CD55 polymorphisms and risk of aspirin-exacerbated respiratory disease

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Abstract. Aspirin-exacerbated respiratory disease (AERD) is a respiratory disease characterized by acute bronchial responses upon the administration of non-steroidal anti-inflammatory drugs (NSAIDs) and the immune response by mast cells is regarded as one of the noteworthy causes of AERD pathogenesis. The complement cascade is regarded as a key mechanism for clearing pathogens from the host. CD55 is one of the proteins involved in self-recognition, a central component of the complement system and autoimmunity. To investigate the associations between *CD55* single nucleotide polymorphisms (SNPs) and the risk of AERD, we carried out logistic analyses with three genetic models and further regression analysis was performed with the fall rate of forced expiratory volume in 1 sec (FEV_1) by aspirin provocation. However, our results demonstrate that no *CD55* polymorphisms are associated with the risk of AERD and the fall rate of FEV_1 ($P>0.05$). Therefore, our results suggest that *CD55* polymorphisms are not genetic markers of aspirin-induced bronchospasm, including FEV_1, in the population studied. Although the genetic role of *CD55* has been found to be integral to human immunity, our results indicate that genetic variations of *CD55* do not influence the risk of AERD and the fall rate of FEV_1 in the population studied.

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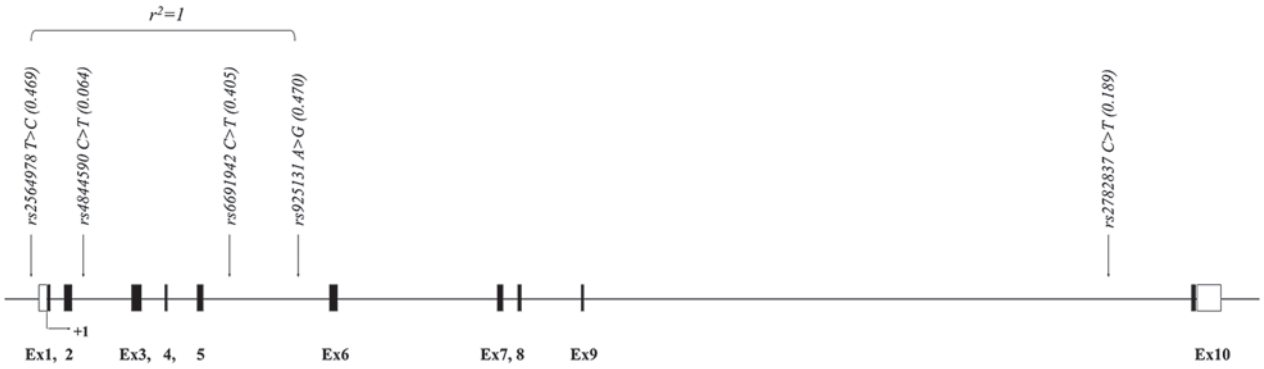
Introduction

Aspirin-exacerbated respiratory disease (AERD) is a chronic bronchial response to oral intake of non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin (1). The symptoms of AERD include aspirin sensitivity, bronchial asthma and chronic rhinosinusitis with nasal polyposis (2-4). Approximately 20% of adult asthmatics are known to have aspirin intolerance (5). Thus, AERD is considered as a major health issue in the epidemiology of asthma.

A hypothesis for AERD pathogenesis states that the cyclooxygenase (COX)-1 enzyme is inhibited by NSAIDs, including aspirin, resulting in a decrease in the level of prostaglandin (PG)-E2 (5). Furthermore, the decreased amount of PG-E2 induces histamine release from mast cells that may influence aspirin sensitivity and induce the production of leukotrienes in the 5-lipoxygenase pathway (5).

