ht4 | 0.076 | 0.092 | 0.81 (0.43-1.52) | 0.51 | - | 0.84 (0.44-1.62) | 0.61 | - | - | - | - | 33.5 |
| CIITA_BL1_ht5 | 0.098 | 0.059 | 1.68 (0.93-3.05) | 0.09 | - | 1.63 (0.84-3.16) | 0.15 | - | 6.10 (0.54-68.76) | 0.14 | - | 24.4 |
| rs6498124 | 0.484 | 0.467 | 1.07 (0.76-1.49) | 0.71 | - | 1.12 (0.66-1.91) | 0.67 | - | 1.05 (0.60-1.85) | 0.86 | - | 64.9 |
| rs4781016 | 0.163 | 0.215 | 0.72 (0.46-1.12) | 0.14 | - | 0.78 (0.47-1.29) | 0.33 | - | 0.18 (0.02-1.37) | 0.10 | - | 55.1 |
| rs4774 | 0.168 | 0.216 | 0.73 (0.47-1.14) | 0.16 | - | 0.79 (0.48-1.31) | 0.36 | - | 0.19 (0.02-1.46) | 0.11 | - | 55.2 |
| rs4781019 | 0.353 | 0.333 | 1.11 (0.76-1.62) | 0.60 | - | 1.11 (0.68-1.81) | 0.67 | - | 1.20 (0.53-2.73) | 0.66 | - | 63.5 |
| rs6498126 | 0.272 | 0.289 | 0.90 (0.60-1.34) | 0.59 | - | 0.76 (0.46-1.23) | 0.26 | - | 1.51 (0.61-3.74) | 0.37 | - | 61.4 |
| rs11074938 | 0.418 | 0.510 | 0.66 (0.46-0.94) | 0.02 | NS | 0.45 (0.27-0.76) | 0.003 | 0.04 | 0.83 (0.46-1.49) | 0.52 | - | 64.0 |
| rs11074939 | 0.413 | 0.337 | 1.40 (0.99-1.99) | 0.06 | - | 1.53 (0.93-2.52) | 0.09 | - | 1.58 (0.80-3.11) | 0.18 | - | 63.7 |
| rs7404786 | 0.185 | 0.184 | 1.01 (0.65-1.56) | 0.97 | - | 0.94 (0.56-1.56) | 0.80 | - | 1.64 (0.47-5.77) | 0.44 | - | 51.2 |
| rs7201430 | 0.141 | 0.142 | 0.99 (0.61-1.61) | 0.96 | - | 0.90 (0.52-1.56) | 0.71 | - | 2.14 (0.46-9.89) | 0.33 | - | 44.4 |
| rs4781024 | 0.386 | 0.318 | 1.36 (0.96-1.95) | 0.09 | - | 1.48 (0.91-2.42) | 0.12 | - | 1.52 (0.74-3.10) | 0.26 | - | 62.9 |
| rs1139564 | 0.196 | 0.239 | 0.78 (0.51-1.18) | 0.24 | - | 0.79 (0.48-1.29) | 0.34 | - | 0.52 (0.15-1.84) | 0.31 | - | 57.6 |
| CIITA_BL2_htl | 0.315 | 0.278 | 1.22 (0.84-1.79) | 0.30 | - | 1.49 (0.92-2.41) | 0.11 | - | 0.71 (0.26-1.97) | 0.51 | - | 60.7 |
| CIITA_BL2_ht2 | 0.141 | 0.188 | 0.71 (0.45-1.14) | 0.16 | - | 0.75 (0.44-1.27) | 0.28 | - | 0.24 (0.03-1.90) | 0.18 | - | 51.8 |
| CIITA_BL2_ht3 | 0.120 | 0.115 | 1.04 (0.62-1.75) | 0.88 | - | 1.01 (0.57-1.82) | 0.96 | - | 1.41 (0.25-7.87) | 0.70 | - | 38.9 |
| CIITA_BL2_ht4 | 0.092 | 0.080 | 1.21 (0.67-2.20) | 0.53 | - | 1.36 (0.71-2.58) | 0.35 | - | - | - | - | 30.4 |
| CIITA_BL2_ht5 | 0.065 | 0.084 | 0.75 (0.39-1.45) | 0.39 | - | 0.79 (0.39-1.58) | 0.50 | - | - | - | - | 31.4 |
| CIITA_BL2_ht6 | 0.060 | 0.061 | 0.97 (0.47-2.01) | 0.93 | - | 0.87 (0.40-1.87) | 0.71 | - | - | - | - | 25.0 |

