ORIGINAL ARTICLE

Variations in the *STK10* Gene and Possible Associations With Aspirin-Intolerant Asthma in a Korean Population

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Abstract

Background and objective: Lymphocyte-oriented kinase deficiency encoded by the serine/threonine kinase 10 (*STK10*) gene correlates with the intracellular adhesion molecule 1 (ICAM-1)/lymphocyte function associated antigen 1 (LFA-1) complex in aspirin hypersensitivity. This study investigated the association between single nucleotide polymorphisms (SNPs) of *STK10* and aspirin-intolerant asthma (AIA).
Methods: A total of 54 SNPs were genotyped in 163 AIA patients and 429 aspirin-tolerant asthma (ATA) controls.
Results: Logistic regression revealed that a synonymous variant (*rs2306961G>A*) had the most significant association with AIA (P=.008 under the codominant model; P=.004 under the dominant model), suggesting that tissue-specific codon usage between Lys_TTT and Lys_CTT could play a role in regulating expression of *STK10* in airway epithelium. Haplotype analysis revealed that 4 haplotypes, including *STK10_BL4-ht1*, which is unique to *rs2306961G>A*, were significantly associated with aspirin hypersensitivity in asthmatics (P<.05).
Conclusions: Although replications in independent cohorts and further functional evaluations are needed, our preliminary findings suggest that *STK10* polymorphisms might be susceptible genetic markers of AIA and that gene expression could be mediated by tissue-specific codon usage.

Key words: Aspirin-intolerant asthma. *STK10*. Single-nucleotide polymorphism. Haplotype.

Resumen

Antecedentes y objetivo: La carencia de cinasa LOK (*lymphocyte-oriented kinase*) codificada por el gen serina/treonina-cinasa 10 (*STK10*) está relacionada con el complejo molécula de adhesión intracelular 1 (ICAM-1)/antígeno 1 asociado a la función linfocitaria (LFA-1) en la hipersensibilidad al ácido acetilsalicílico. En este estudio se investigó la relación entre los polimorfismos de un solo nucleótido (SNP) de *STK10* y el asma con intolerancia al ácido acetilsalicílico (AIAAS).
Métodos: Se genotiparon 54 SNP en 163 pacientes con AIAAS y 429 controles con asma con tolerancia al ácido acetilsalicílico (ATAAS).
Resultados: La regresión logística reveló que una variante sinónima (*rs2306961G>A*) era la que presentaba la relación más significativa con el AIAAS (p = 0,008 según el modelo codominante; p = 0,004 según el modelo dominante), lo que indica que el uso de un codón

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específico de tejido entre Lys_TTT y Lys_CTT podría desempeñar un papel en la regulación de la expresión del gen *STK10* en el epitelio de las vías respiratorias. El análisis de haplotipos reveló que 4 haplotipos, incluido el *STK10_BL4-ht1*, que es único para *rs2306961G>A*, estaban significativamente relacionados con la hipersensibilidad al ácido acetilsalicílico en personas asmáticas ($p < 0,05$).
Conclusiones: Aunque es necesario repetir el estudio en cohortes independientes y realizar más evaluaciones funcionales, los resultados preliminares del presente estudio indican que los polimorfismos de *STK10* pueden ser marcadores genéticos susceptibles de AIAAS, y que la expresión génica puede estar mediada por el uso de codones específicos de tejido.

Palabras clave: Asma con intolerancia al ácido acetilsalicílico. STK10. Polimorfismo de un solo nucleótido. Haplotipo..

Introduction

Acetylsalicylic acid (aspirin) is frequently used to relieve pain and inflammation. The prevalence of aspirin hypersensitivity is about 0.6-2.5% in the general population; however, up to 20% of asthmatics are sensitive to aspirin [1]. Aspirin-intolerant asthma (AIA) is characterized by a severe fall in forced expiratory volume in 1 second (FEV_1) following the ingestion of nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin [2,3]. Patients with AIA generally show the clinical characteristics of the aspirin triad, namely, aspirin hypersensitivity, bronchial asthma, and chronic rhinosinusitis with nasal polyposis [2,4]. Although leukotriene receptor antagonists are used as first-line medication for long-term management of AIA, we still lack a comprehensive understanding of the pathogenesis of AIA.

Aspirin hypersensitivity results from overproduction of proinflammatory cysteinyl leukotrienes (CysLTs), such as LTC_4, LTD_4, and LTE_4 [3]. Inhibition of the cyclooxygenase pathway by aspirin diverts arachidonic acid metabolites to the 5-lipoxygenase pathway, leading eventually to overproduction of CysLTs [3]. Therefore, multiple leukotriene pathway genes and CysLT receptors are considered the main targets for aspirin-induced respiratory disease. Associations between AIA and variants in genes such as 5-lipoxygenase (*ALOX5*) [5], leukotriene C4 synthase (*LTC4S*) [6], and cysteinyl leukotriene receptors (*CYSLTR1* and *CYSLTR2*) [7] have been widely studied. However, new insights into airway remodeling of asthma traits have made it possible to identify novel susceptibility genes (eg, protocadherin-1 [*PCDH1*]) for bronchial hyperresponsiveness in both human and animal models [8,9]. These findings suggest that genes for other functional mechanisms could be more closely related to the development of aspirin-exacerbated respiratory disease than was previously thought.

Protein tyrosine kinases have been reported to play an essential role in the activation of inflammatory and airway smooth muscle and epithelial cells in asthmatics [10]. Furthermore, tyrosine kinase inhibitors have been evaluated to prevent airway hyperresponsiveness and eosinophil infiltration into the airways [11,12], suggesting the importance of phosphorylation in the airway inflammatory response. In addition, lymphocyte-oriented kinase (LOK) deficiency, which is encoded by the serine/threonine kinase 10 gene (*STK10*), has been implicated in the modulation of intracellular adhesion molecule 1 (ICAM-1)/leukocyte-function-associated antigen (LFA-1)–mediated lymphocyte adhesion [13,14]. Moreover, increased expression of ICAM-1 has been observed in patients with aspirin hypersensitivity compared to aspirin-tolerant controls [15]. Therefore, we hypothesized that polymorphisms in the *STK10* gene might be a risk factor in aspirin-exacerbated respiratory complications of AIA.

Patients and Methods

Patients

Patients were recruited from the hospitals of Soonchunhyang, Chung Ang, Chung Nam, Chungbuk, and Seoul National University in Korea. All patients were Korean and provided their written informed consent to participate. The Institutional Review Board of each hospital approved the study protocols. All the patients were diagnosed by a physician and met the definition of asthma set out in the Global Initiative for Asthma guidelines [16]. All patients had a history of dyspnea and wheezing during the previous 12 months, together with one of the following: >15% increase in FEV_1 or >12% increase plus 200 mL following inhalation of a short-acting bronchodilator; provocative concentration of methacholine causing a 20% fall in FEV_1 (PC_{20}) <10 mg/mL; and >20% increase in FEV_1 following 2 weeks of treatment with inhaled corticosteroids and long-acting bronchodilators. Twenty-four common inhalant allergens were used for a skin prick test [17]. Total immunoglobulin (Ig) E was measured using the CAP system (Pharmacia Diagnostics, Uppsala, Sweden). Atopy was defined as a wheal >3 mm in diameter. The oral aspirin challenge was performed with increasing doses of aspirin using methods slightly modified from those described elsewhere [17,18]. Changes in FEV_1 were followed for 5 hours after the last aspirin challenge. Aspirin-induced bronchospasm, as reflected by the percentage decline in FEV_1, was calculated as the prechallenge FEV_1 minus the postchallenge FEV_1 divided by the prechallenge FEV_1. Depending on the reaction to the oral aspirin challenge, patients with a ≥20% decrease in FEV_1 or 15%-19% decrease in FEV_1 with naso-ocular or cutaneous reactions were classed as having AIA, and those with less than <15% decreases in FEV_1 with no naso-ocular or cutaneous reactions were classed as having aspirin-tolerant asthma (ATA).

