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Dipeptidyl-peptidase 10 as a genetic biomarker for the aspirin-exacerbated respiratory disease phenotype

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ARTICLE INFO

Article history:

Received for publication October 9, 2014.

Received in revised form November 26, 2014.

Accepted for publication December 3, 2014.

ABSTRACT

Background: Aspirin-exacerbated respiratory disease (AERD) is an endotype of severe and eosinophilic adult asthma characterized by chronic rhinosinusitis with nasal polyps and hypersensitivity to aspirin and/or nonsteroidal anti-inflammatory drugs. A genetic contribution of dipeptidyl-peptidase 10 (DPP10) to asthma susceptibility and lung function decline has been reported. However, little is known about the role of DPP10 in the pathogenesis of AERD.

Objective: To identify genetic variants of DPP10 that confer susceptibility to AERD or severe asthma.

Methods: A case–control association study of *DPP10* gene polymorphisms was performed in 3 groups of patients: 274 with AERD, 272 with aspirin-tolerant asthma, and 99 normal healthy controls. The rs17048175 single-nucleotide polymorphism was targeted based on a preliminary genomewide association study using an Affymetrix genomewide human single-nucleotide polymorphism array in a Korean population. DPP10, 15-hydroxyeicosatetraenoic acid, and YKL-40/chitinase-3-like protein were measured by enzyme-linked immunosorbent assay in sera taken from the study subjects.

Results: There was a significant association between rs17048175 and the AERD phenotype, but not with aspirin-tolerant asthma. The DPP10 level was significantly higher in sera from patients with AERD compared with patients with aspirin-tolerant asthma and control subjects ($P = .021$ and $P < .001$, respectively). In addition, there was a significant difference of serum DPP10 level according to the single-nucleotide polymorphism ($P = .001$). Serum DPP10 level showed a strong correlation with 15-hydroxyeicosatetraenoic acid ($r = 0.226$, $P = .017$) and YKL-40 ($r = 0.364$, $P = .004$).

Conclusion: This study suggests a genetic contribution of rs17048175 to DPP10 in eosinophilic inflammation induction in the airways and to AERD susceptibility.

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Introduction

Aspirin-exacerbated respiratory disease (AERD) is an endotype of severe persistent eosinophilic asthma¹ with hypersensitivity to aspirin and/or nonsteroidal anti-inflammatory drugs. Patients with AERD are likely to present with severe asthma with chronic rhinosinusitis and/or nasal polyps and eosinophilia that would require a higher dose of leukotriene modifiers.² The high prevalence of chronic rhinosinusitis with nasal polyps in patients with AERD is due to persistent and intense eosinophilic inflammation in the upper and lower airways.^{3–6} Overproduction of cysteinyl

leukotrienes triggered by aspirin (acetylsalicylic acid) or other nonsteroidal anti-inflammatory drugs is a hallmark of AERD.^{7,8} Leukotriene modifiers have a beneficial effect on the asthma symptoms of patients with AERD.⁹ Increased production of 15-hydroxyeicosatetraenoic acid (15-HETE) has been seen in patients with AERD, along with a significant correlation with blood eosinophil counts.^{10,11} Case–control association studies have identified genetic variants involved in arachidonate metabolism or eosinophil activation that have been reported as genetic risk factors for the AERD phenotype.^{12,13}

In this study *DPP10*, encoding dipeptidyl-peptidase 10 (DPP10), was targeted because it has been identified by positional cloning as a marker of asthma susceptibility,¹⁴ and *DPP10* genetic variants could affect lung function decline.¹⁵ DPP10 is moderately expressed in the bronchi and trachea, is localized to the airway epithelium, and was increased after an ovalbumin challenge in a rat model of asthma,¹⁶ suggesting a role in the pathogenesis of asthma. However, little is known about the biological role of DPP10 in lung

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Disclosure: Authors have nothing to disclose.

Funding: This study was supported by a grant from the Korean Health 21 R&D Project, Ministry of Health & Welfare, Republic of Korea (HI14C0065).

