Association study between *TRIM26* polymorphisms and risk of aspirin-exacerbated respiratory disease

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Abstract. Aspirin-exacerbated respiratory disease (AERD) is a clinical syndrome that is characterized by nasal polyposis, general symptoms of asthma and sensitive response to non-steroidal anti-inflammatory drugs (NSAIDs). Although the exact function of tripartite motif-containing 26 (*TRIM26*) still remains unknown, the gene functions in the immune response. Thus, we hypothesized that *TRIM26* polymorphisms may affect aspirin-induced bronchospasm and explored whether the gene can be a marker for diagnosis of AERD. To investigate our hypothesis that *TRIM26* may serve as a genetic marker for diagnosis of AERD, this study focused on demonstrating the associations between single nucleotide polymorphisms (SNPs) of the *TRIM26* gene and AERD. We genotyped 18 polymorphisms of *TRIM26* in a total of 189 asthmatics and examined their associations with the risk of AERD. We performed logistic analysis for obtaining P-values and regression analysis for demonstrating an association between the phenotype with FEV_1 and the genotype. We observed no associations between polymorphisms in *TRIM26* and the risk of AERD in both logistic and regression analyses. Although our results reveal a lack of association, the suggested functional role of *TRIM26* makes it a putative candidate gene for AERD. Thus, replications in other populations using larger samples may provide valuable information for AERD etiology.

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Introduction

Aspirin-exacerbated respiratory disease (AERD) is a disease that induces a severe clinical syndrome characterized by eosinophilic rhinosinusitis with nasal polyposis, general symptoms of asthma, and sensitive response upon uptake of non-steroidal antiinflammatory drugs (NSAIDs), including aspirin. The side effects of aspirin ingestion have been reported to be prevalent in 10-20% of asthmatic patients (1-3). Although the mechanisms of AERD are not fully understood, abnormal secretion of eicosanoids including leukotrienes by blockage of the arachidonic acid pathway by aspirin is regarded as a significant factor of AERD pathophysiology (4-6). The COX pathway is involved in the immune response by releasing leukotrienes in immune cells, such as mast cells and eosinophils (7-10). Indeed, this process has been implicated in the etiology of nasal polyposis, a symptom that affects around two thirds of patients with AERD. Moreover, the polyps are filled with mast cells and eosinophils due to high level secretion of the proinflammatory cysteinyl leukotrienes (cysLTs) (11).

The leukotrienes are important molecules in recruitment of other immune cells to the inflammation site, an event that is established by signaling cascades. In line with this, the protein motifs used in protein-protein interactions and DNA-binding activity are remarkable. The tripartite motif-containing 26 (*TRIM26*) contains three zinc-binding domains, RING, B-box type 1 and B-box type 2, and a coiled-coil region (12). Although the exact function of *TRIM26* still remains unknown, the protein may function in DNA binding through its motifs. To date, Reymond *et al* (13) have suggested that the TRIM family have partially overlapping functions with that of cellular compartmentalization and protein-protein interaction, processes that play relevant roles in recruitment of other proteins. Moreover,