CD55, also known as decay accelerating factor (DAF), is a membrane protein that is associated with the complement system. In the innate and adaptive immunity, the complement system plays a key role as a biochemical cascade, clearing pathogens from the host. However, the complement system is also able to cause critical damage to the host cell and this leads to immune diseases affecting the host, including asthma. The complement system is tightly regulated by several complement control proteins including the membrane cofactor protein (MCP), C4b-binding protein (C4BP), factor H (fH) and CD55. Among the complement control proteins, CD55 plays a key role in the regulation of the complement system by preventing the assembly of the C3bBb complex or accelerating the disassembly of pre-formed convertase, resulting in a block of the complement system cascade. This regulation inhibits and limits production of anaphylatoxins, including C3a, C4a and C5a (6,7). Although not in asthma, it has been demonstrated that NSAID blocks *CD55* expression and is correlated with the

A



B

Hap.	*rs2564978*	*rs4844590*	*rs6691942*	*rs925131*	*rs2782837*	Freq.
ht1	C	C	T	G	C	0.365
ht2	T	C	C	A	C	0.363
ht3	T	C	C	A	T	0.199
ht4	C	T	C	G	C	0.068
ht5	C	C	C	A	T	0.003
Others	-	-	-	-	-	0.002

Others includes: CCTGT and CTCAC

C

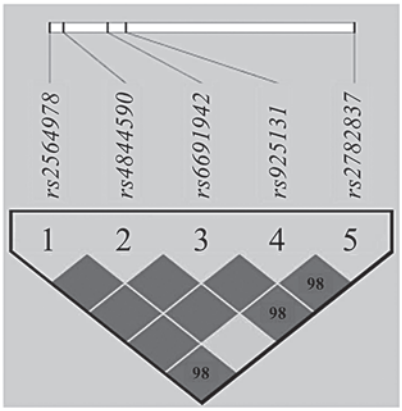


Figure 1. Schematic physical map, haplotypes and LD plot of *CD55*. (A) Polymorphisms identified in *CD55*. Coding exons are marked by shaded blocks and untranslated region (UTR) by white blocks. The LD coefficients (r^2) are based on the genotypes of Korean samples. (B) Haplotypes of *CD55* in the Korean 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 whole study subjects in this study (n=592). LD, linkage disequilibrium; SNP, single nucleotide polymorphism.

level of COX-1 (8). In line with these studies, we established a hypothesis that the polymorphisms in CD55 may cause AERD. Therefore, we examined the genetic association of *CD55* polymorphisms with the risk of AERD.

Materials and methods

Study subjects. A total of 163 subjects with AERD and 429 aspirin-tolerant asthma (ATA) subjects were recruited from the Asthma Genome Research Center comprising hospitals of Soonchunhyang, Chonnam, Chungbuk, Seoul national and Chung-Ang Universities in Korea. Oral aspirin challenge (OAC) was performed with increasing doses of aspirin (9,10). Briefly, patients with a history of aspirin hypersensitivity were provided with 30 mg orally. Respiratory and nasal symptoms, blood pressure, external signs (urticaria and angioedema) and forced expiratory volume in 1 sec (FEV_1) were documented every 30 min for a period of 1.5 h. In the absence of any indication of an adverse reaction after 1.5 h, increasing dosages of aspirin (60, 100, 300 and 400 mg) were administered until the patient developed the reaction and the same measurements were repeated every hour. Those with no history of aspirin hypersensitivity were started on 100 mg of aspirin and gradually the dosage was increased to 200 mg, 350 mg and 450 mg until the patient developed the reaction. If no reaction occurred 4 h after the final dose, the test was deemed negative. Aspirin-induced bronchospasm, reflected by a decline (%) in FEV_1, was calculated as the pre-challenge FEV_1 minus the post-challenge FEV_1, divided by the pre-challenge FEV_1. OAC reactions were categorized into three groups as follows: i) 15% or greater decrease in FEV_1 or nasal reactions (AERD), ii) less than 15% decrease in FEV_1 without naso-ocular or cutaneous reactions (ATA), or iii) less than 15% decrease in FEV_1 with cutaneous reactions [aspirin-induced urticaria (AIU)]. All individuals provided informed consent to participate in the study. The methods were approved by the local ethics committees of hospital.

Single nucleotide polymorphism (SNP) selection and genotyping. We selected candidate polymorphic SNPs in the National Center for Biotechnology Information (NCBI; build 36) and the International HapMap Project (http://hapmap.ncbi.nlm.nih.gov/) based on the frequencies in the Asian population and linkage disequilibrium (LD) status. For examination of AERD risk association, a total of five polymorphisms were selected for this study. The location of the variants is indicated in the genetic map of *CD55* as shown in Fig. 1A. Among the five SNPs, only

Table I. Clinical profiles for association analysis between aspirin-exacerbated respiratory disease and control subjects.