<http://dx.doi.org/10.1016/j.anai.2014.12.003>

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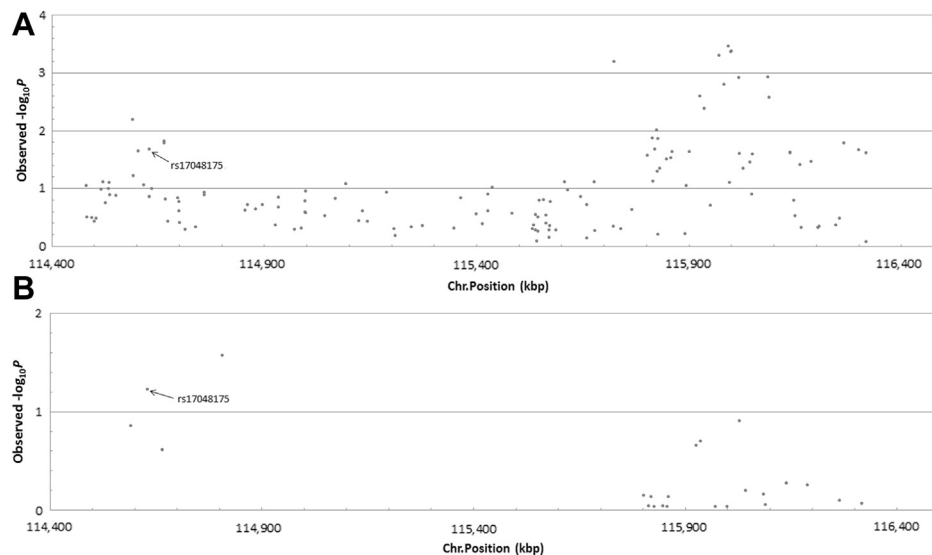


Figure 1. *P* value plots of dipeptidyl-peptidase 10 single-nucleotide polymorphisms (A) associated with the aspirin-exacerbated respiratory disease phenotype compared with normal control subjects and (B) correlated with serum dipeptidyl-peptidase 10 levels. The distribution of negative logarithm *P* values is plotted against chromosomal location.

function in asthma. There have been no published data to suggest any role of DPP10 in the pathogenesis of AERD.

To identify genetic variants of *DPP10* associated with the development of aspirin hypersensitivity in adult patients with asthma, a case–control association study was performed in a patient group with AERD, a patient group with aspirin-tolerant asthma (ATA), and a healthy normal control group (NC). A target single-nucleotide polymorphism (SNP) was selected from a genome-wide association study (GWAS) previously performed using an Affymetrix genome-wide human SNP array (Affymetrix, Inc, Santa Clara, California). Verification of a potential DPP10 biomarker was by examination of serum DPP10 levels from patients with AERD. This report describes a newly identified SNP, rs1704817, as a genetic marker of the AERD phenotype.

Methods

Recruitment of Study Participants

A total of 645 Korean adult participants, including 274 with AERD, 272 with ATA, and 99 NCs, from Ajou University Hospital (Suwon, South Korea) were enrolled for a case–control association study. Asthma was diagnosed according to Global Initiative for Asthma and American Thoracic Society (ATS) recommendations based on clinical asthma symptoms and a lung function test. Patients with AERD were diagnosed by a positive lysine–aspirin bronchoprovocation test (L-ASA BPT) result in patients with asthma who showed typical clinical features of asthma.¹⁷ Patients with ATA were defined as patients with asthma showing a negative response to the L-ASA BPT. Asthma was graded as severe and nonsevere based on the degree of asthma severity according to ATS criteria. The NCs were healthy participants who had no history of asthma symptoms. All participants provided written informed consent before participating in this study.

Atopy was defined as at least 1 positive reaction to a skin prick test of 55 common inhalant allergens (Bencard Co, Brentford, United Kingdom), with histamine and saline controls. Methacholine bronchial challenge tests were performed as described previously using double doses of methacholine (0.075–25 mg/mL).¹⁸ The clinical characterization of AERD and ATA in patients, including rhinosinusitis, pulmonary function, and aspirin provocation tests, was carried out as described previously.¹⁹ Serum total IgE and eosinophil cationic protein levels were measured using the ImmunoCAP system (Thermo Fisher Scientific, Uppsala, Sweden).

