

Association analysis of tapasin polymorphisms with aspirin-exacerbated respiratory disease in asthmatics

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Background Aspirin-exacerbated respiratory disease (AERD) is characterized by the development of airway obstruction in asthmatic individuals following the ingestion of aspirin or other nonsteroidal anti-inflammatory drugs. *TAPBP* (TAP-binding protein, tapasin) is upregulated by eicosanoids, which act as potent inflammatory molecules in aspirin-related reactions. Thus, functional alterations in the *TAPBP* gene may contribute toward AERD.

Objectives We examined the relationship between the single nucleotide polymorphisms on the *TAPBP* gene and AERD.

Materials and methods A group of asthmatic patients ($n=1252$) underwent the oral aspirin challenge. Oral aspirin challenge reactions were categorized into two groups as follows: 15% or greater decreases in forced expiratory volume in 1 s or naso-ocular and skin reactions (AERD), or 15% or less decreases in forced expiratory volume in 1 s without naso-ocular and skin reactions (aspirin-tolerant asthma). Five single nucleotide polymorphisms of the *TAPBP* gene were genotyped.

Results Logistic regression analysis showed that the minor allele frequencies of *TAPBP* rs2071888 C>G (Thr260Arg) on exon 4 ($P>0.05$), which was in absolute linkage disequilibrium with rs1059288 T>C on 3'UTR, were significantly higher in the AERD group than in the aspirin-tolerant asthma group, and the P values remained significant after multiple comparisons ($P_{\text{corr}}=0.006$, odds

ratio: 1.37, 95% confidence interval: 1.11–1.69, additive model; $P_{\text{corr}}=0.009$, odds ratio: 1.52, 95% confidence interval: 1.14–2.03, dominant model). Alpha-helical wheel plotting showed that 260Arg had greater hydrophilic helical property than 260Thr.

Conclusion *TAPBP* polymorphisms may play a role in the development of AERD. *Pharmacogenetics and Genomics* 23:341–348 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Keywords: aspirin-exacerbated respiratory disease, aspirin-tolerance asthma, single nucleotide polymorphism, TAP-binding protein

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Introduction

Aspirin-exacerbated respiratory disease (AERD) involves bronchoconstriction and nasal obstruction in asthmatic individuals following the ingestion of aspirin or other nonsteroidal anti-inflammatory drugs. This syndrome is characterized by aspirin hypersensitivity, bronchial asthma, nasal polyposis, and chronic hyperplastic eosinophilic sinusitis [1,2]. Although the pathophysiology of AERD has been closely linked to the overproduction of cysteinyl leukotrienes [3], recent genetic studies have reported that some genes that control immune responses, such as interleukin 4 [4], T-BOX [5], high-affinity immuno-

globulin E (IgE) receptors [6], toll-like receptor 3 [7], and NLRP3 [8], are associated with the development of AERD. Immune responses are tightly controlled by the major histocompatibility complex (MHC) molecules. The expression of MHC class I molecules on the cell surface is critical for recognition by cytotoxic T lymphocytes [9]. Before they can be transported to the cell surface, MHC class I molecules associate with their peptide ligands in the endoplasmic reticulum (ER) of the cell [10]. Within the ER, numerous proteins assist in the appropriate assembly and folding of MHC class I molecules. These include the heterodimeric transporters associated with antigen processing (*TAP1* and *TAP2*), *TAPBP* (TAP-binding protein, also known as tapasin), *Erp57*, and ER chaperones such as calreticulin and calnexin. *TAPBP* is required for the transport of antigenic

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peptides across the ER membrane because the *TAPBP* stabilizes empty MHC class I molecules for the binding of high-affinity peptides [11].

The Tap (*TAP1* and *TAP2*) immunodeficiency syndrome is characterized by recurrent bacterial infection in the upper and lower respiratory tract [12]. *TAPBP* gene-deficient mice have decreased CD8⁺ T-cell responses against viral infections and other processes that depend on the expression of cell surface classical MHC class I molecules [13,14]. Because mutations in *TAPBP* impair the translocation of peptides from the cytosol into the ER [15], single nucleotide polymorphisms (SNPs) on the *TAPBP* gene likely increase the risk of immune disorders. SNP of *TAP1* was found to be associated with atopy [16]. In addition, we have found that SNPs and haplotypes of *TAP1* and *TAP2* are associated with aspirin-induced bronchospasm [17]. However, SNPs of the *TAPBP* gene have not been evaluated with respect to the development of AERD. In the present study, we carried out an association analysis of SNPs on *TAPBP* between 255 individuals with AERD and 997 individuals with aspirin-tolerant asthma (ATA).