Selection and Genotyping of Single-Nucleotide Polymorphisms

A total of 54 common single-nucleotide polymorphisms (SNPs) were selected for genotyping based on minor allele frequency (MAF, >0.05) in an Asian population from the

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International HapMap Project (http://hapmap.ncbi.nlm.nih.gov/index.html.en). Genotyping was performed in 592 asthmatics including 163 AIA patients and 429 ATA controls using the TaqMan assay on the ABI prism 7900HT sequence detection system (Applied Biosystems, Foster City, California, USA), and data quality was assessed using duplicate DNAs (n=10). Genotyped data were obtained using ABI-PRISM sequence detection system (SDS) software, version 2.3. We excluded SNPs that did not satisfy the following criteria: a minimum call rate of 95%, no duplicate error, and Hardy-Weinberg equilibrium greater than $P>.05$.

Statistics

Haploview v4.1 was downloaded from the Broad Institute (http://www.broadinstitute.org/mpg/haploview) and used to analyze linkage disequilibrium (LD) of SNPs in the *STK10* gene [19]. Lewontin's D' (|*D*'|) and LD coefficient r^2 between all pairs of biallelic loci were examined to determine LD among the SNPs. Haplotypes were estimated using the PHASE algorithm (version 2.0) [20]. Logistic regression analysis adjusted for age, gender, smoking status, atopy, and body mass index as covariates was applied to assess the association between each genotype and haplotype in the *STK10* gene and AIA using Statistical Analysis System (SAS, Cary, North Carolina, USA). Significant associations were indicated by a P value <.05.

Results

Patient Characteristics

The group of patients with AIA comprised 59 males (36.2%) and 104 females (63.8%) with a mean age of 43.1 years; the ATA controls comprised 147 males (34.3%) and 282 females (65.7%) with a mean age of 47.3 years. AIA patients had an approximately 7-fold higher decline in FEV_1 after aspirin provocation than ATA controls ($P<.0001$, Table 1). Also significantly lower in AIA patients than in ATA controls were the provocative concentration of methacholine causing a 20% fall in FEV_1 (PC_{20}), age at onset, body mass index, and smoking status ($P<.05$).

STK10 Polymorphisms Associated With Risk of AIA

A total of 54 common polymorphisms with MAF >0.05 were successfully genotyped in 592 patients (Figure 1A). Most SNPs were distributed in the introns, except for the *rs2306961 A>G* (*K210K*) genotype in exon 6 and *rs15963 T>C* in the 3'-untranslated region (3'UTR). Two complete LDs (r^2=1: *rs6555999 G>A* and *rs11134732 T>A*; and *rs3111491 T>G* and *rs3111492 C>T*) were found among the 54 SNPs genotyped (Figure 1A). Pair-wise comparisons showed 6 tight LD blocks (Figure 1B), and their haplotypes were inferred using *PHASE* software (Figure 2). Multiple logistic regression

Table 1. Clinical Profiles of Aspirin-Intolerant and Aspirin-Tolerant Asthmatics

Clinical profile	All Patients	AIA	ATA
Number of subjects	592	163	429
Age, y, mean (range)	46.15 (15.40-77.88)	43.13 (17.22-72.73)a	47.30 (15.40-77.88)
Male/Female, No.	206/386	59/104	147/282
Total smokers, % (current smoker; ex-smoker) (%)	27.70 (12.50; 15.20)	21.47 (12.88; 8.59)a	30.07 (12.35; 17.72)
Body mass index, kg/m^2	24.24 (3.39)	23.39 (3.25)a	24.58 (3.39)
Decline in FEV_1 by aspirin provocation, %	9.27 (13.24)	24.63 (16.11)b	3.54 (4.85)
Blood eosinophils, %	6.01 (5.73)	5.96 (5.21)	6.03 (5.92)
FEV_1, % predicted	90.54 (16.97)	90.35 (14.04)a	91.66 (16.87)
PC_{20} methacholine, mg/mL	6.43 (8.67)	5.02 (7.83)a	6.91 (8.90)
Total IgE, IU/mL	357.65 (604.09)	348.60 (596.44)	361.00 (607.56)
Positive skin test result, %	56.42)	52.76	57.81

Abbreviations: AIA, aspirin-intolerant asthma; ATA, aspirin-tolerant asthma; FEV_1, forced expiratory volume in 1 second; Ig, immunoglobulin; PC_{20}, provocative concentration that causes a 20% fall in FEV_1.
[a]$P<.05$ compared to the respective ATA controls.
[b]$P<.0001$ compared to the respective ATA controls.

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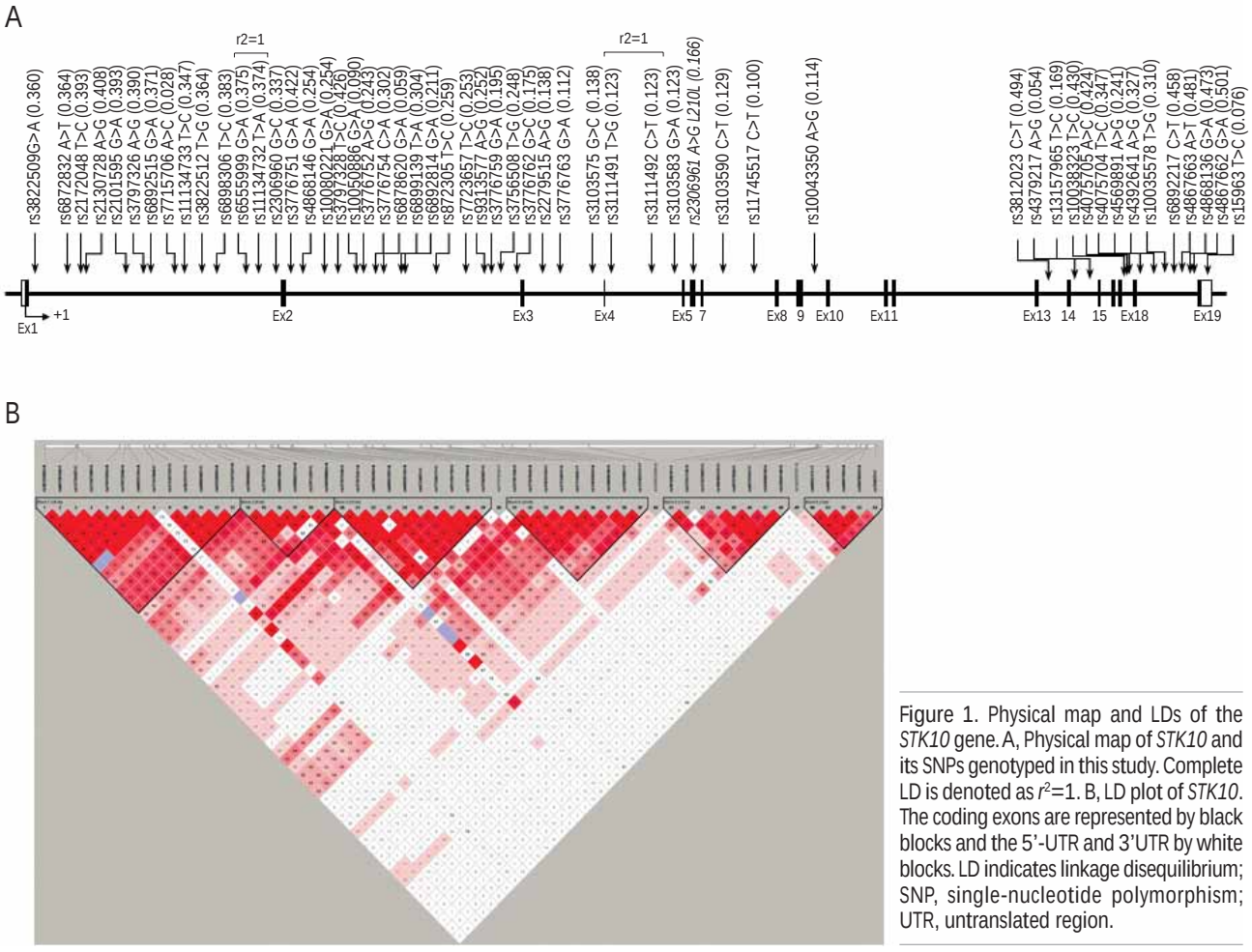

Figure 1. Physical map and LDs of the *STK10* gene. A, Physical map of *STK10* and its SNPs genotyped in this study. Complete LD is denoted as r^2=1. B, LD plot of *STK10*. The coding exons are represented by black blocks and the 5'-UTR and 3'UTR by white blocks. LD indicates linkage disequilibrium; SNP, single-nucleotide polymorphism; UTR, untranslated region.

models revealed that 14 common SNPs of the *STK10* gene had statistically significant association signals with AIA depending on the genetic models applied (*P*<.05, Table 2).