The threshold cutoff value of specific IgE was 0.35 kU/L. The presence of rhinosinusitis and nasal polyps was determined based on paranasal sinus radiographs, computed tomograms, and/or rhinoscopic images. The presence of moderate to severe chronic rhinosinusitis was defined as a Lund-Mackay score higher than 3.²⁰

SNP Selection and Genotyping

A preliminary GWAS using an Affymetrix genome-wide human SNP array indicated 23 *DPP10* SNPs that showed an association with the AERD phenotype, from which rs17048175 was selected for a replication study (Fig 1). There was an association between the SNP and the AERD phenotype ($P < .05$ by χ^2 test; Fig 1A) and a strong correlation with serum DPP10 levels ($P < .05$; Fig 1B). Targeted SNP genotyping was performed by the primer extension method using a SNaPshot ddNTP primer extension kit (Applied Biosystems, Foster City, California) in a larger study cohort comprised of the AERD ($n = 274$), ATA ($n = 272$), and NC ($n = 99$) groups. The amplifying and extension primer sequences were 5'-ATGGACAGGGAGTTCTGAG-3' (forward) and 5'-CTTCAGAGGGA GGAGTGAG-3' (reverse) and 5'-TGTGGACTGTTGTGCAATGTCTTC-3' for the extension.

Measurement of Serum Biomarkers

To investigate their involvement in chronic eosinophilic inflammation, 15-HETE, DPP10, and YKL-40 levels were measured. The 15-HETE level was measured in cell supernatants of peripheral blood leukocytes treated with arachidonic acid (40 μ mol/L) at 37°C for 5 minutes, as described previously,^{11,21} and quantified using an enzyme immunoassay kit (Cayman Chemicals, Ann Arbor, Michigan). Serum DPP10 levels were measured using a human DPP10 enzyme-linked immunosorbent assay kit (Uscn Life Science, Inc, Wuhan, China). Serum YKL-40 levels were measured by a human YKL-40/chitinase-3-like protein (CHI3L1) enzyme-linked immunosorbent assay kit (R&D Systems, Inc, Minneapolis, Minnesota).

Statistical Analyses

Statistical analyses were performed using IBM SPSS 19 for Windows (SPSS, Inc, Chicago, Illinois). A χ^2 test was used to detect significant departures of the SNP genotype frequency from the Hardy-Weinberg equilibrium. Differences in genotype frequencies between the 2 groups were assessed using multiple logistic regression models (codominant, dominant, and recessive analysis

Table 1
Clinical demographics of study subjects for a case–control association study^a