Materials and methods

Participants

Nine-hundred and ninety-seven ATA and 255 AERD patients were recruited from the Asthma Genome Research Center, which comprises eight university hospitals in Korea. All patients were Korean and provided informed consent to participate in the study. All patients were diagnosed by physicians and fulfilled the criteria for asthma according to the Global Initiative for Asthma guidelines [18]. All patients had a history of dyspnea and wheezing during the previous 12 months, and one of the following: (a) more than 15% increase in forced expiratory volume in 1 s (FEV₁) or more than 12% increase plus 200 ml following inhalation of a short-acting bronchodilator, (b) less than 10 mg/ml PC20 methacholine, and (c) more than 20% increase in FEV₁ following 2 weeks of treatment with inhaled or systemic corticosteroids. Twenty-four commonly inhaled allergens were used in a skin-prick test. Total IgE was measured using the CAP system (Pharmacia Diagnostics, Uppsala, Sweden). Atopy was defined as a wheal reaction with a diameter of 3 mm or greater than the reaction to histamine.

In the questionnaires designed to identify aspirin hypersensitivity, questions related to five specific elements of aspirin hypersensitivity and nonsteroidal anti-inflammatory drugs (dyspnea, wheezing, nasal blockage, skin eruption, loss of consciousness) were incorporated. The asthmatic patients had experienced no exacerbation of asthma or respiratory tract infection in the 6 weeks preceding oral aspirin challenge (OAC). OAC was performed in all patients with increasing doses of aspirin using methods slightly modified from those described

previously [19,20]. Briefly, patients with a history of aspirin hypersensitivity were administered a dose of 30 mg and those with no history were started on 100 mg of aspirin orally. Symptoms, external signs (urticaria, angioedema, and rhinorrhea), blood pressure, and FEV₁ were documented every 30 min for a period of 1.5 h. In the absence of any symptoms or signs suggestive of adverse reaction, 100 mg of aspirin was administered and the same measurements were repeated every hour, with doses of 450 mg administered until the patient developed a reaction. If no reaction occurred within 4 h after the final dose, the test was deemed negative. Aspirin-induced bronchospasms, as reflected by a decrease (%) in FEV₁, were calculated as the prechallenge FEV₁ minus the postchallenge FEV₁ divided by the prechallenge FEV₁. OAC reactions were categorized into two groups: (a) a 15% or greater decrease in FEV₁ or naso-ocular reactions (AERD) and (b) a decrease of less than 15% in FEV₁ without naso-ocular or cutaneous reactions (ATA). Peripheral blood buffy coat was collected before OAC. The study protocol was approved by the Ethics Committee of the Soonchunhyang University Bucheon Hospital.

Genotyping of *TAPBP* polymorphisms

Five polymorphisms found in the *TAPBP* gene in the National Center for Biotechnology Information (Build 36) were selected for this study considering their linkage disequilibrium (LD) status ($r^2 > 0.98$) and minor allele frequencies (MAF > 0.05). Primers and probes were designed for TaqMan [21]. Primer Express (Applied Biosystems, Foster City, California, USA) was used to design both the PCR primers and the MGB TaqMan probes. One allelic probe was labeled with 6-carboxy-fluorescein dye and the other with fluorescent VIC dye. PCRs were run in TaqMan Universal Master mix without uracil-DNA glycosylase (Applied Biosystems) at PCR primer concentrations of 900 nmol/l and TaqMan MGB-probe concentrations of 200 nmol/l. Reactions were performed in a 384-well plate with a total reaction volume of 5 μ l using 20 ng of genomic DNA. Plates were then placed in a thermal cycler (PE 9700; Applied Biosystems) and heated at 50°C for 2 min and 95°C for 10 min, followed by 40 amplification cycles (95°C for 15 s and 60°C for 1 min). TaqMan assay plates were then transferred to a Prism 7900HT instrument (Applied Biosystems) and the fluorescence intensities in each well were read. Fluorescence data files from each plate were analyzed using automated software (SDS 2.1; SABiosciences, Frederick, Maryland, USA). Probe information is shown in Supplementary Table 1 (<http://links.lww.com/FPC/A595>).