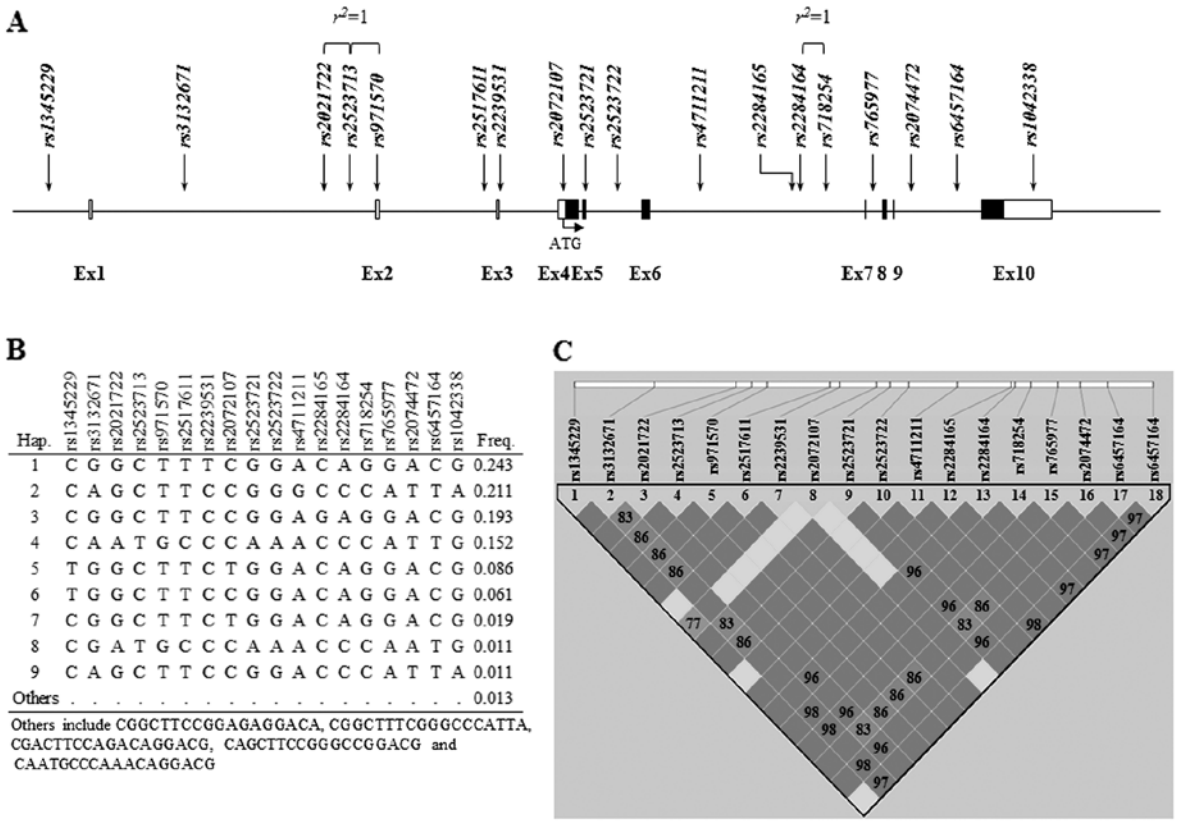

Figure 1. Schematic physical map, haplotypes and linkage disequilibrium (LD) plot of *TRIM26*. (A) Polymorphisms identified in *TRIM26*. Coding exons are marked by shaded blocks and 3'-untranslated region (UTR) by white blocks. The LD coefficients (r^2) are based on the genotypes of Korean samples. (B) Haplotypes of *TRIM26* in the Korean population. Only those with frequencies over 0.05 are shown. (C) LD coefficients (|D'| and r^2) among the selected SNPs based on the genotypes of all the study subjects in this study (n=189).

with its localization in the human histocompatibility complex (MHC) class I region, *TRIM26* is speculated to have a role in the immune response in relation to its predicted protein function.

As described above, *TRIM26* may possibly affect the risk of AERD by mediating immune responses. Therefore, we hypothesized that the polymorphisms in *TRIM26* may affect AERD susceptibility and we explored whether the gene can be a marker for diagnosis of AERD in a Korean asthmatic population.