	Asthma (n = 546)	NC (n = 99)	P value ^b for asthma vs NC	Asthma severity		P value ^b for SA vs NSA	Aspirin hypersensitivity		P value ^b for AERD vs ATA
				SA (n = 75)	NSA (n = 370)		AERD (n = 274)	ATA (n = 272)	
Age (y)	42.5 ± 13.57	28.64 ± 7.89	.013	46.36 ± 12.78	41.72 ± 13.48	.007	43.5 ± 13.18	41.5 ± 13.91	.086
Women	333/546 (61)	45/96 (46.9)	<.001	44/74 (59.5)	222/370 (60)	1.000	182/274 (66.4)	151/272 (55.5)	.011
Atopy present	313/532 (58.9)	9/52 (17.3)	<.001	41/74 (55.4)	210/370 (56.8)	.898	141/260 (54.2)	172/272 (63.2)	.043
Total IgE (kU/L)	397.16 ± 707.76	111.9 ± 164.8	.073	360.80 ± 643.89	402.75 ± 751.53	.657	396.9 ± 620.6	397.4 ± 781.3	.994
PC ₂₀ (mg/mL)	5.98 ± 8.50	—	—	3.63 ± 7.33	6.34 ± 8.69	.057	4.36 ± 7.35	7.50 ± 9.22	<.001
Baseline FEV ₁ (%)	86.14 ± 18.79	—	—	75.23 ± 16.02	88.7 ± 18.81	.001	85.6 ± 18.5	89.4 ± 20.9	.394
Decrease of FEV ₁ by aspirin challenge (%)	17.77 ± 12.31	—	—	20.74 ± 12.31	16.7 ± 11.92	.051	23.3 ± 11.6	7.4 ± 4.5	<.001
Chronic rhinosinusitis (LM score 3–4)	87/139 (62.6)	—	—	20/31 (64.5)	61/100 (61)	.727	73/107 (68.2)	14/32 (43.8)	.021
Total eosinophil count/ μ L	453.75 ± 909.74	—	—	412.95 ± 355.66	464.74 ± 1,009.32	.665	425.6 ± 411.0	477.2 ± 1,173.9	.544
ECP (μ g/L)	30.52 ± 34	—	—	33.88 ± 31.15	28.55 ± 32.61	.26	31.8 ± 32.1	29.2 ± 36.0	.501
Sputum eosinophil (%)	22.7 ± 34.45	—	—	25.93 ± 36.62	21.39 ± 33.57	.421	25.1 ± 35.8	17.8 ± 31.1	.109
Sputum neutrophil (%)	57.18 ± 34.13	—	—	63.81 ± 34.76	55.14 ± 33.57	.185	56.8 ± 34.6	58.0 ± 33.5	.845
DPP10 (ng/mL)	13.7 ± 15.01	6.9 ± 2.9	<.001	12.22 ± 10.95	13.1 ± 11.22	.659	14.7 ± 13.0	11.1 ± 8.1	.021
YKL-40 (ng/mL)	54.46 ± 48.31	47.8 ± 39.7	.739	67.62 ± 48.9	49.97 ± 50.24	.059	57.4 ± 56.2	51.0 ± 36.9	.375
15-HETE (pg/mg protein)	47.67 ± 24.62	26.0 ± 4.7	<.001	45.53 ± 22.53	48.65 ± 26.01	.679	45.6 ± 24.9	50.5 ± 24.4	.437

Abbreviations: 15-HETE, 15-hydroxyeicosatetraenoic acid; AERD, aspirin-exacerbated respiratory disease; ATA, aspirin-tolerant asthma; DPP10, dipeptidyl-peptidase 10; ECP, eosinophil cationic protein; FEV₁, forced expiratory volume in 1 second; IgE, immunoglobulin E; LM score, Lund-Mackay computed tomographic score; NC, normal control; NSA, nonsevere asthma; PC₂₀, provocative concentration of methacholine required to cause a 20% decrease in forced expiratory volume in 1 second; SA, severe asthma.

^aValues are presented as count number/valid number (percentage) for categorical variables and mean ± SD for continuous variables.

^bP values were determined using Pearson's χ^2 test for categorical variables and the independent *t*-test for continuous variables.

Table 2
Genotype distribution of the single-nucleotide polymorphism rs17048175 of dipeptidyl-peptidase 10

	Asthma (n = 546)	NC (n = 99)	P value ^a for asthma vs NC	Asthma severity		P value ^a for SA vs NSA	Aspirin hypersensitivity		P value ^a for AERD vs ATA
				SA (n = 75)	NSA (n = 370)		AERD (n = 274)	ATA (n = 272)	
TT, n (%)	367 (67.2)	69 (69.7)	.611	58 (78.7)	239 (64.6)	.007	195 (71.2)	172 (63.2)	.083
CT, n (%)	152 (27.8)	28 (28.3)	.84	15 (20.3)	108 (29.2)	.097	64 (23.4)	88 (32.4)	.738
CC, n (%)	27 (4.9)	2 (2)	.509	1 (1.3)	23 (6.2)	.012	15 (5.5)	12 (4.4)	.022

Abbreviations: AERD, aspirin-exacerbated respiratory disease; ATA, aspirin-tolerant asthma; NC, normal control; NSA, nonsevere asthma; SA, severe asthma.