Statistical analysis

We applied two widely used measures of LD to all pairs of biallelic loci: Lewontin's D' ($|D'|$) and r^2 [22]. Haplotypes for each individual were inferred using the PHASE

algorithm [ver. 2.0 (<http://www.stat.washington.edu/stephens/software.html>)], developed by Stephens *et al.* [23]. Genotype and haplotype distributions were analyzed using logistic models with age (continuous value), sex (male = 0, female = 1), smoking status (nonsmoker = 0, exsmoker = 1, smoker = 2), and atopy (absence = 0, presence = 1) as covariates. Differences between the rates of FEV₁ decrease following aspirin challenge and the genotypes and haplotypes were examined using a linear regression model. Statistical data were managed and analyzed using SAS version 9.1 (SAS Inc., Cary, North Carolina, USA) and SPSS version 11.0 (SPSS Inc., Chicago, Illinois, USA). To correct *P* values, the effective number of independent markers in *TAPBP* was calculated using SNPSpD software (<http://genepi.gimr.edu.au/general/daleN/SNPSpD>) [24]. This program is based on the spectral decomposition of matrices of pairwise LD between SNPs. The corrected *P* value (P_{corr}) was calculated as *P* value $\times$ 1.982. Genotypes were assigned codes of 0, 1, and 2 to a common homozygote, a heterozygote, and a rare homozygote in the additive model, respectively. The dominant model was designed as 0, 1, and 1, and the recessive model was designed as 0, 0, and 1, respectively. The additive model was designed as 0, 1, and 2. In the additive model, the odds ratio was expressed per difference in the number of rare alleles.

Helical wheel prediction

A helical wheel is a type of plot or visual representation used to illustrate the properties of alpha-helices in proteins. The alpha-helical wheel structure of *TAPBP* peptides was predicted using a Java applet (<http://cti.itc.Virginia.EDU/~cmg/Demo/wheel/wheelApp.html>). Motifs including 260Arg and nearby 260Arg for the functional site were identified using a prediction program (<http://ehm.eu.org/index.html>).

Results

Characteristics of the study participants

The clinical characteristics of the study participants are summarized in Table 1. Significant differences in the mean age, age of onset, and BMI were present between the AERD and the ATA groups ($P < 0.001$), although the total IgE level, PC20 methacholine (mg/ml), and blood eosinophil count (%) were not significantly different between the subgroups ($P > 0.05$). The FEV₁ decrease by aspirin provocation was significantly higher in the AERD group than in the ATA group ($P < 0.001$). The history of aspirin hypersensitivity was eight times higher in AERD patients compared with those with ATA ($P < 0.001$). In addition, the incidence of nasal polyposis in AERD patients was ~ 2.3 times higher than that in the ATA controls ($P < 0.001$).

Polymorphisms, LD, and haplotypes of *TAPBP*

A total of five common SNPs [two SNPs in 5'UTR, one SNP in 3'UTR, one SNP in intron, and one nonsynon-

ymous SNP in exon 4 (Thr260Arg)] were selected from the National Center for Biotechnology Information database (Build 36) on the basis of their LD status and MAF in the Asian population (Fig. 1a). Five SNPs were genotyped in 255 AERD patients and 997 in the ATA patients. All SNPs showed no departure from HWE ($P > 0.05$, Supplementary Table 2, <http://links.lww.com/FPC/A595>). The MAFs of the five SNPs in the AERD and ATA groups are summarized in Supplementary Table 2 (<http://links.lww.com/FPC/A595>). The LD coefficients ($|D'|$ and r^2) for the *TAPBP* polymorphisms were calculated for all study participants (Fig. 1b). Pairwise comparisons of the selected SNPs showed that absolute LD ($|D'| = 1$ and $r^2 = 1$) was present between rs2071888 (Fig. 1c). Among the inferred haplotypes in *TAPBP*, only one common haplotype (ht3) was used for further statistical analysis because rs2071888 and rs2239841 were almost equivalent to ht1 and ht2. Haplotypes with frequencies below 0.05 were excluded from haplotype-based association analyses with AERD.