Among the SNPs with significant signals, *rs2306961 A>G* (*K210K*; a synonymous variant) in exon 6 was infrequent in AIA patients and showed the highest significant association signal with aspirin hypersensitivity in asthmatics (OR, 0.59; 95% CI, 0.40-0.87; *P*=.008 under the codominant model; *P*=.004 under the dominant model, Table 2) compared with that of ATA controls. There was also nominal evidence of association in other SNPs (*P*=.007-0.04, Table 2). To further investigate a potential association between this synonymous variation and expression of *STK10*, reports on tissue-specific codon usage were analyzed. Although there were no direct results in the bronchial epithelia, codon usage between Lys_TTT and Lys_CTT varied with tissue type (Table 3), indicating that synonymous *rs2306961 A>G* (*K210K*) could be a susceptible genetic marker of AIA.

Association Between STK10 Haplotypes and AIA

Among the 54 SNPs genotyped in this study, 51 (except *rs3776762 G>C*, *rs10043350 A>G*, and *rs10035578 T>G*) were used to construct 6 LD blocks and their relevant haplotypes. Only the common haplotypes with a frequency >5% were used in the association analyses (Figure 2). Logistic regression analysis showed that 4 haplotypes (*BL2_ht4, BL3_ht1, BL3_ht2*, and *BL4_ht1*) had significant association signals (*P*<.05, Table 4) with AIA. Haplotype *STK10_BL3_ht2* (unique to most of the minor alleles of SNPs showing significance) had the most significant association with AIA (*P*=.01 under the codominant model). In addition, haplotype *STK10_BL4_ht1* (unique to synonymous *rs2306961 A>G* and *rs3103590 C>T* among the frequent haplotypes in Block 4) in AIA patients was significantly infrequent at about >30% compared to that of ATA controls and was associated with AIA (*P*=.03 under the codominant model; *P*=.02 under the recessive model, Table 4).

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Block 1

Hap	rs3822509 G>A	rs6872832 A>T	rs2172048 T>C	rs2130728 A>G	rs2101595 G>A	rs3797326 A>G	rs6892515 G>A	rs7715706 A>C	rs11134733 T>C	rs3822512 T>G	rs6898306 T>C	rs65559999 G>A	rs11134732 T>A	Freq
ht1	A	T	C	G	A	G	A	A	T	T	T	G	T	0.298
ht2	G	A	T	A	G	A	G	A	C	G	C	A	A	0.283
ht3	G	A	T	A	G	A	G	A	T	T	T	G	T	0.251
ht4	G	A	T	A	G	A	G	A	T	T	C	A	A	0.037
ht5	G	A	C	G	A	G	A	C	T	T	T	G	T	0.021
ht6	A	T	C	G	A	G	A	A	C	G	C	A	A	0.019
ht7	A	T	C	G	A	A	G	A	C	G	C	A	A	0.017
ht8	A	T	C	G	A	G	A	A	T	G	T	G	T	0.017
ht9	G	A	T	A	G	G	G	A	C	G	C	A	A	0.016
ht10	G	A	T	G	G	A	G	A	T	T	T	G	T	0.010
Others	.	.	.	.	.	.	.	.	.	.	.	.	.	0.031

Block 2

Hap	rs2306960 G>C	rs3776751 G>A	rs4868146 G>A	rs10080221 G>A	rs3797328 T>C	rs10050886 G>A	Freq
ht1	G	G	G	G	C	G	0.284
ht2	G	G	A	A	T	G	0.239
ht3	C	A	G	G	T	G	0.203
ht4	G	A	G	G	C	G	0.086
ht5	C	A	G	G	T	A	0.079
ht6	C	A	G	G	C	G	0.047
ht7	G	G	G	G	T	G	0.034
ht8	G	G	A	A	T	A	0.008
ht9	C	G	G	G	T	G	0.005
ht10	G	G	A	A	C	G	0.005
Others	.	.	.	.	.	.	0.010

Block 3

Hap	rs3776752 A>G	rs3776754 C>A	rs6878620 G>A	rs6899139 T>A	rs6892814 G>A	rs872305 T>C	rs7723657 T>C	rs9313577 A>G	rs3776759 G>A	rs3756508 T>G	Freq
ht1	A	C	G	T	G	T	T	A	G	T	0.672
ht2	G	A	G	A	A	C	C	G	A	G	0.181
ht3	G	A	G	A	G	T	T	A	G	T	0.046
ht4	A	A	A	A	G	C	C	G	G	G	0.043
ht5	G	A	G	A	A	C	T	A	G	T	0.014
ht6	A	A	A	A	A	C	T	A	G	T	0.012
ht7	A	C	G	T	G	T	C	G	G	G	0.009
ht8	A	A	A	A	A	C	C	G	A	G	0.005
ht9	A	C	G	T	G	T	C	G	A	G	0.005
ht10	A	C	G	T	G	T	C	G	G	T	0.004
Others	.	.	.	.	.	.	.	.	.	.	0.010

Block 4

Hap	rs2279515 A>G	rs3776763 G>A	rs3103575 G>C	rs3111491 T>G	rs3111492 C>T	rs3103583 G>A	rs2306961 A>G	rs3103590 C>T	rs11745517 C>T	Freq
ht1	A	G	G	T	C	G	A	C	C	0.797
ht2	G	A	C	G	T	A	G	T	T	0.067
ht3	A	G	G	T	C	G	G	T	C	0.021
ht4	G	A	C	G	T	A	G	C	C	0.016
ht5	G	G	C	T	C	G	A	C	C	0.014
ht6	A	G	G	G	T	A	G	T	T	0.013
ht7	G	A	C	G	T	A	A	C	C	0.013
ht8	A	G	G	T	C	G	G	C	C	0.012
ht9	G	G	C	T	C	G	G	C	C	0.010
ht10	G	A	C	G	T	A	G	T	C	0.009
Others	.	.	.	.	.	.	.	.	.	.0.026

Block 5

Hap	rs3812023 C>T	rs4379217 A>G	rs13157965 T>C	rs10038323 T>C	rs4075705 A>C	rs4075704 T>C	rs4569891 A>G	rs4392641 A>G	Freq
ht1	C	A	T	T	A	C	A	G	0.249
ht2	T	A	T	C	C	T	A	A	0.188
ht3	T	A	T	T	A	T	G	A	0.174
ht4	C	A	C	C	C	T	A	A	0.130
ht5	T	A	T	T	A	C	A	G	0.057
ht6	C	A	T	C	C	T	A	A	0.045
ht7	T	G	T	C	C	T	A	A	0.044
ht8	C	A	T	T	A	T	G	A	0.038
ht9	T	A	C	T	A	T	G	A	0.016
ht10	C	A	C	T	A	C	A	G	0.012
Others	.	.	.	.	.	.	.	.	0.046

Block 6

Hap	rs6892217 C>T	rs4867663 A>T	rs4868136 G>A	rs4867662 G>C	rs15963 T>C	Freq
ht1	C	A	G	A	T	0.478
ht2	T	T	A	G	T	0.375
ht3	T	T	A	G	C	0.068
ht4	C	A	G	G	T	0.026
ht5	C	T	A	G	T	0.024
ht6	T	T	G	A	T	0.012
ht7	C	A	G	A	C	0.007
ht8	C	A	A	G	T	0.005
ht9	T	T	A	A	T	0.002
ht10	T	T	G	G	T	0.002
ht11	T	A	G	G	T	0.001

Figure 2. Haplotypes of the *STK10* gene. Haplotypes in each LD block of *STK10*. Fifty-one SNPs, except *rs3776762 G>C*, *rs10043350 A>G*, and *rs10035578 T>G*, are involved in the construction of the haplotypes. Associations of haplotypes with frequency >0.05 (in italics) are shown in Table 4.