Clinical profile	Total no. of subjects	AERD	ATA
Number of subjects	592	163	429
Mean age (range)[a,c]	46.15 (15.40-77.88)	43.13 (17.22-72.73)	47.30 (15.40-77.88)
Height (cm)	160.78±8.63	161.72 (143.00-196.00)	160.42 (140.00-199.00)
Weight (kg)	62.81±10.84	61.25±10.38	63.40±10.97
FEV_1 decrease following aspirin challenge (%)[b]	9.27±13.24	24.63±16.11	3.54±4.85
Blood eosinophil (%)	6.01±5.73	5.96±5.21	6.03±5.92
FVC %, predicted	88.54±14.08	90.35±14.04	87.85±14.05
FEV_1 %, predicted[a]	90.54±16.97	87.58±16.94	91.66±16.87
PC20, methacholine (mg/ml)[a]	6.43±8.67	5.02±7.83	6.91±8.90
Total IgE (IU/ml)	357.65±604.09	348.60±596.44	361.00±607.56
Gender (male/female)	206/386	59/104	147/282
Current Smoker (%)	27.70	21.47	30.07
Positive rate of Nasal polyP (%)[b]	33.83	57.89	26.06
Positive rate of skin test (%)	56.42	52.76	57.81
Positive rate of specific IgE (Df, %)	36.38	38.30	35.75
Positive rate of specific IgE (Dp, %)	44.56	45.77	44.16

AERD, aspirin-exacerbated respiratory disease; ATA, aspirin-tolerant asthma; Nasal polyP,nasal polyposis; FEV_1, forced expiratory volume in 1 sec; FVC, forced vital capacity. [a]P<0.05; [b]P<0.0001 compared to ATA control; [c]age at first medical examination.

Table II. Association analysis of *CD55* polymorphisms and haplotypes with risk of AERD.

	Co-dominant		Dominant		Recessive	
Polymorphism	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
rs2564978 T>C	1.10 (0.85-1.42)	0.47	0.98 (0.66-1.47)	0.93	1.34 (0.87-2.06)	0.18
rs4844590 C>T	1.21 (0.72-2.02)	0.48	1.30 (0.76-2.23)	0.34	-	0.99
rs6691942 C>T	1.05 (0.81-1.37)	0.7	0.97 (0.66-1.42)	0.87	1.26 (0.78-2.04)	0.35
rs925131 A>G	1.09 (0.85-1.42)	0.5	0.97 (0.65-1.46)	0.9	1.33 (0.87-2.05)	0.19
rs2782837 C>T	1.14 (0.82-1.56)	0.44	1.09 (0.74-1.61)	0.66	1.61 (0.69-3.75)	0.27
CD55_ht1	1.06 (0.82-1.38)	0.65	0.98 (0.67-1.43)	0.91	1.28 (0.79-2.08)	0.31
CD55_ht2	0.81 (0.61-1.07)	0.14	0.85 (0.59-1.23)	0.39	0.57 (0.30-1.08)	0.08
CD55_ht3	1.14 (0.83-1.57)	0.41	1.11 (0.75-1.64)	0.61	1.60 (0.69-3.72)	0.27
CD55_ht4	1.21 (0.72-2.02)	0.48	1.30 (0.76-2.23)	0.34	-	0.99

AERD, aspirin-exacerbated respiratory disease; ATA, aspirin-tolerant asthma; OR, odds ratio; CI, confidence interval. The P-values and OR with 95%CI of polymorphisms in a co-dominant model were reported in our previous genome-wide association study [Kim *et al* (9)].

one SNP (*rs2564978*) is located in the promoter region while the other four SNPs (*rs4844590*, *rs6691942*, *rs925131* and *rs2782837*) are located in introns of *CD55* (Table II). The minor allele frequencies (MAFs) of all SNPs and allelic variations are listed in Table II. Genotyping was carried out with 20 ng of genomic DNA using the TaqMan assay in the ABI prism 7900HT sequence detection system (Applied Biosystems, CA, USA) in 163 AERD cases and 429 ATA controls with the assessment of data quality by duplicate DNAs (n=10).

Statistical analysis. We calculated LD in all the pairs of biallelic loci using Lewontin's D' (|D'|) (11) and r^2. PHASE algorithm (ver. 2.0), developed by as previously described by Stephens *et al*, was used for inferring haplotypes (12). Associations of genotypes and haplotypes in the *CD55* 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. The data were adjusted, managed and analyzed using Statistical Analysis System (SAS) version 9.1 (SAS Inc., Cary, NC, USA). Statistical power was calculated by PGA (Power for Genetic Association analysis) software with

Table III. Regression analysis of *CD55* polymorphisms and haplotypes with fall rate of FEV_1 by aspirin provocation.