Subjects and methods

Study subjects. The subjects used in the present study were recruited from the Asthma Genome Research Center comprising hospitals of Soonchunhyang, Chonnam, Chungbuk, the Seoul National and the Chung-Ang Universities in Korea. The diagnosis for all of the subjects was conducted following criteria for asthma according to the Global Initiative for Asthma (GINA) (14). Diagnosis of AERD was determined using a method that is slightly modified from our previous description (15). Additionally, we also performed aspirin challenge in subjects who have a history of aspirin hypersensitivity and those observed to have urticaria, nasal polyp and sinusitis. The AERD subjects are characterized with 20% or greater decreases in forced expiratory volume in 1 sec (FEV_1) or 15 to 19% decreases in FEV_1 with nasoocular or cutaneous reactions. In contrast, the aspirin-tolerant asthma (ATA) group have a rate of FEV_1 decline <15% without extrabronchial nasal or skin symptoms. The diagnosis tests were performed with consent of all subjects and the study protocols were approved by the Institutional Review Board of each hospital.

Single nucleotide polymorphism (SNP) selection and genotyping. We selected candidate polymorphic SNPs from the National Center for Biotechnology Information (NCBI; build 36) and the International HapMap Project (http://hapmap.ncbi.nlm.nih.gov/) databases based on the frequencies in Asian population and linkage disequilibrium (LD) status. For the validation of AERD risk association, we genotyped 18 SNPs in the *TRIM26* gene (Fig. 1A). Genotyping was carried out with 20 ng of genomic DNA using TaqMan assay in the ABI PRISM 7900HT sequence detection system software version 2.3 (Applied Biosystems, Foster City, CA, USA) in 93 AERD cases and 96 ATA controls with the assessment of data quality by duplicate DNAs (n=10).

Statistics. We calculated the LD in all pairs of biallelic loci using Lewontin's D' (|D'|) (16) and r^2 (Fig. 1). The PHASE algorithm (ver. 2.0) developed by Stephens *et al* (17) was used for inferring haplotypes. Associations of genotypes and haplotypes in the *TRIM26* gene with AERD were calculated using logistic analysis adjusted for age, gender, smoking status, atopy and body mass index (BMI) as covariates. We also performed linear regression analysis to determine the differences in the rates of decline in FEV_1 following aspirin challenge among the genotypes and haplotypes. Data were adjusted, managed and analyzed using Statistical Analysis System (SAS) version 9.1 (SAS Inc., Cary, NC, USA).

Table I. Clinical characteristics of case and control subjects.

Characteristics	AERD	ATA	P-value
Number of subjects	93	96	
Age (years), mean (range)	44.39 (17-73)	45.79 (15-77)	0.497
Age of onset (years), mean (range)	38.01 (0-70)	37.99 (5-73)	0.995
BMI (kg/m^2), mean ± SD	23.47±3.18	24.41±3.29	0.049
Blood eosinophil (%), mean ± SD	6.29±5.80	4.88±4.19	0.060
FVC %, predicted, mean ± SD	89.90±14.74	87.76±12.80	0.293
FEV_1 %, predicted, mean ± SD	86.63±16.74	88.26±17.04	0.509
PC_{20}, methacholine (mg/ml), mean ± SD	4.23±7.18	3.04±4.27	0.193
Total IgE (IU/ml), mean ± SD	321.65±623.31	309.54±426.04	0.878
Decline after aspirin challenge, mean ± SD	23.61±14.48	0.94±2.76	0.001
Gender (male/female)	32/61	24/72	0.156
Ex-smoker/current smoker (%)	15.63/9.38	6.45/12.90	0.219
Skin test (% positive)	61.46	56.99	0.532
ASA side effect (% positive)	26.67	8.42	0.001
Polyposis (% positive)	63.86	29.27	0.001

Age indicates age at first medical examination. AERD, aspirin-exacerbated respiratory disease; ATA, aspirin-tolerant asthma; BMI, body mass index; FVC, forced volume vital capacity; FEV_1, forced expiratory volume in 1 sec; PC_{20}, methacholine concentration causing 20% fall in FEV; ASA, acetylsalicylic acid (aspirin).

Table II. Allele information of *TRIM26* used in this study.