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Table 2. Associations Between Single-Nucleotide Polymorphisms in the *STK10* Gene and Aspirin-Intolerant Asthma

No.	LD block	SNP ID	Position	MAF		Codominant		Dominant		Recessive	
				AIA	ATA	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
1	Block 1	*rs3822509 G>A*	Intron1	0.380	0.358	1.09 (0.82-1.44)	0.55	1.47 (1.00-2.17)	0.05	0.58 (0.31-1.09)	0.09
2		*rs6872832 A>T*	Intron1	0.387	0.360	1.12 (0.84-1.48)	0.45	1.50 (1.01-2.22)	0.04	0.61 (0.32-1.15)	0.12
3		*rs2172048 T>C*	Intron1	0.402	0.394	1.02 (0.77-1.34)	0.90	1.45 (0.98-2.17)	0.07	0.51 (0.28-0.92)	0.03
4		*rs2130728 A>G*	Intron1	0.417	0.410	1.01 (0.77-1.32)	0.95	1.38 (0.92-2.07)	0.12	0.59 (0.34-1.02)	0.06
5		*rs2101595 G>A*	Intron1	0.399	0.397	0.98 (0.75-1.29)	0.91	1.37 (0.92-2.04)	0.12	0.50 (0.28-0.91)	0.02
6		*rs3797326 A>G*	Intron1	0.390	0.393	0.97 (0.74-1.27)	0.82	1.30 (0.88-1.92)	0.19	0.52 (0.29-0.93)	0.03
7		*rs6892515 G>A*	Intron1	0.365	0.378	0.93 (0.71-1.22)	0.60	1.27 (0.86-1.86)	0.23	0.42 (0.22-0.79)	0.007
8		*rs7715706 A>C*	Intron1	0.015	0.031	0.47 (0.18-1.27)	0.14	0.47 (0.18-1.27)	0.14		
9		*rs11134733 T>C*	Intron1	0.350	0.350	0.98 (0.75-1.29)	0.90	1.03 (0.71-1.50)	0.87	0.86 (0.49-1.52)	0.61
10		*rs3822512 T>G*	Intron1	0.365	0.367	0.98 (0.75-1.29)	0.89	1.02 (0.70-1.48)	0.93	0.89 (0.51-1.56)	0.69
11		*rs6898306 T>C*	Intron1	0.393	0.383	1.02 (0.78-1.34)	0.88	1.15 (0.79-1.69)	0.47	0.83 (0.49-1.41)	0.49
12		*rs6555999 G>A*	Intron1	0.383	0.375	1.01 (0.78-1.32)	0.93	1.11 (0.76-1.62)	0.60	0.86 (0.51-1.47)	0.59
13		*rs11134732 T>A*	Intron1	0.387	0.374	1.03 (0.79-1.35)	0.83	1.14 (0.78-1.67)	0.51	0.87 (0.51-1.49)	0.62
14	Block 2	*rs2306960 G>C*	Intron1	0.337	0.331	0.98 (0.74-1.29)	0.86	1.12 (0.77-1.63)	0.54	0.66 (0.35-1.23)	0.19
15		*rs3776751 G>A*	Intron2	0.448	0.413	1.15 (0.88-1.50)	0.30	1.35 (0.90-2.01)	0.15	1.03 (0.64-1.67)	0.90
16		*rs4868146 G>A*	Intron2	0.206	0.274	0.72 (0.53-0.98)	0.04	0.69 (0.47-1.01)	0.06	0.57 (0.26-1.28)	0.18
17		*rs10080221 G>A*	Intron2	0.212	0.273	0.75 (0.55-1.02)	0.07	0.73 (0.50-1.07)	0.11	0.57 (0.26-1.28)	0.18
18		*rs3797328 T>C*	Intron2	0.466	0.413	1.23 (0.94-1.60)	0.13	1.42 (0.95-2.13)	0.09	1.19 (0.74-1.89)	0.48
19		*rs10050886 G>A*	Intron2	0.099	0.084	1.19 (0.75-1.90)	0.46	1.25 (0.78-2.02)	0.36		
20	Block 3	*rs3776752 A>G*	Intron2	0.188	0.264	0.69 (0.50-0.94)	0.02	0.69 (0.47-1.01)	0.06	0.40 (0.16-0.99)	0.05
21		*rs3776754 C>A*	Intron2	0.258	0.319	0.75 (0.56-1.01)	0.06	0.72 (0.50-1.05)	0.09	0.64 (0.32-1.28)	0.21
22		*rs6878620 G>A*	Intron2	0.071	0.057	1.25 (0.72-2.15)	0.43	1.25 (0.72-2.15)	0.43		
23		*rs6899139 T>A*	Intron2	0.261	0.322	0.76 (0.57-1.01)	0.06	0.74 (0.51-1.07)	0.10	0.61 (0.30-1.23)	0.16
24		*rs6892814 G>A*	Intron2	0.163	0.234	0.66 (0.47-0.92)	0.01	0.65 (0.44-0.97)	0.03	0.35 (0.12-1.05)	0.06
25		*rs872305 T>C*	Intron2	0.221	0.277	0.74 (0.54-1.01)	0.06	0.73 (0.50-1.06)	0.10	0.54 (0.23-1.27)	0.16
26		*rs7723657 T>C*	Intron2	0.209	0.273	0.72 (0.53-0.98)	0.04	0.66 (0.45-0.96)	0.03	0.70 (0.32-1.54)	0.37
27		*rs9313577 A>G*	Intron2	0.209	0.270	0.72 (0.53-0.99)	0.04	0.66 (0.45-0.97)	0.03	0.72 (0.33-1.58)	0.41
28		*rs3776759 G>A*	Intron2	0.150	0.213	0.67 (0.48-0.95)	0.02	0.61 (0.41-0.93)	0.02	0.63 (0.25-1.63)	0.34
29		*rs3756508 T>G*	Intron2	0.206	0.265	0.73 (0.53-1.00)	0.05	0.67 (0.45-0.98)	0.04	0.74 (0.34-1.64)	0.46
30		*rs3776762 G>C*	Intron2	0.181	0.175	1.02 (0.73-1.43)	0.91	1.01 (0.68-1.50)	0.97	1.14 (0.42-3.14)	0.80
31	Block 4	*rs2279515 A>G*	Intron3	0.108	0.152	0.71 (0.48-1.07)	0.10	0.71 (0.45-1.11)	0.13	0.45 (0.10-2.07)	0.31
32		*rs3776763 G>A*	Intron3	0.080	0.127	0.66 (0.42-1.03)	0.07	0.62 (0.38-1.03)	0.06	0.56 (0.12-2.66)	0.47
33		*rs3103575 G>C*	Intron3	0.110	0.151	0.74 (0.49-1.09)	0.13	0.73 (0.47-1.14)	0.17	0.45 (0.10-2.06)	0.30
34		*rs3111491 T>G*	Intron4	0.089	0.136	0.67 (0.44-1.04)	0.07	0.65 (0.40-1.05)	0.08	0.53 (0.11-2.46)	0.42
35		*rs3111492 C>T*	Intron4	0.089	0.136	0.67 (0.44-1.04)	0.07	0.65 (0.40-1.05)	0.08	0.53 (0.11-2.46)	0.42
36		*rs3103583 G>A*	Intron4	0.092	0.138	0.69 (0.45-1.06)	0.09	0.67 (0.42-1.07)	0.10	0.53 (0.11-2.46)	0.42
37		*rs2306961 A>G (K210K)*	Exon6	0.113	0.191	0.59 (0.40-0.87)	0.008	0.52 (0.34-0.81)	0.004	0.76 (0.24-2.37)	0.63
38		*rs3103590 C>T*	Intron7	0.086	0.147	0.61 (0.40-0.95)	0.03	0.58 (0.36-0.94)	0.03	0.49 (0.11-2.28)	0.36
39		*rs11745517 C>T*	Intron7	0.077	0.110	0.75 (0.47-1.20)	0.23	0.69 (0.42-1.16)	0.16	1.42 (0.25-8.15)	0.70
40		*rs10043350 A>G*	Intron9	0.104	0.118	0.93 (0.62-1.40)	0.74	1.02 (0.65-1.62)	0.93	0.25 (0.03-2.00)	0.19
41	Block 5	*rs3812023 C>T*	Intron13	0.482	0.497	0.98 (0.76-1.27)	0.87	0.83 (0.55-1.26)	0.38	1.15 (0.75-1.76)	0.52
42		*rs4379217 A>G*	Intron14	0.055	0.055	1.08 (0.61-1.91)	0.78	1.17 (0.64-2.11)	0.62		
43		*rs13157965 T>C*	Intron14	0.153	0.166	0.93 (0.66-1.31)	0.69	0.98 (0.65-1.48)	0.91	0.64 (0.23-1.78)	0.39
44		*rs10038323 T>C*	Intron17	0.425	0.428	1.00 (0.78-1.29)	0.99	0.88 (0.60-1.30)	0.52	1.19 (0.76-1.87)	0.45
45		*rs4075705 A>C*	Intron17	0.420	0.421	1.01 (0.78-1.30)	0.94	0.89 (0.60-1.30)	0.53	1.23 (0.78-1.94)	0.38
46		*rs4075704 T>C*	Intron17	0.377	0.341	1.13 (0.86-1.47)	0.38	1.11 (0.76-1.61)	0.59	1.31 (0.77-2.21)	0.32
47		*rs4569891 A>G*	Intron18	0.218	0.248	0.87 (0.64-1.20)	0.41	0.90 (0.62-1.32)	0.59	0.62 (0.25-1.56)	0.31
48		*rs4392641 A>G*	Intron18	0.350	0.325	1.07 (0.81-1.41)	0.62	1.07 (0.74-1.55)	0.73	1.16 (0.66-2.05)	0.61
49		*rs10035578 T>G*	Intron18	0.362	0.298	1.28 (0.97-1.69)	0.08	1.37 (0.94-1.99)	0.10	1.40 (0.78-2.51)	0.26
50	Block 6	*rs6892217 C>T*	Intron18	0.442	0.469	0.89 (0.69-1.16)	0.38	0.85 (0.57-1.27)	0.42	0.86 (0.55-1.36)	0.52
51		*rs4867663 A>T*	Intron18	0.482	0.486	0.96 (0.74-1.25)	0.78	1.02 (0.67-1.55)	0.94	0.88 (0.57-1.37)	0.58
52		*rs4868136 G>A*	Intron18	0.472	0.479	0.96 (0.74-1.24)	0.75	0.96 (0.63-1.45)	0.84	0.93 (0.60-1.44)	0.75
53		*rs4867662 G>A*	Intron18	0.497	0.497	1.02 (0.79-1.32)	0.88	1.24 (0.81-1.90)	0.32	0.85 (0.55-1.31)	0.45
54		*rs15963 T>C*	3'UTR	0.055	0.083	0.63 (0.36-1.08)	0.09	0.64 (0.36-1.12)	0.12		