Association of *TAPBP* polymorphisms with the risk of AERD

All of the SNPs and one haplotype (ht3) were analyzed for association with AERD using logistic models (Table 2). Association analysis showed that two SNPs, *TAPBP* rs2071888, were significantly associated with AERD in codominant and dominant models. The number of patients with rare alleles of *TAPBP* rs2071888 was significantly greater among AERD patients than the ATA patients in the dominant model (63.2 vs. 53.6%, $P_{\text{corr}} = 0.009$, odds ratio: 1.52, Table 2). No association of other SNPs with haplotype-3 was observed. Given that the FEV₁ decrease after aspirin provocation is the most important indicator of aspirin intolerance in asthmatics, we investigated the association between *TAPBP* SNPs and FEV₁ decrease after aspirin challenge using a linear regression model (Table 3). The patients who had a rare allele of rs2071888 showed a greater decrease in FEV₁ induced by aspirin provocation than patients with homozygotes of the common allele; for example, 8.18% of CG + GG versus 6.36% of CC in rs2071888 ($P_{\text{corr}} = 0.01$) (Fig. 2).

Alpha-helix prediction of *TAPBP* (Thr260Arg)

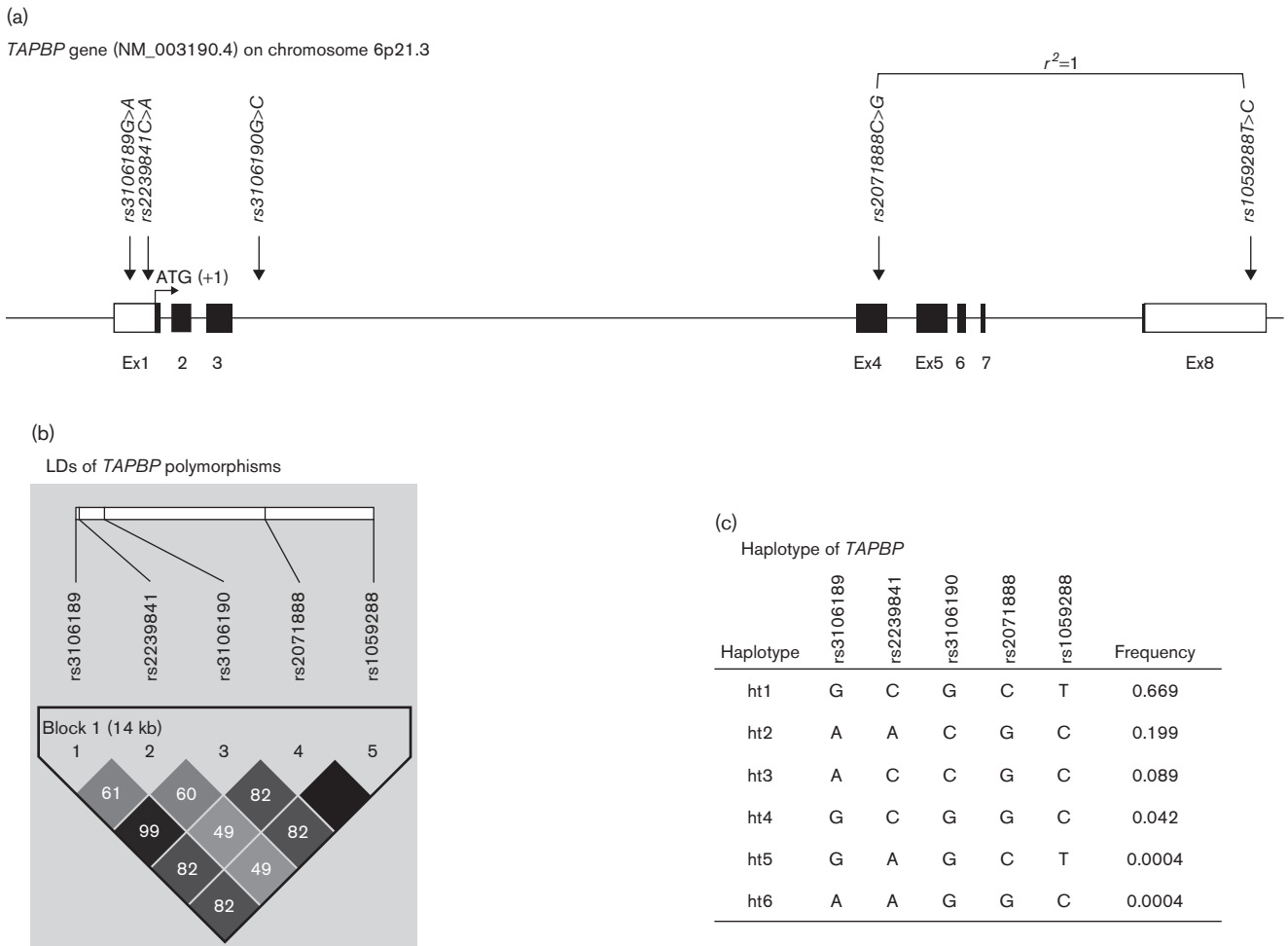
Alpha-helical wheel plotting showed that 260Arg had a greater hydrophilic helical property than 260Thr because a positively charged amino acid (Arg) is more hydrophilic than a polar, uncharged amino acid (Thr). The surfaces of proteins that must bind to negatively charged molecules are rich in positively charged amino acids such as arginine (R), whereas proteins binding to positively charged molecules have surfaces rich in negatively charged chains, such as glutamate and aspartate (Fig. 2).