SNP ID	Allele change	Frequency	TF binding site	Splicing site (ESE/ESS)	miRNA	HWE	
						AERD	ATA
rs1042338	G>A	0.230	-	-	Y	0.197	0.102
rs1345229	C>T	0.384	Y	-	-	0.483	0.144
rs2021722	A>T	0.377	-	-	-	0.764	0.066
rs2072107	G>A	0.388	-	-	-	0.636	0.144
rs2074472	G>C	0.390	-	-	-	0.561	0.125
rs2239531	A>C	0.386	-	Y	-	0.328	0.144
rs2284164	C>G	0.195	-	-	-	0.175	0.994
rs2284165	A>G	0.214	-	-	-	0.066	0.049
rs2517611	G>A	0.164	-	-	-	0.202	0.040
rs2523713	G>A	0.168	-	-	-	0.190	0.060
rs2523721	C>T	0.104	-	Y	-	0.790	0.205
rs2523722	C>T	0.246	-	-	-	0.291	0.196
rs3132671	T>C	0.167	-	-	-	0.171	0.040
rs4711211	T>G	0.164	-	Y	-	0.202	0.040
rs6457164	C>T	0.166	-	-	-	0.190	0.040
rs718254	G>A	0.167	-	-	-	0.202	0.060
rs765977	G>A	0.377	-	-	-	0.452	0.066
rs971570	C>T	0.146	-	Y	-	0.603	0.257

TF, transcription factor; ESE, exonic splicing enhancer; ESS, exonic splicing silencer; AERD, aspirin-exacerbated respiratory disease; ATA, aspirin-tolerant asthma; HWE, Hardy-Weinberg Equilibrium; Y, yes.

Results

In present study, we recruited a total of 189 subjects including 93 AERD patients as cases and 96 ATA patients as controls. Among the diagnostic factors, airways decline after aspirin challenge showed obvious differences after comparing each group, with 23.61±14.48 for the AERD cases and 0.94±2.76 for the ATA group (P=0.001). The case group also showed a

Table III. Logistic analysis for validation between polymorphisms in *TRIM26* and risk of AERD.