P values were adjusted for initial diagnosis, age, sex, smoking, atopy, and body mass index.
Abbreviations: AIA, aspirin-intolerant asthma; ATA, aspirin-tolerant asthma; CI, confidence interval; MAF, minor allele frequency; OR, odds ratio; SNP, single-nucleotide polymorphism; UTR, untranslated region.

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Discussion

This study is the first to investigate genetic associations between 54 common *STK10* variants and their haplotypes and aspirin hypersensitivity in patients with asthma. We found that the significantly associated polymorphisms of *STK10* were more infrequent in AIA patients than in ATA controls. Furthermore, a synonymous *rs2306961 A>G* (*K210K*) variant proved to be significantly susceptible to development of AIA.

Table 3. Codon Usage Preferences in Tissues According to tRNA Expression

tRNA	Codon	Liver	Spleen	Testis
Lys_TTT	AAA	–0.36	–0.45	–0.14
Lys_CTT	AAG	0.36++	0.45++	0.14

The relative synonymous codon usage (ΔRSCU) between Lys_TTT and Lys_CTT is compared among 3 tissues (Ref. [35] *Comeron JM, 2004*). Scores indicate the relative synonymous codon usage (ΔRSCU).

Table 4. Associations Between Haplotypes of the *STK10* Gene and Aspirin-Intolerant Asthma

		Frequency		Codominant		Dominant		Recessive	
LD block	Haplotype	AIA	ATA	OR (95%, CI)	*P*	OR (95%, CI)	*P*	OR (95%, CI)	*P*
Block 1	*STK10_BL1_ht1*	0.294	0.305	0.94 (0.70-1.26)	.68	1.07 (0.74-1.55)	.72	0.54 (0.25-1.15)	.11
	STK10_BL1_ht2	0.261	0.290	0.86 (0.64-1.16)	.31	0.91 (0.63-1.32)	.63	0.55 (0.25-1.22)	.14
	STK10_BL1_ht3	0.255	0.244	1.11 (0.82-1.51)	.49	1.21 (0.83-1.76)	.32	0.86 (0.37-1.97)	.71
Block 2	*STK10_BL2_ht1*	0.294	0.274	1.06 (0.80-1.41)	.69	1.07 (0.74-1.55)	.72	1.10 (0.58-2.09)	.77
	STK10_BL2_ht2	0.196	0.259	0.75 (0.55-1.02)	.06	0.71 (0.48-1.04)	.08	0.61 (0.27-1.38)	.24
	STK10_BL2_ht3	0.193	0.206	0.88 (0.63-1.23)	.46	0.83 (0.56-1.22)	.34	1.13 (0.44-2.87)	.80
	STK10_BL2_ht4	0.110	0.083	1.60 (1.02-2.51)	.04	1.67 (1.04-2.68)	.03	1.14 (0.10-13.81)	.92
	STK10_BL2_ht5	0.092	0.073	1.29 (0.79-2.09)	.31	1.34 (0.82-2.19)	.25		
Block 3	*STK10_BL3_ht1*	0.273	0.351	0.72 (0.55-0.96)	.03	0.56 (0.29-1.07)	.08	0.70 (0.48-1.01)	.06
	STK10_BL3_ht2	0.132	0.203	0.63 (0.44-0.90)	.01	0.62 (0.41-0.94)	.02	0.32 (0.09-1.11)	.07
Block 4	*STK10_BL4_ht1*	0.153	0.224	0.69 (0.48-0.97)	.03	0.84 (0.33-2.17)	.72	0.61 (0.41-0.91)	.02
	STK10_BL4_ht2	0.052	0.078	0.69 (0.40-1.20)	.19	0.61 (0.33-1.11)	.11	2.13 (0.30-15.31)	.45
Block 5	*STK10_BL5_ht1*	0.267	0.253	1.01 (0.76-1.36)	.93	0.99 (0.69-1.44)	.97	1.11 (0.56-2.21)	.77
	STK10_BL5_ht2	0.190	0.191	0.96 (0.69-1.32)	.78	0.87 (0.59-1.30)	.50	1.41 (0.60-3.29)	.43
	STK10_BL5_ht3	0.163	0.169	0.98 (0.69-1.40)	.92	1.01 (0.68-1.51)	.96	0.71 (0.19-2.64)	.61
	STK10_BL5_ht4	0.120	0.129	0.91 (0.62-1.33)	.62	0.95 (0.61-1.48)	.82	0.56 (0.16-2.00)	.37
	STK10_BL5_ht5	0.061	0.055	1.17 (0.67-2.03)	.59	1.24 (0.70-2.21)	.46		
Block 6	*STK10_BL6_ht1*	0.482	0.474	1.05 (0.81-1.37)	.70	1.33 (0.87-2.04)	.18	0.84 (0.54-1.32)	.44
	STK10_BL6_ht2	0.380	0.378	1.01 (0.78-1.32)	.93	1.09 (0.74-1.59)	.67	0.90 (0.53-1.52)	.69
	STK10_BL6_ht3	0.049	0.075	0.62 (0.35-1.10)	.10	0.63 (0.35-1.15)	.13		