^aP values were determined by logistic regression analysis with sex and age as covariates.

models), with age and sex as covariates. Differences in the mean values of the phenotypic characteristics between the 2 groups were compared by a χ^2 test for categorical variables and by an independent t test for continuous variables. A receiver operating characteristic curve analysis discriminated patients with AERD from healthy controls. A Pearson correlation analysis identified associations among continuous clinical parameters. A multivariate analysis was conducted after adjustment for age and sex. P values less than .05 were considered statistically significant.

Results

Clinical Characteristics of Study Subjects

The clinical characteristics of the study subjects are listed in Table 1. Patients with asthma were older and had greater atopy than NCs ($P = .013$ and $P < .006$). Asthma was graded as severe and nonsevere based on the degree of asthma severity according to ATS criteria. Patients with severe asthma were older and had lower baseline percentage of predicted forced expiratory volume in 1 second than those with nonsevere asthma ($P = .007$ and $P = .001$). When asthma was graded according to aspirin hypersensitivity, patients with AERD were mostly women, with less atopy, a lower provocation concentration of inhaled methacholine, and a higher prevalence of chronic rhinosinusitis compared with the ATA group ($P = .011$, $P = .043$, $P < .001$, and $P = .021$, respectively). Patients with AERD showed a greater decrease in the percentage of predicted forced expiratory volume in 1 second after aspirin challenge ($P < .001$).

Genetic Association of DPP10 with AERD

The rs17048175 SNP was chosen for a replication study because of its association with AERD and strong correlation with serum DPP10 levels based on preliminary GWAS data (Fig 1). In this study, the SNP had a significant association with the AERD phenotype in a replication study cohort comprised of the AERD, ATA, and NC groups (Table 2). The major genotype frequency (TT) was significantly higher in the AERD than in the ATA group ($P = .022$ in a recessive analysis model). Grading of asthma according to ATS criteria resulted in a significantly higher frequency of the TT

Table 3

Clinical features according to the single-nucleotide polymorphism rs17048175 in 546 patients with asthma^a

	rs17048175		<i>P</i> value ^b
	TT (n = 367)	CT + CC (n = 179)	
Age (y)	41.4 ± 13.6	44.7 ± 13.4	.007
Women	218 (59.4)	115 (64.2)	.304
Atopy present	211 (59.6)	102 (57.3)	.338
Total IgE (IU/mL)	445.6 ± 823.2	297.3 ± 351.2	.006
PC ₂₀ (mg/mL)	5.6 ± 7.9	6.8 ± 9.6	.232
Baseline FEV ₁ (%)	85.5 ± 17.8	87.4 ± 20.8	.552
Decrease of FEV ₁ by aspirin challenge (%)	18.5 ± 12.3	16.3 ± 12.4	.175
Chronic rhinosinusitis (LM score 3–4)	65 (63.7)	22 (59.5)	.694
Total eosinophil count/ μ L	477.9 ± 1,044.1	404.5 ± 540.7	.415
ECP (μ g/L)	30.8 ± 32.9	30.0 ± 36.0	.847
Sputum eosinophil (%)	23.1 ± 35.0	21.9 ± 33.3	.803
Sputum neutrophil (%)	56.1 ± 34.9	60.0 ± 32.2	.527
DPP10 (ng/mL)	14.4 ± 12.6	9.9 ± 5.6	.001
YKL-40 (ng/mL)	57.8 ± 55.2	47.9 ± 30.4	.123
15-HETE (pg/mg protein)	48.3 ± 26.2	46.0 ± 20.8	.74

Abbreviations: 15-HETE, 15-hydroxyeicosatetraenoic acid; AERD, aspirin-exacerbated respiratory disease; ATA, aspirin-tolerant asthma; DPP10, dipeptidyl-peptidase 10; ECP, eosinophil cationic protein; FEV₁, forced expiratory volume in 1 second; IgE, immunoglobulin E; LM score, Lund-Mackay computed tomographic score; NC, normal control; NSA, nonsevere asthma; PC₂₀, provocative concentration of methacholine required to cause a 20% decrease in forced expiratory volume in 1 second; SA, severe asthma.

^aValues are presented as count number of valid number (percentage) for categorical variables and mean ± SD for continuous variables.