[^3]SNP. Two linkage disequilibrium (LD) blocks were inferred from the pairwise comparison of the genotype polymorphisms, and 11 major haplotypes (frequency $>0.05$ ) were examined for association with the presence of nasal polyps among asthmatic patients (Fig. 1B-D).

Associations of CIITA variants with nasal polyposis. Table II shows the results of the logistic analyses of variants in CIITA gene with nasal polyps in all the asthmatic patients. Two SNPs (rs12932187 and rs11074938) and 2 haplotypes (CIITA_BL1_ $h t 2$ and CIITA_BL1_ht5) were demonstrated to be associated with nasal polyps ( $\mathrm{P}=0.001-0.01$, $\mathrm{OR}=0.53-2.35$ depending on the genetic model). When multiple testing correction was conducted with a Meff of 16.5417, a SNP (rs12932187) retained the associations with nasal polyps ( $\mathrm{P}^{\text {corr }}=0.02$ ). Since nasal polyposis is usually accompanied with aspirin hypersensitivity in asthma, further comparison of this association in AERD and ATA subgroups was performed. As a result, one SNP (rs1139564) was demonstrated to have a nominal association with nasal polyps in the AERD group ( $\mathrm{P}=0.01$ in co-dominant model; $\mathrm{P}=0.02$ in dominant model). However, the association was not retained after multiple testing corrections (Table III).

In further association analysis, 4 CIITA variations (rs12932187, rs6498119, rs11074938 and CIITA_BL1_ht2) were significantly associated with nasal polyps ( $\mathrm{P}=0.001-0.05$, $\mathrm{OR}=0.45-2.61$ depending on the genetic model; Table IV) in ATA patients. Of these variations, the association of 2 variations (rs12932187 and CIITA_BL1_ht2) were retained following multiple testing corrections ( $\mathrm{P}^{\text {corr }}=0.02$ in $r s 12932187$ and $\mathrm{P}^{\text {corr }}=0.04$ in CIITA_BL1_ht2; Table IV). These findings showed that CIITA polymorphisms were more significantly associated with nasal polyposis in ATA compared to AERD patients.

## Discussion

Although small polyps in the nasal may be harmless, the development of nasal polyps could cause breathing difficulties and infections. As a result, it is important to clarify the exact mechanisms underlying nasal polyps pathogenesis. Nasal polyps often occur with asthma and aspirin intolerance. Additionally, since the formation of nasal polyps has been related to various immune responses, cytokines and the MHC system have been considered to be important molecules for the development of nasal polyps $(18,19)$. Although the development of nasal polyps has been associated with AERD and ATA, the exact genetic factors in the pathogenesis of nasal polyps have yet to be adequately elucidated.