P values were adjusted with initial diagnosed age, sex, smoking, atopy, and body mass index.
Abbreviations: AIA, aspirin-intolerant asthma; ATA, aspirin-tolerant asthma; CI, confidence interval; OR, odds ratio.

In addition, *STK10_BL3_ht2* (*G-A-G-A-A-C-C-G-A-G*), a haplotype that is unique to most of the minor alleles of the SNPs showing significant signals, could be a susceptible marker for AIA.

Genetic polymorphisms on several of the genes involved in pathways related to 5-lipoxygenase [5,17], thromboxane [21], and leukotriene [6,22] have been suggested as associated markers of AIA. The *HLA-DPB1*0301* allele was identified as a strong marker for AIA [23]. In addition, tandem repeat variations in the promoter and a haplotype of *ALOX5* are also associated with AIA [5,17]. Variant *–444A>C* in the promoter of *LTC4S* has been found to be associated with AIA in Polish patients [6], but not in populations from the United States [24], Japan [25], and Korea [5]. However, *PCDH1*, a structural gene for cell adhesion, has been identified as a novel candidate for susceptibility to bronchial hyperresponsiveness [8], suggesting that genetic variations in genes in other pathways might be more correlated with aspirin hypersensitivity in asthma than previously thought. Since methacholine in the airways utilizes the muscarinic acetylcholine M3 receptor, which is coupled to G proteins of class G_q (in turn related to the signaling pathways for inositol triphosphate and intracellular calcium by regulation of phospholipase C) [26,27], our results for an association between *STK10* polymorphisms and methacholine PC_{20} suggest the potential involvement of other pathways (Table 5).

The *STK10* gene encodes LOK, a basophilic kinase [28]. Although the role of basophil activation in the diagnosis of aspirin sensitivity is controversial, it has recently been reported that NSAIDs activate basophils in clinically hypersensitive patients [29], suggesting that STK10 as a basophilic kinase could respond to IgE-dependent stimulation through increased levels of histamine, LTC_4, and interleukins in relation to aspirin

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Table 5. Associations Between *STK10* Polymorphisms and PC_{20} Methacholine