^b P value was determined by the Fisher exact test for categorical variables and the independent t test for continuous variables.

genotype in severe asthma than in nonsevere asthma ($P = .007$ and $P = .012$ in codominant and recessive analysis models). However, there was no significant difference in the rs17048175 SNP genotype between the asthma and NC groups.

The clinical features according to the SNP are listed in Table 3. Adult patients with asthma and the riskier TT genotype were younger and had higher total IgE levels than those without the genotype ($P = .007$ and $P = .006$, respectively; Table 3). The SNP did

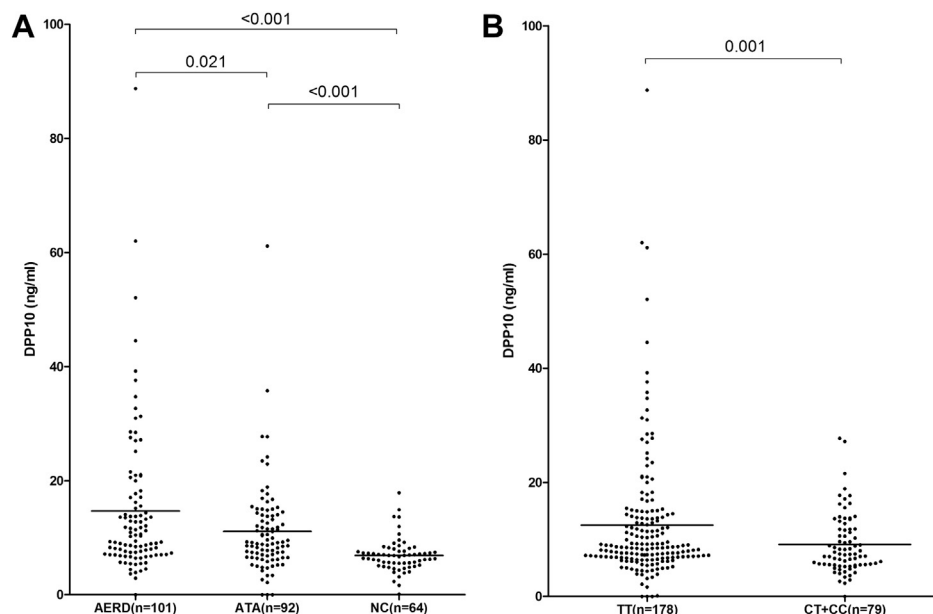


Figure 2. Serum dipeptidyl-peptidase 10 (DPP10) levels (nanograms per milliliter) according to (A) aspirin hypersensitivity and (B) the rs17048175 single-nucleotide polymorphism. AERD, aspirin-exacerbated respiratory disease; ATA, aspirin-tolerant asthma; NC, normal controls.

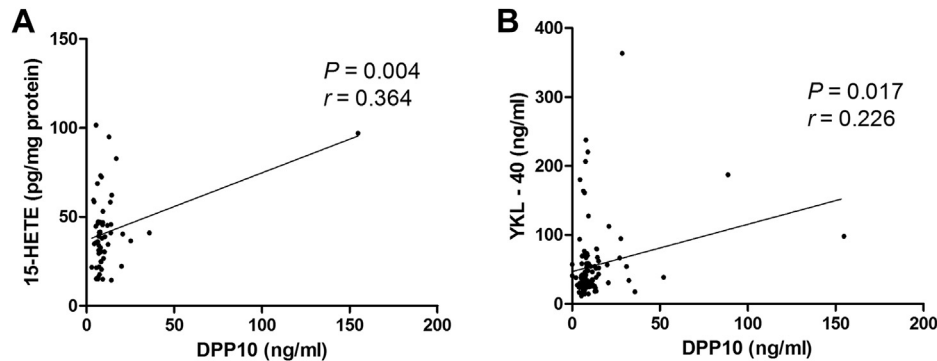


Figure 3. Correlations between serum dipeptidyl-peptidase 10 (DPP10) levels and markers of inflammation. Pearson correlation analysis showed a significant correlation between serum DPP10 levels. (A) Serum 15-hydroxyeicosatetraenoic acid (15-HETE) levels ($r = 0.226$, $P = .017$). (B) Serum YKL-40 levels ($r = 0.364$, $P = .004$).

not account for any differences in chronic rhinosinusitis, total eosinophil count, and sputum eosinophil count.