	MAF		Co-dominant			Domiant			Recessive		
Loci	AERD	ATA	OR (95% CI)	P-value	P^{corr}	OR (95% CI)	P-value	P^{corr}	OR (95% CI)	P-value	P^{corr}
rs1042338	0.209	0.250	0.79 (0.48-1.32)	0.37	-	0.62 (0.34-1.13)	0.12	-	2.24 (0.54-9.34)	0.27	-
rs6457164	0.366	0.401	0.83 (0.54-1.29)	0.40	-	0.65 (0.35-1.19)	0.16	-	1.16 (0.49-2.71)	0.74	-
rs2074472	0.368	0.385	0.92 (0.58-1.44)	0.70	-	0.73 (0.40-1.35)	0.31	-	1.39 (0.56-3.42)	0.48	-
rs765977	0.375	0.401	0.87 (0.56-1.35)	0.53	-	0.70 (0.38-1.29)	0.26	-	1.18 (0.50-2.77)	0.71	-
rs718254	0.374	0.405	0.85 (0.54-1.32)	0.46	-	0.66 (0.36-1.23)	0.19	-	1.19 (0.51-2.80)	0.69	-
rs2284164	0.371	0.401	0.85 (0.55-1.32)	0.47	-	0.65 (0.35-1.19)	0.16	-	1.26 (0.54-2.92)	0.59	-
rs2284165	0.214	0.177	1.31 (0.76-2.27)	0.33	-	1.48 (0.80-2.73)	0.21	-	0.67 (0.11-4.14)	0.66	-
rs4711211	0.188	0.240	0.74 (0.44-1.24)	0.26	-	0.54 (0.30-1.00)	0.05	NS	3.35 (0.65-17.30)	0.15	-
rs2523722	0.172	0.156	1.06 (0.61-1.83)	0.84	-	1.36 (0.72-2.57)	0.35	-	0.16 (0.02-1.43)	0.10	-
rs2523721	0.176	0.161	1.04 (0.60-1.80)	0.89	-	1.31 (0.69-2.48)	0.40	-	0.16 (0.02-1.48)	0.11	-
rs2072107	0.092	0.115	0.75 (0.37-1.50)	0.41	-	0.68 (0.33-1.41)	0.29	-	-	-	-
rs2239531	0.258	0.234	1.22 (0.74-2.01)	0.43	-	1.05 (0.57-1.93)	0.88	-	3.09 (0.78-12.34)	0.11	-
rs2517611	0.177	0.156	1.10 (0.64-1.90)	0.74	-	1.43 (0.75-2.70)	0.28	-	0.16 (0.02-1.43)	0.10	-
rs971570	0.172	0.156	1.06 (0.61-1.83)	0.84	-	1.36 (0.72-2.57)	0.35	-	0.16 (0.02-1.43)	0.10	-
rs2523713	0.176	0.156	1.09 (0.63-1.89)	0.76	-	1.40 (0.74-2.67)	0.30	-	0.16 (0.02-1.48)	0.11	-
rs2021722	0.172	0.161	1.01 (0.58-1.74)	0.97	-	1.27 (0.67-2.40)	0.46	-	0.16 (0.02-1.43)	0.10	-
rs3132671	0.368	0.385	0.91 (0.58-1.42)	0.68	-	0.69 (0.38-1.27)	0.24	-	1.50 (0.62-3.65)	0.37	-
rs1345229	0.130	0.161	0.71 (0.38-1.31)	0.27	-	0.67 (0.35-1.29)	0.23	-	1.16 (0.07-19.64)	0.92	-
TRIM26_ht4	0.161	0.141	1.14 (0.63-2.08)	0.66	-	1.38 (0.72-2.66)	0.33	-	-	-	-
TRIM26_ht5	0.078	0.094	0.77 (0.36-1.64)	0.49	-	0.69 (0.31-1.52)	0.35	-	-	-	-
TRIM26_ht6	0.056	0.068	0.74 (0.30-1.83)	0.52	-	0.74 (0.30-1.83)	0.52	-	-	-	-

P-values were adjusted with initial diagnosed age, gender, smoking status and atopy. AERD, aspirin-exacerbated respiratory disease; ATA, aspirin-tolerant asthma; MAF, minor allele frequency; OR, odds ratio; CI, confidence interval; NS, not significant; P^{corr*}, P-values were corrected by the effective number obtained using SNPSpD (http://genepi.qimr.edu.au/general/ daleN/SNPSpD/), which is based on the spectral decomposition (SpD) of matrices of pair-wise LD between SNPs.

Table IV. Regression analysis for validation between allele dose effect in *TRIM26* and phenotype with FEV_1.