SNP/Haplotype	Position	C/C	C/R	R/R	*Pa*	*Pb*	*Pc*
rs3822509 G>A	Intron1	227 (0.61±0.45)	284 (0.61±0.47)	67 (0.62±0.44)	0.95	0.87	0.90
rs6872832 A>T	Intron1	221 (0.61±0.45)	292 (0.61±0.47)	65 (0.63±0.44)	0.84	0.94	0.75
rs2172048 T>C	Intron1	208 (0.60±0.45)	287 (0.61±0.47)	83 (0.65±0.45)	0.47	0.75	0.35
rs2130728 A>G	Intron1	198 (0.60±0.45)	289 (0.61±0.47)	91 (0.65±0.44)	0.43	0.62	0.40
rs2101595 G>A	Intron1	206 (0.60±0.45)	286 (0.61±0.47)	83 (0.65±0.45)	0.48	0.77	0.33
rs3797326 A>G	Intron1	212 (0.60±0.45)	282 (0.60±0.46)	84 (0.68±0.44)	0.37	0.89	0.12
rs6892515 G>A	Intron1	228 (0.60±0.46)	271 (0.60±0.46)	79 (0.67±0.45)	0.40	0.79	0.20
rs7715706 A>C	Intron1	549 (0.61±0.46)	29 (0.72±0.47)		0.23	0.23	
rs11134733 T>C	Intron1	244 (0.65±0.46)	262 (0.57±0.44)	71 (0.63±0.49)	0.36	0.12	0.66
rs3822512 T>G	Intron1	229 (0.66±0.47)	274 (0.57±0.44)	74 (0.64±0.48)	0.27	0.06	0.62
rs6898306 T>C	Intron1	217 (0.65±0.46)	277 (0.58±0.45)	84 (0.63±0.48)	0.47	0.21	0.73
rs6555999 G>A	Intron1	225 (0.64±0.46)	271 (0.58±0.45)	82 (0.64±0.48)	0.57	0.24	0.61
rs11134732 T>A	Intron1	224 (0.64±0.46)	272 (0.58±0.45)	81 (0.63 ±0.48)	0.49	0.22	0.72
STK10_BL1_ht1		275 (0.61±0.45)	256 (0.60±0.47)	47 (0.67±0.43)	0.85	0.77	0.34
STK10_BL1_ht2		293 (0.65±0.46)	241 (0.57±0.44)	44 (0.63±0.50)	0.24	0.10	0.74
STK10_BL1_ht3		323 (0.62±0.46)	222 (0.58±0.45)	33 (0.70±0.43)	0.93	0.54	0.28
rs2306960 G>C	Intron1	255 (0.61±0.45)	261 (0.61±0.46)	62 (0.62±0.46)	0.84	0.97	0.72
rs3776751 G>A	Intron2	191 (0.61±0.44)	287 (0.62±0.47)	100 (0.61±0.45)	0.99	0.97	0.98
rs4868146 G>A	Intron2	321 (0.61±0.46)	216 (0.60±0.45)	41 (0.66±0.45)	0.90	0.84	0.48
rs10080221 G>A	Intron2	321 (0.61±0.46)	216 (0.60±0.45)	41 (0.66±0.45)	0.85	0.89	0.48
rs3797328 T>C	Intron2	191 (0.63±0.46)	274 (0.59±0.45)	107 (0.65±0.47)	0.76	0.67	0.28
rs10050886 G>A	Intron2	479 (0.62±0.46)	96 (0.56±0.44)	2 (0.51±0.63)	0.24	0.24	0.74
STK10_BL2_ht1		304 (0.61±0.46)	224 (0.61±0.46)	50 (0.61±0.46)	0.81	0.85	0.82
STK10_BL2_ht2		335 (0.61±0.46)	204 (0.61±0.46)	39 (0.65±0.44)	0.80	0.96	0.59
STK10_BL2_ht3		366 (0.61±0.46)	189 (0.63±0.45)	23 (0.62±0.47)	0.74	0.67	0.92
STK10_BL2_ht4		478 (0.62±0.46)	97 (0.60±0.47)	3 (0.40±0.31)	0.42	0.48	0.49
STK10_BL2_ht5		489 (0.62 ±0.46)	88 (0.56±0.43)	1 (0.95)	0.35	0.29	0.42
rs3776752 A>G	Intron2	336 (0.61±0.46)	196 (0.61±0.46)	41 (0.66±0.44)	0.77	0.98	0.50
rs3776754 C>A	Intron2	283 (0.61±0.46)	240 (0.60±0.46)	54 (0.68±0.46)	0.70	0.93	0.31
rs6878620 G>A	Intron2	508 (0.62 ±0.46)	70 (0.60±0.47)		0.78	0.78	.
rs6899139 T>A	Intron2	280 (0.61±0.46)	240 (0.60 ±0.46)	55 (0.67±0.46)	0.73	0.92	0.35
rs6892814 G>A	Intron2	359 (0.60±0.45)	186 (0.62±0.47)	30 (0.69±0.43)	0.47	0.68	0.30
rs872305 T>C	Intron2	313 (0.61±0.45)	227 (0.61±0.47)	38 (0.68±0.42)	0.66	0.92	0.37
rs7723657 T>C	Intron2	320 (0.60±0.44)	218 (0.62±0.48)	40 (0.66±0.43)	0.55	0.75	0.40
rs9313577 A>G	Intron2	321 (0.60±0.44)	218 (0.62±0.48)	39 (0.64±0.42)	0.60	0.72	0.56
rs3776759 G>A	Intron2	378 (0.60±0.45)	171 (0.62±0.48)	29 (0.70±0.44)	0.40	0.62	0.25
rs3756508 T>G	Intron2	325 (0.60±0.44)	214 (0.62±0.48)	38 (0.64±0.42)	0.65	0.77	0.60
rs3776762 G>C	Intron2	394 (0.63±0.47)	166 (0.57±0.43)	18 (0.60±0.44)	0.27	0.19	0.94
STK10_BL3_ht1		266 (0.61±0.45)	242 (0.60±0.46)	70 (0.66±0.45)	0.81	0.37	0.79
STK10_BL3_ht2		389 (0.60±0.45)	165 (0.64±0.49)	24 (0.65±0.37)	0.38	0.40	0.62
rs2279515 A>G	Intron3	427 (0.61±0.47)	135 (0.60 ±0.44)	15 (0.69±0.37)	0.98	0.77	0.47
rs3776763 G>A	Intron3	454 (0.61±0.46)	112 (0.63±0.45)	12 (0.71±0.41)	0.54	0.70	0.36
rs3103575 G>C	Intron3	427 (0.61±0.46)	135 (0.61±0.44)	15 (0.69±0.37)	0.81	0.99	0.46
rs3111491 T>G	Intron4	444 (0.61± 0.46)	121 (0.62±0.44)	13 (0.77±0.44)	0.41	0.67	0.15
rs3111492 C>T	Intron4	444 (0.61±0.46)	121 (0.62±0.44)	13 (0.77±0.44)	0.41	0.67	0.15
rs3103583 G>A	Intron4	442 (0.61±0.46)	124 (0.62±0.45)	12 (0.80±0.44)	0.32	0.56	0.11
rs2306961 A>G L210L	Exon6	397 (0.60±0.46)	163 (0.60±0.43)	18 (0.88±0.46)	0.19	0.61	**0.008**
rs3103590 C>T	Intron7	439 (0.60±0.46)	126 (0.65±0.44)	13 (0.77±0.46)	0.12	0.18	0.18
rs11745517 C>T	Intron7	465 (0.60±0.46)	106 (0.66±0.44)	6 (0.82±0.50)	0.12	0.17	0.23
rs10043350 A>G	Intron9	455 (0.59±0.45)	111 (0.68±0.47)	11 (0.89±0.51)	**0.006**	**0.02**	0.03
STK10_BL4_ht1		364 (0.61±0.47)	187 (0.60±0.43)	27 (0.79±0.44)	0.34	**0.03**	0.86
STK10_BL4_ht2		499 (0.60±0.46)	75 (0.68±0.44)	4 (0.69±0.52)	0.21	0.20	0.70
rs3812023 C>T	Intron13	151 (0.60±0.49)	284 (0.61±0.46)	143 (0.62±0.42)	0.71	0.77	0.75
rs4379217 A>G	Intron14	514 (0.61±0.46)	62 (0.64±0.48)	2 (0.57±0.15)	0.51	0.49	0.99
rs13157965 T>C	Intron14	415 (0.62±0.45)	140 (0.61±0.47)	23 (0.52±0.44)	0.27	0.42	0.21
rs10038323 T>C	Intron17	201 (0.63±0.47)	256 (0.61±0.44)	117 (0.60±0.48)	0.34	0.45	0.41
rs4075705 A>C	Intron17	205 (0.63±0.47)	260 (0.61±0.44)	113 (0.59±0.48)	0.36	0.55	0.35
rs4075704 T>C	Intron17	245 (0.64±0.47)	258 (0.59±0.45)	75 (0.62±0.46)	0.49	0.32	0.96
rs4569891 A>G	Intron18	334 (0.59±0.46)	212 (0.65±0.44)	32 (0.67±0.51)	0.07	0.05	0.57
rs4392641 A>G	Intron18	256 (0.62±0.46)	257 (0.61±0.46)	65 (0.60±0.45)	0.73	0.72	0.85
rs10035578 T>G	Intron18	271 (0.62±0.47)	249 (0.61±0.46)	58 (0.57±0.42)	0.65	0.81	0.56
STK10_BL5_ht1		322 (0.61±0.45)	216 (0.60±0.46)	40 (0.65±0.48)	0.78	0.97	0.56
STK10_BL5_ht2		383 (0.63±0.47)	170 (0.58±0.42)	25 (0.58±0.44)	0.22	0.20	0.67
STK10_BL5_ht3		401 (0.60±0.46)	163 (0.64±0.45)	14 (0.67±0.50)	0.19	0.17	0.71
STK10_BL5_ht4		449 (0.62±0.45)	113 (0.59±0.49)	16 (0.59±0.49)	0.42	0.45	0.62

Contd.

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(Contd.) Table 5. Associations Between *STK10* Polymorphisms and PC_{20} Methacholine

SNP/Haplotype	Position	C/C	C/R	R/R	*Pa*	*Pb*	*Pc*
rs3822509 G>A	Intron1	227 (0.61±0.45)	284 (0.61±0.47)	67 (0.62±0.44)	0.95	0.87	0.90
rs6872832 A>T	Intron1	221 (0.61±0.45)	292 (0.61±0.47)	65 (0.63±0.44)	0.84	0.94	0.75
rs2172048 T>C	Intron1	208 (0.60±0.45)	287 (0.61±0.47)	83 (0.65±0.45)	0.47	0.75	0.35
rs2130728 A>G	Intron1	198 (0.60±0.45)	289 (0.61±0.47)	91 (0.65±0.44)	0.43	0.62	0.40
rs2101595 G>A	Intron1	206 (0.60±0.45)	286 (0.61±0.47)	83 (0.65±0.45)	0.48	0.77	0.33
rs3797326 A>G	Intron1	212 (0.60±0.45)	282 (0.60±0.46)	84 (0.68±0.44)	0.37	0.89	0.12
rs6892515 G>A	Intron1	228 (0.60±0.46)	271 (0.60±0.46)	79 (0.67±0.45)	0.40	0.79	0.20
rs7715706 A>C	Intron1	549 (0.61±0.46)	29 (0.72±0.47)		0.23	0.23	
rs11134733 T>C	Intron1	244 (0.65±0.46)	262 (0.57±0.44)	71 (0.63±0.49)	0.36	0.12	0.66

Abbreviations: *Pa*, *P* value of the codominant model; *Pb*, *P* value of the dominant model; *Pc*, *P* value of the recessive model.
[a]C/C, C/R and R/R indicate the homozygote of the common allele, and the heterozygote and homozygote of the rare allele, respectively.

intolerance in asthma patients. The STK10 protein is also a major kinase of ezrin-radixin-moesin (ERM) proteins, which are related to many cellular functions, including regulation of actin cytoskeleton and adhesion and motility in cells such as airway epithelial and T cells [30,31]. In addition, ERM proteins regulate increases in endothelial permeability in pulmonary microvascular endothelial cells [32], suggesting that phosphorylation of ERM proteins by STK10 might have an important role in the modulation of respiratory responses, lung vascular integrity, or both.