Table 1 Clinical profiles of aspirin-induced asthma patients and controls

Clinical profile	AERD	ATA	P value
Number	255	997	–
Age [mean (range)] (years)	40.6 (16–73)	44.9 (11–77)	0.0001*
Onset of age [mean (range)]	34.4 (1–70)	38.8 (1–76)	0.0001*
Sex (male/female)	103/152	378/619	0.512
Exsmoker/current smoker (%)	8.3/11.8	16.6/13.6	0.017*
BMI (kg/m ²)	23.46±3.41	24.38±3.59	0.0003*
Blood eosinophil (%)	5.73±5.24	5.61±5.22	0.745
FVC%, predicted	85.74±17.07	83.18±17.93	0.071
FEV ₁ %, predicted	84.48±18.16	83.45±19.92	0.434
% decrease of FEV ₁ by aspirin challenge	22.82±15.36	3.83±4.90	0.0001*
PC20, methacholine (mg/ml)	5.47±8.20	6.35±8.46	0.156
Total IgE (IU/ml)	346.3±595.7	388.6±620.9	0.328
History of aspirin hypersensitivity (%)	64.7	8	0.0001*
Presence of nasal polyp (%)	52.85	22.56	0.0001*

Values are mean±SE.
AERD, aspirin-exacerbated respiratory disease; ATA, aspirin-tolerant asthma; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; IgE, immunoglobulin E.
*P value less than 0.05 is regarded significant.

Fig. 1



Gene map, LD, and haplotypes of the *TAPBP* gene. (a) Gene map and SNPs of *TAPBP* on chromosome 6p21.3. Coding exons are indicated by black blocks, and the 5' and 3' untranslated regions by white blocks. The base at which translation begins is denoted as nucleotide +1. (b) LD coefficients (r^2) among SNPs. (c) Haplotypes of *TAPBP* SNPs. LD, linkage disequilibrium; SNPs, single nucleotide polymorphisms; *TAPBP*, TAP-binding protein.

Table 2 Comparisons of genotype and haplotype distributions of *TAPBP* between the patients with AERD and those with ATA

Loci	Position	Genotype	N (%)		Codominant			Dominant			Recessive		
			AERD	ATA	OR (95% CI)	P	P _{corr}	OR (95% CI)	P	P _{corr}	OR (95% CI)	P	P _{corr}
rs3106189	5'UTR	GG	111 (44.2)	503 (51.0)	1.24 (0.99–1.54)	0.06	0.11	1.33 (1.00–1.76)	0.05	0.10	1.25 (0.75–2.07)	0.40	0.78
		AG	118 (47.0)	412 (41.8)									
		AA	22 (8.8)	71 (7.2)									
rs2239841	5'UTR	CC	152 (60.6)	633 (63.9)	1.17 (0.91–1.49)	0.23	0.45	1.16 (0.87–1.55)	0.31	0.62	1.45 (0.71–2.97)	0.31	0.62
		AC	88 (35.1)	328 (33.1)									
		AA	11 (4.4)	29 (2.9)									
rs3106190	Intron 3	GG	113 (44.7)	508 (51.2)	1.24 (0.99–1.54)	0.06	0.12	1.31 (0.99–1.74)	0.06	0.12	1.27 (0.76–2.10)	0.36	0.72
		CG	118 (46.6)	414 (41.7)									
		CC	22 (8.7)	70 (7.1)									
rs2071888	Exon 4	CC	93 (36.8)	459 (46.4)	1.37 (1.11–1.69)	0.003	0.006	1.52 (1.14–2.03)	0.004	0.009	1.45 (0.95–2.23)	0.09	0.17
		CG	127 (50.2)	435 (44.0)									
		GG	33 (13.0)	95 (9.6)									
ht3	–	–/–	204 (81.0)	829 (83.8)	1.27 (0.91–1.76)	0.16	0.31	1.28 (0.89–1.83)	0.19	0.37	1.72 (0.51–5.82)	0.39	0.76
		ht3/–	44 (17.5)	152 (15.4)									
		ht3/ht3	4 (1.6)	8 (0.8)									

The effective number of independent markers for correction in *TAPBP* was 1.982.