Loci	C/C	C/R	R/R	*Pa*	Pa^{corr}	*Pb*	Pb^{corr}	*Pc*	Pc^{corr}
rs1042338	110 (12.41±14.81)	68 (10.60±15.88)	9 (15.53±17.39)	0.85	-	0.59	-	0.49	-
rs6457164	70 (12.21±15.78)	93 (11.92±15.37)	26 (12.40±14.68)	0.91	-	0.93	-	0.93	-
rs2074472	69 (11.81±15.92)	95 (11.92±15.20)	23 (13.00±15.42)	0.83	-	0.88	-	0.84	-
rs765977	68 (12.00±15.96)	94 (11.98±15.30)	26 (12.40±14.68)	0.99	-	0.98	-	0.95	-
rs718254	67 (12.24±15.95)	93 (11.92±15.37)	26 (12.40±14.68)	0.90	-	0.91	-	0.94	-
rs2284164	70 (12.21±15.78)	92 (12.03±15.41)	27 (11.98±14.56)	0.85	-	0.93	-	0.82	-
rs2284165	119 (10.37±14.85)	63 (15.68±16.32)	5 (5.00±7.38)	0.17	-	0.05	NS	0.27	-
rs4711211	116 (13.25±15.18)	65 (9.37±15.18)	8 (17.35±17.65)	0.46	-	0.21	-	0.34	-
rs2523722	133 (11.50±16.04)	50 (14.55±13.92)	6 (4.73±5.57)	0.87	-	0.49	-	0.18	-
rs2523721	130 (11.50±16.14)	51 (14.18±14.04)	6 (4.73±5.57)	0.98	-	0.60	-	0.19	-
rs2072107	150 (12.57±15.73)	37 (8.78±11.99)	1 (54.00)	0.61	-	0.30	-	0.006	NS
rs2239531	106 (12.64±15.50)	70 (11.61±16.02)	11 (8.56±10.31)	0.59	-	0.76	-	0.47	-
rs2517611	132 (11.43±16.08)	51 (14.68±13.81)	6 (4.73±5.57)	0.82	-	0.44	-	0.18	-
rs971570	133 (11.50±16.04)	50 (14.55±13.92)	6 (4.73±5.57)	0.87	-	0.49	-	0.18	-
rs2523713	131 (11.38±16.13)	50 (14.55±13.92)	6 (4.73±5.57)	0.84	-	0.46	-	0.19	-
rs2021722	132 (11.62±16.04)	51 (14.18±14.04)	6 (4.73±5.57)	0.98	-	0.63	-	0.18	-
rs3132671	70 (11.94±15.84)	93 (11.97±15.30)	24 (12.50±15.28)	0.95	-	0.95	-	0.97	-
rs1345229	135 (12.18±14.59)	51 (10.67±15.81)	2 (25.00±41.01)	0.74	-	0.53	-	0.22	-
TRIM26_ht4c	133 (11.34±16.06)	50 (14.36±13.90)	3 (1.67±2.52)	0.64	-	0.40	-	0.24	-
TRIM26_ht5c	155 (12.34±15.56)	30 (8.81±12.89)	1 (54.00)	0.76	-	0.39	-	0.006	NS
TRIM26_ht6c	163 (12.02±14.95)	23 (11.83±19.04)	-	0.85	-	0.85	-	-	-

C/C, common allele/common allele; C/R, common allele/rare allele; R/R, rare allele/rare allele; NS, not significant; *Pa*, *Pb* and *Pc*, P-values of co-dominant model, dominant model and recessive model, respectively.

higher positive rate (26.67%) of side effects after ingestion of ASA compared to the ATA control group (8.42%). For other diagnostic factors of AERD, the positive rate of polyposis was observed to be 63.86% in AERD subjects and 29.27% in ATA asthmatics (P=0.001). Except for the three characteristics described above, other diagnostic factors of AERD showed no significant differences between the two groups. All the information of the study subjects are displayed in Table I.

For the analysis, we performed genotyping with 18 polymorphisms in a total of 189 subjects. Information about the 18 polymorphisms including allele change, minor allele frequencies (MAF), position and also the predicted function of polymorphisms using the web based software (snpinfo.niehs.nih.gov/snpfunc.htm) are listed in Table II. The prediction method shows that one polymorphism is associated with microRNA binding and another allele is included in the transcription binding site. In addition, among the polymorphisms in the exonic region, four SNPs affecting the splicing association site were identified using the exonic splicing enhancer (ESE) and exonic splicing silencer (ESS).

Initial logistic analysis revealed that the one polymorphism, *rs4711211*, is associated with the risk of AERD. The variant has a P-value of 0.05 and an odds ratio (OR) of 0.54 with a 0.30-1.00 confidence interval (CI) in the dominant model. However, the signal disappeared after multiple testing corrections using the SNPSpD software. The other polymorphisms showed no associations with the risk of AERD in all three models of logistic analysis. Results of logistic analysis are displayed in Table III. Further regression analysis was conducted which focused on the FEV_1 phenotype, and results are similar with the logistic analysis. Two SNPs, *rs2284165* and *rs2072107*, showed associations with decline of FEV_1 by aspirin provocation. Both SNPs show P<0.05 in the initial analysis, which disappeared after multiple testing corrections. For the haplotype analysis, only one haplotype, *TRIM26_ht5*, shows significance in the regression analysis via a rare allele homozygote. However, the haplotype also failed to reach the threshold of significance after multiple comparisons. Results of the regression analysis are listed in Table IV.