Polymorphism	C/C	C/R	R/R	Pa	Pb	Pc
rs2564978 T>C	172 (9.30±12.79)	285 (8.94±13.49)	135 (9.78±13.26)	0.88	0.87	0.66
rs4844590 C>T	518 (9.17±13.17)	71 (10.17±13.63)	3 (-2.07±7.59)	0.98	0.79	0.17
rs6691942 C>T	213 (9.49±13.36)	279 (8.63±12.85)	99 (10.41±14.02)	0.86	0.68	0.39
rs925131 A>G	171 (9.32±12.82)	284 (8.95±13.51)	135 (9.78±13.26)	0.88	0.87	0.67
rs2782837 C>T	393 (9.08±13.58)	172 (8.83±11.82)	25 (13.95±16.30)	0.40	0.76	0.10
CD55_ht1	214 (9.48±13.33)	280 (8.60±12.84)	98 (10.50±14.07)	0.83	0.69	0.36
CD55_ht2	255 (9.51±13.20)	266 (9.60±13.47)	71 (6.88±12.25)	0.35	0.70	0.18
CD55_ht3	396 (9.09±13.55)	171 (8.88±11.84)	25 (13.95±16.30)	0.36	0.70	0.10
CD55_ht4	518 (9.17±13.17)	71 (10.17±13.63)	3 (-2.07±7.59)	0.98	0.79	0.17

C/C, common allele/common allele; C/R, common allele/rare allele; R/R, rare allele/rare allele; Pa, P-values of co-dominant model; Pb, P-values of dominant model; Pc, P-values of recessive model; FEV_1, forced expiratory volume in 1 sec.

Table IV. Information of *CD55* polymorphisms, minor allele frequencies of Korean AERD/ATA patients and controls from other populations.

				MAFs of present study		MAFs of other ethnic groups			
Polymorphism	Heterozygosity	HWE	Statistical power	AERD	ATA	Caucasian	Chinese	Japanese	African
rs2564978 T>C	0.498	0.387	94.52	0.485	0.459	0.228	0.558	0.413	0.013
rs4844590 C>T	0.120	0.767	38.41	0.074	0.059	0.305	0.044	0.089	0.167
rs6691942 C>T	0.482	0.552	94.36	0.411	0.400	0.398	0.395	0.488	0.190
rs925131 A>G	0.498	0.384	94.52	0.485	0.460	0.712	0.442	0.587	0.987
rs2782837 C>T	0.307	0.138	81.99	0.204	0.181	-	0.256	0.170	0.000
CD55_ht1	0.481	0.601	94.34	0.411	0.397	-	-	-	-
CD55_ht2	0.451	0.837	93.35	0.313	0.361	-	-	-	-
CD55_ht3	0.305	0.119	81.83	0.202	0.179	-	-	-	-
CD55_ht4	0.120	0.767	38.41	0.074	0.059	-	-	-	-

HWE, Hardy-Weinberg equilibrium; MAF, minor allele frequency; AERD, aspirin-exacerbated respiratory disease; ATA, aspirin-tolerant asthma. The MAFs of Caucasian, Chinese, Japanese and African populations were obtained from the dbSNP database of NCBI (http://www.ncbi.nlm.nih.gov/snp/).

5.4% disease prevalence, relative risk of 1.3 and MAFs of our subjects and subject sizes (13,14).

Results

Patients. A total of 592 asthma patients including 163 AERD cases and 429 ATA controls were recruited for analysis. The characteristics of the patients are summarized in Table I. Among the factors of diagnosis, percentage of FEV_1 fall rate by aspirin provocation showed significant differences between the AERD and ATA groups (24.63±16.11 and 3.54±4.85, respectively, P<0.0001; Table I). In addition, predicted FEV_1 and amount of PC20 methacholine also proved to be significantly different between AERD and ATA patients (P=0.05). The average value of predicted FEV_1 was 87.58±16.94 in AERD patients and 91.66±16.87 in ATA patients (Table I), while the amount of PC20 methacholine was 5.02±7.83 and 6.91±8.90 in AERD and ATA patients (Table I). For an adequate logistic regression analysis, gender, percentage of current smoking status, existence of atopy and BMI were adjusted.