AERD, aspirin-exacerbated respiratory disease; ATA, aspirin-tolerant asthma; CI, confidence interval; OR, odds ratio; *TAPBP*, TAP-binding protein.

P value is adjusted for age, sex, smoking, and atopy as co-variables. P_{corr}, corrected P value after multiple testing correction.

P value less than 0.05 regarded as significant is given in bold.

Table 3 Associations of *TAPBP* polymorphisms and haplotypes with the decrease of FEV₁ on aspirin provocation

Loci	C/C	C/R	R/R	P _a	P _a _{corr}	P _b	P _b _{corr}	P _c	P _c _{corr}
rs3106189	576 (6.59±9.88)	502 (8.01±12.53)	86 (8.46±11.85)	0.03	0.05	0.02	0.05	0.33	0.66
rs2239841	740 (7.15±10.78)	392 (7.59±12.21)	36 (9.11±11.45)	0.30	0.59	0.39	0.77	0.37	0.73
rs3106190	583 (6.62±9.88)	504 (8.02±12.60)	85 (8.51±11.91)	0.03	0.05	0.03	0.05	0.32	0.63
rs2071888	521 (6.36±9.57)	528 (8.13±12.58)	120 (8.40±12.00)	0.009	0.02	0.005	0.01	0.27	0.53
rs1059288	523 (6.40±9.63)	528 (8.12±12.58)	119 (8.43±12.05)	0.01	0.02	0.007	0.01	0.26	0.52
ht3	970 (7.12±10.99)	187 (8.25±12.14)	11 (13.67±19.45)	0.05	0.09	0.09	0.17	0.08	0.16

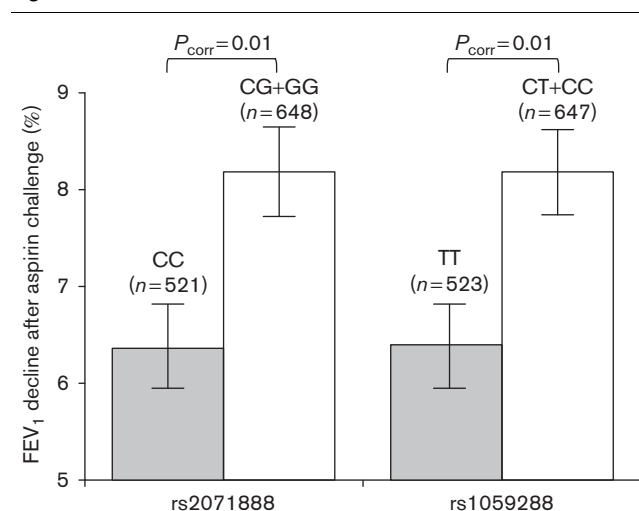
C/C, C/R, and R/R indicate the homozygote of common allele, the heterozygote, and the homozygote of rare allele, respectively.

P_a, P_b, and P_c indicate the P values of codominant, dominant, and recessive models, respectively.

The effective number of independent markers for correction in *TAPBP* was 1.982.

FEV₁, forced expiratory volume in 1 s; *TAPBP*, TAP-binding protein.

P value less than 0.05 regarded as significant is given in bold.