To investigate causal genetic factor showing associations between genetic effect and the development of nasal polyps, numerous studies have been performed thus far on candidate genes of nasal polyps including interleukins (ILs), TNF- $\alpha$, NOS2A, IFN, CD14, CCL5, CCL2, GSTT1, GSTM1, MMPs and MHC class II genes (5,20-26). Most studies were conducted in Caucasian population, with the exception of one study investigating Taiwanese and Chinese population ( $\mathrm{n}=75-933$ in all subjects; $\mathrm{n}=75-245$ in nasal polyp subjects) (5,20-26). Among the variations in the tested candidate genes, $-308 G / A$ in $T N F-\alpha(\mathrm{P}=0.02)$, rs 17561 in ILIA
( $\mathrm{P}=0.02$ ), (CCTTT) $n$ in NOS2A ( $\mathrm{P}=0.001$ ), rs 3939286 in IL33 ( $\mathrm{P}=0.004$ ), HLA-DR7-DQA1*0201 and HLA-DQB1*0202 haplotype, - 174 G/C in IL6 ( $\mathrm{P}=0.03$ ) and rs3918242 in MMP-9 ( $\mathrm{P}=0.02$ ) were significantly associated with the formation of nasal polyps. However, no associations also were identified in CD14, CCL2, CCL5, TNF- $\beta 1$, deletion in GSTT1 and GSTM1, and MMP-2. Although numerous studies have been performed to identify genetic factors for nasal polyps, these studies were mainly performed on Caucasian and not Asian populations. Moreover, additional association studies on genes in the MHC region, which is considered an important immunologic factor for the formation of nasal polyps, are needed. CIITA, which is located on chromosome 16 p13 and distinguished from the MHC cluster (27), plays an important role in the physiological regulation of the expression of MHC class II genes. The mutational alteration of CIITA is able to cause a complete lack of MHC class II expression in all tissues (28). Furthermore, CIITA SNPs have been reported to be associated with immune diseases such as multiple sclerosis (7) and persistent hepatitis B virus (HBV) infection (29).

We investigated 18 polymorphisms in the CIITA gene and carried out a case-control association analysis based on three genetic models of inheritance in asthmatic patients, classified into AERD and ATA groups. The results demonstrated that a total of four SNPs were significantly associated with the presence of nasal polyps in the overall asthmatic, AERD and ATA groups. The results indicate that the genetic effect of CIITA variations is likely to contribute to the formation of nasal polyps in asthmatic patients. Furthermore, two variations (rs12932187 and CIITA_BL1_ht2) were shown to be associated with nasal polyps in ATA ( ${ }^{\text {corr }}=0.02-0.04$; Table IV) compared to AERD patients ( $\mathrm{P}>0.05$ for the variations). By contrast, the association signals of rsl139564 were higher in the AERD ( $\mathrm{P}=0.01$ ) compared to the ATA group. These findings indicate that the four CIITA SNPs are potential markers of genetic susceptibility to nasal polyposis between AERD and ATA groups.

Results of the present study have shown nominal correlation between nasal polyposis and aspirin hypersensitivity in asthma (Tables II and IV). Although this suggests that CIITA potentially contributes to the development of nasal polyps in AERD patients, the modest signal may also suggest a putative relationship. Factors such as the decrease of the sample size in the AERD group might influence the findings. Therefore, additional large-scale studies as well as functional evaluations that provide useful information for the pathogenesis of nasal polyp development, are needed.

The association between CIITA variations and nasal polyposis in asthmatic patients was investigated. To the best of our knowledge, this study is the first to investigate the association between CIITA variations and nasal polyposis in allergic and non-allergic asthmatic patients. It was found that rs12932187 and rs11074938 may be susceptibility markers of inflammation of the nasal passages. However, the average statistical power to detect the effect sizes of the significantly associated SNPs was $67.89 \%$, suggesting an insufficient sample size. Therefore, further studies comparing patients with healthy subjects are needed to confirm the conclusions of the present study.

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[^1]:    P-values at 0.05 level of significance adjusted for initial diagnosed age, gender, smoking status, atopy and AERD. ${ }^{\mathrm{b}}$ - values after multiple testing corrections (Meff=16.5417). MAF, minor allele frequency; OR, odds ratio; CI, confidence interval; NS, not significant. Significant values are shown in bold.

[^2]:    ${ }^{\text {P }}$-values at 0.05 level of significance adjusted for initial diagnosed age, gender, smoking status, atopy and AERD. ${ }^{\mathrm{b}} \mathrm{P}$-values after multiple testing corrections (Meff=16.5417). AERD, aspirin-exacerbated respiratory

[^3]:    ${ }^{\text {a }}$ P-values at 0.05 level of significance adjusted for initial diagnosed age, gender, smoking status, atopy and AERD. ${ }^{\text {b }}$ P-values after multiple testing corrections (Meff=16.5417). ATA, aspirin-tolerant asthma; MAF minor allele frequency; OR, odds ratio; CI, confidence interval; NS, not significant. Significant values are shown in bold.