Genotype distribution. We also calculated the genotype distributions and all loci were in Hardy-Weinberg equilibrium (Table IV, P>0.05). In addition, we established an LD plot and haplotypes using the five genotyped variants. LDs between each variant are shown in Fig. 1C and r^2=1 is also displayed in Fig. 1A. Results of logistic analyses revealed that *CD55* variants are not associated with the risk of AERD. P-values did not reach statistical significance in all genetic models (P>0.05). These data with odds ratios are summarized in Table III. In further regression analysis, we investigated the differences between allele distributions and the decline of FEV_1 by aspirin provocation. However, we failed to find significant differences between allele distribution, including haplotypes and risk of

AERD. P-values of each polymorphism showed no association signal higher than 0.05 in co-dominant, dominant and recessive models. The results of regression analysis are summarized in Table III.

Discussion

According to a hypothesis that AERD is not correlated with IgE, immune responses including eosinophil infiltration are considered as important factors of AERD pathogenesis (15). Additionally, a previous study demonstrated that leukotriene molecules are correlated with an expression of complement receptors, including C3b (16). C3a and C5a play key roles in attraction of immune cells, including eosinophil (17). In addition, another group demonstrated that the inflammatory cytokines IL-4 and IL-1β enhance the expression and release of CD55 (18). The cytokine is able to activate neutrophils, leading to CD55 expression on neutrophils (19). Therefore, the concentration of CD55 protein may affect the activity of eosinophils and neutrophils, which are important in AERD pathogenesis.

Previous studies have demonstrated that the pro-inflammatory mediators, including lipopolysaccharide, tumor necrosis factor-α and IL-1β, regulate the expression level of *CD55* (18,20,21). In addition, it has been reported that the cyclooxygenase (COX)-2 pathway expressed in the inflammatory cells is also upregulated by the pro-inflammatory mediators (22). PG-E2, which is generated from the COX-1 and COX-2 pathways, modulates immune function through a variety of mechanisms (23,24). Thus, *CD55* may affect the risk of AERD through the COX pathways.

The study by Kim *et al* (9) shows only the results from a co-dominant model of logistic analysis. However, in order to investigate a possible association between the *CD55* SNPs and the risk of AERD in this study, we carried out more comprehensive analyses using dominant and recessive models. In addition, we performed a regression analysis using the fall rate of FEV_1 due to aspirin provocation. However, although we have performed more thorough analyses, all of our results did not support our hypothesis. However, the comparison between allele frequencies in our subjects and other ethnic groups from dbSNP database shows that the allele frequencies of the SNPs were similar within the Asian population, but different when compared to those of Caucasian and African subjects (Table IV). Therefore, further studies with other ethnic groups are required to validate the exact function of *CD55* polymorphisms in AERD.

In the present study, we used only common polymorphisms which have frequencies higher than 0.05. Thus, in order to validate the exact function of polymorphisms in *CD55*, replication studies using rare variants which have frequencies lower than 0.05 may be required. Additionally, the average statistical power of the present study is 79.08%, indicating that our sample size was not sufficient for this analysis. However, rarity of AERD makes it difficult to recruit sufficient patients for an analysis in Korean asthma cohorts. Thus, further study using larger independent groups and/or meta-analysis may be required to investigate the functions of *CD55* gene further. In addition, a comparison between asthmatics and a healthy normal control is also needed for an full understanding of the gene.

In conclusion, we identified five SNPs in the human CD55 gene and explored the effect of polymorphisms in aspirin-exacerbated respiratory disease subjects in a Korean population. However, statistical analyses showed no association between polymorphisms in the promoter and intron and fall rate of FEV_1. Despite the importance of CD55 protein in the immune system, we failed to find convincing evidence of association between polymorphisms in *CD55* and development of AERD. Due to various limitations of the present study, further studies using a large independent population and rare alleles may be required. Although our P-values did not show significance, results from this study may be useful for future research in human airway diseases.

We failed to find evidence of association between polymorphisms in *CD55* and risk of AERD in both logistic and regression analysis. However, various limitations of the present study, further studies using large independent population and rare alleles may be required. Although our P-values did not show significance, results from this study may be useful in the etiology of AERD and other bronchial diseases.

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