Fig. 2

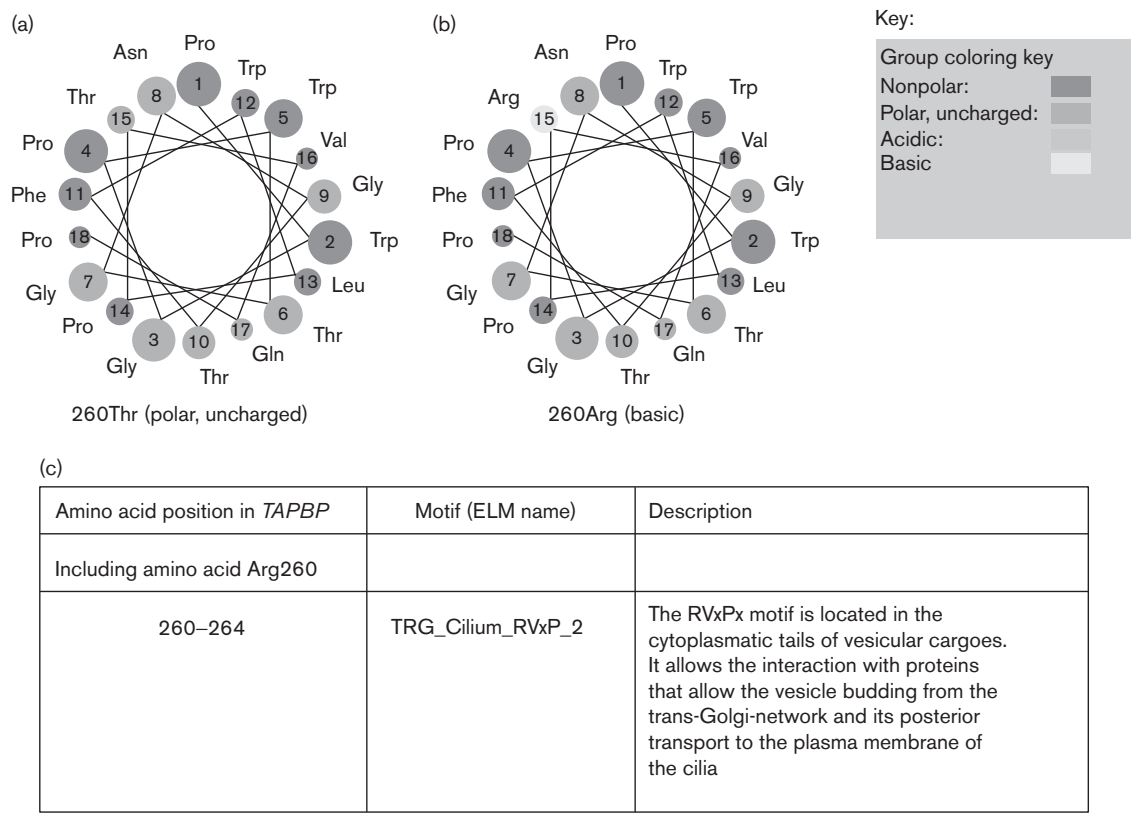
Comparison of the FEV₁ decline (%) induced by aspirin provocation between patients with the rare allele and those with the common alleles of rs2071888 of the *TAPBP* gene. FEV₁, forced expiratory volume in 1 s; P_{corr}, corrected P value; *TAPBP*, TAP-binding protein.

Discussion

In the present study, we showed that the MAFs of *TAPBP* rs2071888 C > G (Thr260Arg) on exon 4 and rs1059288 T > C on 3'UTR may be genetic risk factors for AERD. *TAPBP* is considered to be important for efficient MHC class I assembly with peptides as the absence of *TAPBP* results in poor MHC class I export from the ER to the cell surface, decreasing its expression on the surface [25]. Accordingly, AERD may be related to altered antigen presentation through MHC class I molecules.

In addition to the overproduction of cysteinyl leukotrienes and deficiency of prostaglandin E₂ in AERD development [3], overproduction of 15(S)-hydroxyeicosatetraenoic acid [15(S)-HETE] has been found in cases of AERD. Aspirin *in vitro* causes the accumulation of 15(s)-HETE in epithelial cells of nasal polyps from aspirin-sensitive patients [26]. Various target tissues including airway epithelial cells [27] and peripheral blood leukocytes [28] of AERD patients synthesize more 15(S)-HETE than ATA, spontaneously or when exposed to aspirin. Recent microarray experiments have shown that 15(S)-HETE upregulates the MHC class I

Fig. 3



Helical wheel projection and motif search between 260Thr and 260Arg. The helical wheel projection of Thr260Arg was performed with the Wheel App applet. The change from 260Thr (a) to 260Arg (b) caused an increase in the positively charged basicity. (c) Motifs, including 260Arg and the nearby 260Arg, of the functional site were identified using a prediction program (<http://elm.eu.org/index.html>). TAPBP, TAP-binding protein.

antigen-processing gene family, including *HLA-E*, *TAP1*, *TAP2*, and *TAPBP* [29,30]. Considering that the transcription of *TAPBP* is upregulated by 15(S)-HETE [29,30], the mechanism of induction of the *TAPBP* gene may differ between AERD and ATA in the presence of aspirin.