Recently, tyrosine kinase inhibitors have also been considered an attractive strategy in the treatment of airway hyperresponsiveness [10]. Inhibitors of nonreceptor tyrosine kinases (eg, genistein, Syk tyrosine kinase-selective antisense oligonucleotides) have been shown to regulate airway responses in asthma. Genistein suppressed antigen-induced bronchoconstriction and airway hyperresponsiveness in a guinea pig model of asthma [33], and a Lyn tyrosine kinase-binding peptide inhibitor blocked the influx of antigen-induced eosinophils in mice [34]. These observations suggest that dysfunctional STK10 derived from genetic variations plays an important role in allergic airway responses in asthma.

More importantly, there is a large body of evidence for the correlation between LOK deficiency and aspirin hypersensitivity. Prevention of prostaglandin synthesis by NSAIDs increases expression of ICAM-1, a substrate that interacts with LFA-1 via the ICAM-1/LFA-1 complex [14]. Upregulation of ICAM-1 also plays an important role in the pathogenesis of nasal polyps in aspirin-hypersensitive patients [15]. In addition, activation of LFA-1 that is detected by binding of soluble ICAM-1 has been observed in the absence of LOK [13], indicating that the LOK deficiency encoded by *STK10* could affect aspirin intolerance in asthmatics.

In this study, the synonymous variant *rs2306961 A>G* (*K210K*) in exon 6 was infrequent in AIA patients, yet it had the most significant association signal with AIA. Despite the lack of a direct functional analysis, a potential explanation for the association is suggested by differential codon usage, which could affect expression of *STK10* in AIA patients. Although codon usage varies with tissue type, it has not been observed in the epithelia of the respiratory tract. Transfer RNAs of Lys_CTT are more commonly expressed than those

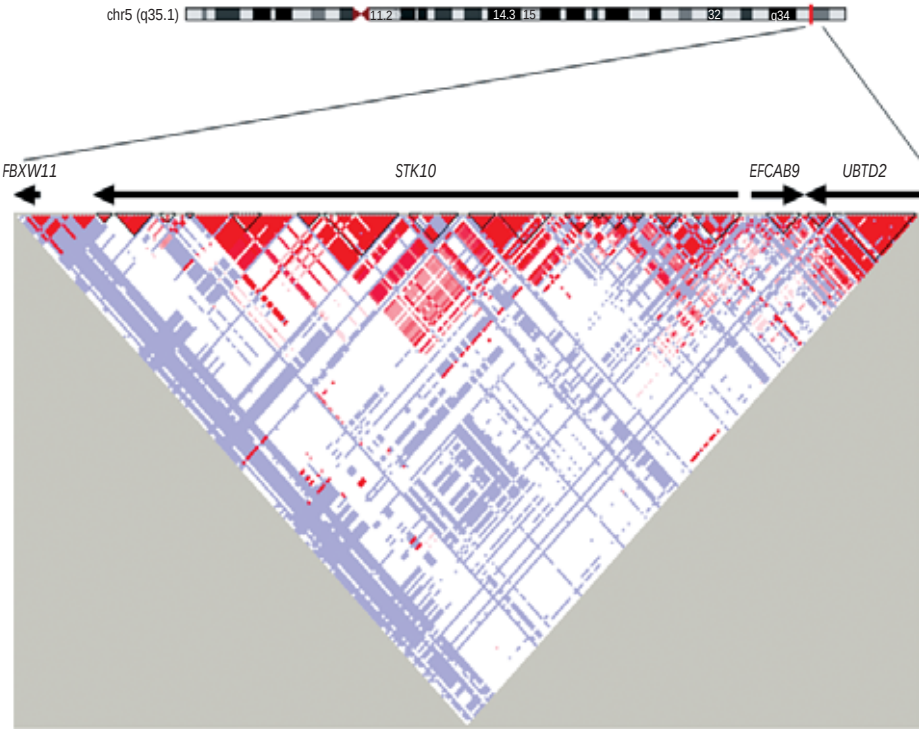

Figure 3. LD plot nearby the *STK10* gene. LDs near *STK10* in Asian populations (Chinese and Japanese) are analyzed from the International HapMap Project (http://hapmap.ncbi.nlm.nih.gov/). LD coefficient (D') among SNPs of *FBXW11*, *STK10*, *EFCAB9*, and *UBTD2* are shown. LD indicates linkage disequilibrium; SNP, single-nucleotide polymorphism.

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Table 6. Comparison of Minor Allele Frequencies of *STK10* SNPs Among Korean AIA/ATA Patients and Controls From Other Populations[a]

		MAF (Korean)		*P* Value			MAF			
SNP ID	Position	AIA	ATA	Codominant	Dominant	Recessive	CEU	HCB	JPT	YR1
rs6872832 A>T	Intron1	0.387	0.360	0.45	0.04	0.12	0.145	0.263	0.293	0.457
rs2172048 T>C	Intron1	0.402	0.394	0.90	0.07	0.03	0.417	0.278	0.378	0.833
rs2101595 G>A	Intron1	0.399	0.397	0.91	0.12	0.02	0.373	0.273	0.360	0.778
rs3797326 A>G	Intron1	0.390	0.393	0.82	0.19	0.03	0.367	0.311	0.367	0.817
rs6892515 G>A	Intron1	0.365	0.378	0.60	0.23	0.007	0.356	0.289	0.337	0.731
rs4868146 G>A	Intron2	0.206	0.274	0.04	0.06	0.18	0.283	0.311	0.200	0.667
rs3776752 A>G	Intron2	0.188	0.264	0.02	0.06	0.05	0.250	0.333	0.200	0.237
rs6892814 G>A	Intron2	0.163	0.234	0.01	0.03	0.06	0.333	0.222	0.178	0.592
rs7723657 T>C	Intron2	0.209	0.273	0.04	0.03	0.37	0.441	0.268	0.233	0.776
rs9313577 A>G	Intron2	0.209	0.270	0.04	0.03	0.41	0.408	0.256	0.189	0.767
rs3776759 G>A	Intron2	0.150	0.213	0.02	0.02	0.34	0.258	0.200	0.178	0.550
rs3756508 T>G	Intron2	0.206	0.265	0.05	0.04	0.46	0.433	0.256	0.233	0.350
rs2306961 A>G (K210K)	Exon6	0.113	0.191	0.008	0.004	0.63	0.267	0.144	0.156	0.308
rs3103590 C>T	Intron7	0.086	0.147	0.03	0.03	0.36	0.117	0.100	0.100	0.033

Abbreviations: AIA, aspirin-intolerant asthma; ATA, asthma-tolerance asthma; MAF, minor allele frequency.
[a]The MAFs of Caucasian (CEU), Chinese (HCB), Japanese (JPT), and African (YRI) individuals are obtained from dbSNP database of NCBI (http://www.ncbi.nlm.nih.gov/snp/).

of Lys_TTT in liver and spleen but not in testis (Table 3) [35]. This observation indicates that codon-mediated translational control between Lys_CTT and Lys_TTT might modulate expression of *STK10* in AIA patients. Further analysis for potential associations between *STK10* and other nearby genes revealed that *FBXW11*, *EFCAB9*, and *UBTD2* are located near *STK10*, although they do not have strong LD with *STK10* (Figure 3).

In comparison with controls of nonallergic subjects from other populations, the MAFs of several SNPs (*rs6872832 A>T*, *rs2172048 T>C*, *rs2101595 G>A*, *rs3797326 A>G*, *rs6892515 G>A*) among 14 significantly associated SNPs in Korean AIA/ATA subjects showed higher frequencies, even when compared to Asians (Table 6). Although further replications are needed to confirm these findings, we showed that human *STK10* polymorphisms might be associated with AIA in a Korean population. Transcriptional and translational alterations of *STK10* derived from its genetic variations might be correlated with the ICAM-1/LFA-1 pathway in the development of AIA. Our preliminary findings have established a new connection between *STK10* and aspirin hypersensitivity in asthmatics and could contribute to strategies for the treatment of aspirin hypersensitivity in these patients.

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