Discussion

In the present study, we examined whether *TRIM26* may serve as a genetic marker for the diagnosis of AERD. To test our hypothesis, we obtained P-values for the association between *TRIM26* genetic variations and the risk of AERD. Although the significant signals disappeared after multiple testing corrections were performed, 3 of the 18 SNPs showed association signals in one of the two analyses. To date, a previous study has reported that MHC region polymorphisms, including *TRIM27* from the *TRIM* gene family that is implicated in immune-associated diseases, showed high association with systemic lupus erythematosus (SLE) (18). From analysis of 1,974 SNPs for finding association with SLE, 12 SNPs included in this investigation have been found to be associated with SLE (18). Although SLE and AERD occur in different sites of the human body, *TRIM26* has been found to be expressed in various tissues including lung tissue (12). In line with this, although mechanisms of AERD are not fully understood, respiratory inflammation by eosinophil infiltration in airway tissues has been regarded as one of the causes of AERD. These research reports support an important role of *TRIM26* in inflammation as a factor in AERD pathogenesis.

The *TRIM* gene family members have a RING domain and are suggested to have a role as intracellular molecular scaffolds (19). In the last decade, many researchers have reported that proteins linked with scaffolds are important in the pathogenesis of asthma (20,21). In addition, it is known that protein scaffolds associated with the TNF receptor affect the cyclooxygenase pathway, one of the key mechanisms in AERD and in the production of prostaglandin E2 (22). The intracellular scaffold proteins form protein complexes that affect airway remodeling and are needed in triggering downstream signaling to recruit inflammation associated cells, such as mast cells (23-25). These reports suggest that *TRIM26* may be associated with the risk of AERD and thus, more investigations on the role of *TRIM26* in AERD are needed.

Another suggested functional role of *TRIM26* is related to the ubiquitin protein ligase (26,27). It has been demonstrated that ubiquitination is closely related with airway inflammation, as demonstrated by an experiment using the inhibitor of IκB ubiquitination in a mouse model (28). Moreover, our previous study showed that polymorphisms in ubiquitin-protein ligase E3C (*UBE3C*) are significantly associated with pathogenesis of AERD (29). According to a previous study, IκB kinase ubiquitination in the classical NF-κB activation pathway is important for inflammation and proteolysis of IκB, leading to translocation of NF-κB to nucleus. The signaling pathway triggers production of cytokines and chemokines and causes airway inflammation by recruiting eosinophils and lymphocytes (28,30). Thus, although our results showed no association between polymorphisms in *TRIM26* and risk of AERD, the reports described above support a possible association of *TRIM26* in AERD pathogenesis. Furthermore, prediction methods show that four polymorphisms (*rs2239531*, *rs2523721*, *rs4711211* and *rs971570*) in *TRIM26* play certain roles in splicing-associated sites, thereby changing the protein expression pattern. Although the genetic distribution of Koreans is similar to that of Japanese and Chinese populations, it still differs from that of other populations. Thus, extrapolation of the present finding in other populations, such as Caucasians using larger sample sizes are needed.

In conclusion, the results of the present study show a lack of association between *TRIM26* polymorphisms that are located in the MHC region and the risk of AERD in both logistic and regression analyses. However, the results may be valuable for further studies investigating the association between genes that are located in the MHC region and respiratory disease. Therefore, findings from this study may aid in a better understanding of the etiology of AERD and other bronchial diseases.

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