The MHC, also known as the HLA system, is a key feature of the human immune system. Even a single amino acid substitution in these regions may sufficiently alter the shape of the HLA-peptide binding pocket to alter its specificity [31]. In a limited number of White patients, a significant increase in HLA-DQw2 was associated with aspirin-intolerant asthma (AIA) [32]. In British and German populations, the incidence of DPB1*0401 was higher in AIA than in ATA [33]. The DPB1*0301 frequency was four times higher in AIA patients than in ATA patients in a Polish population [34]. DPB1*0301 was also identified as a strong marker of AIA in the Korean population, as patients with this allele had characteristics typical of AIA, such as decreased FEV₁ levels and increased prevalence of rhinosinusitis with nasal polyps [35].

In the present study, the minor allele *TAPBP* rs2071888 C > G on exon 4 caused a peptide change from Thr to Arg. Thr260Arg substitution in exon 4 of the *TAPBP* gene could alter the polarity of the protein structure from uncharged polar to positively charged basic (Fig. 3a and b), thereby modulating interactions with other molecules such as the MHC complex. Given the multifunctionality of tapasin, it seems plausible that different domains or regions of the protein could contribute toward its functions. Indeed, an ER retention/recycling motif and TAP interaction interface are located at the C-terminal part of tapasin [36,37]. The cysteine in position 95 in the ER luminal part of tapasin forms a disulfide conjugate with ERp57, which has been suggested to be required for tapasin peptide editing [38]. Furthermore, the ER luminal part of tapasin associates with MHC-I but not with TAP [15,39]. The N-terminal region of tapasin (Tpn1-87), which is contained in the ER luminal domain, facilitates folding of HLA-A*0201 in the absence of other ER proteins [40]. In functional site prediction, it was found that amino acids, including 260Arg and nearby amino acids, could be RVxPx motifs (Fig. 2c). The RVxPx motif is known to interact with proteins that allow vesicle

budding from the trans-Golgi-network and its posterior transport to the plasma membrane of the cilia [41]. Thus, Thr260Arg substitution in exon 4 of the *TAPBP* could alter the immune response through MHC class I.

Individuals with *TAPBP* deficiencies have a markedly decreased level of MHC-I molecules on the outside of their cells, which is similar to what is observed in a *TAP* deficiency. Individuals who have a *TAP* deficiency are diagnosed with a disease called bare lymphocyte syndrome. Recently, some individuals who were considered to be affected by bare lymphocyte syndrome were found to actually have exon 4-deleted forms of *TAPBP*, which led to similar findings [42]. Almost all patients with *TAP* deficiency syndrome have ear/nose/throat diseases (e.g. chronic sinusitis and nasal polyps), and ~80% of the patients have lung diseases (e.g. chronic spastic bronchitis and recurrent bacterial infection) [12,42]. In the present study, we examined the association of *TAPBP* polymorphisms with the presence of nasal polyps. There was no significant association between the genotypes and haplotype and the incidence of nasal polyps (Supplementary Table 3, <http://links.lww.com/FPC/A595>).

The *TAPBP* gene locates in the extended HLA class II subregion at 6q21.3. As there are considerable variability and extensive LD throughout the HLA region, identification of causal variants for diseases within the HLA has remained difficult. We have already published an association of SNPs on *TAP2*, *TAP1* [17], *HLA-DPB1* [43], and *WDR46* [44] with AERD in asthmatics. As seen in LD blocks between these genes (Supplementary Fig. 1, <http://links.lww.com/FPC/A596>), there was no significant LD between SNPs on the *TAP2*, *TAP1*, *HLA-DPB1*, and *TAPBP*. However, strong LDs were found between *WDR46*, *DAXX*, and *TAPBP*. These data suggest that AERD responsible SNP might be on *WDR21* or *DAXX*.

Conclusion

Asthmatics who have a minor allele of the rs2071888 C>G showed a greater FEV₁ decrease after aspirin challenge than patients who were homozygous for the common allele. Although five SNPs were in relatively tight LDs with each other, only a nonsynonymous SNP in exon 4, rs2071888, showed a significant association. These data indicate that the minor alleles rs2071888 C>G (Thr260Arg) may be associated with aspirin-induced bronchospasms in asthmatics through a structural change in the *TAPBP* protein. Therefore, although functional evaluations are required, our findings on the association of *TAPBP* with AERD-related symptoms, particularly the FEV₁ decrease on aspirin provocation, provide evidence for the role of this gene in AERD. One limitation of the present study is the presentation of a preliminary finding and needs to be replicated before any true meaning can be ascribed.

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Conflicts of interest

There are no conflicts of interest.

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