Serum DPP10 Levels Based on Asthma Phenotype and SNP Allele

Serum DPP10 levels in patients with asthma were significantly higher than in the NC group ($P < .001$; Table 1); however, there was no significant difference in DPP10 levels in patients with severe vs nonsevere asthma ($P = .659$). Regarding aspirin hypersensitivity, significantly increased DPP10 levels were present in patients with AERD compared with patients with ATA ($P = .021$). Figure 2 shows the serum DPP10 levels in the 3 study groups (AERD, 14.7 ± 13.0 ng/mL; ATA, 11.1 ± 8.1 ng/mL; NC, 6.9 ± 2.9 ng/mL; Table 1, Fig 2A), which were significantly different. In addition, the SNP allele could affect DPP10 levels ($P = .001$; Table 3, Fig 2B).

In the asthma group, serum DPP10 levels showed a positive correlation with eosinophilic inflammation markers, such as 15-HETE (Pearson $r = 0.364$, $P = .004$; Fig 3A) and YKL-40/CHI3L1 (Pearson $r = 0.226$, $P = .017$; Fig 3B). No significant correlations were found with total and sputum eosinophil counts.

To verify the potential of DPP10 as a serum biomarker for the asthma phenotype, receiver operating characteristic curve analysis was performed. Figure 4 shows the cutoff value of the serum DPP10 levels that discriminated the AERD phenotype from the NC group, which was 7.81 ng/mL, with 72.1% sensitivity and 75.9% specificity (area under the curve 0.792, $P < .001$).

Discussion

Dipeptidyl-peptidase 10 is a recently cloned dipeptidyl peptidase with structural similarity to DPP4, which is involved in cell–extracellular matrix interactions, apoptosis, and immunomodulation^{22,23}; however, it lacks the DPP4-like enzyme activity owing to the substitution of serine with glycine in its active site.²⁴ However, it can bind to specific voltage-gated potassium channels.²⁵ Localized expression of DPP10 in the bronchi, trachea, and leukocytes,¹⁶ increased expression of DPP10 in sera (based on an animal model of asthma), and a significant association of the DPP10 variant with asthma susceptibility^{15,26,27} suggest a potential role for DPP10 in the pathogenesis of asthma.

After a preliminary GWAS demonstrating an association of DPP10 SNPs with the AERD phenotype and a strong correlation with DPP10 levels, the rs17048175 SNP was targeted for a case–control association study composed of AERD, ATA, and NC groups. In this study, an association of the rs17048175 SNP with AERD was found. Enhanced DPP10 expression in the sera also occurred in the AERD group compared with the ATA and NC groups. The rs17048175 SNP could affect serum DPP10 levels and increase susceptibility to AERD. In addition, receiver operating characteristic curve analysis suggested DPP10 as a potential biomarker in the diagnosis of AERD.

A significantly different genotype distribution of the rs17048175 SNP was found between the severe and nonsevere asthma groups, although no significant difference was found in serum DPP10 level between these 2 groups. This finding might indicate an inadequate sample of patients with severe asthma and a large variance in individual values.

In this study, there was a significant correlation of serum DPP10 levels with serum 15-HETE levels. 15-HETE is the major metabolite of arachidonic acid on the 15-lipoxygenase pathway in humans.²⁸ Recently, eosinophils from patients with severe AERD have been shown to release 5-fold higher 15-HETE levels than from patients with mild asthma, suggesting that 15-HETE could be used as a biomarker for asthma severity.¹⁰ These findings mirror those in a previous report of the role of 15-HETE as a potential biomarker in patients with AERD in an in vitro diagnosis.¹¹ Therefore, serum DPP10 might be a potential biomarker for the AERD phenotype in which a genetic variant of DPP10 could be involved.

The DPP10 levels were significantly correlated with those of YKL-40, which has been reported as a serum biomarker in adult asthma, with a significant correlation with disease severity and airway remodeling.^{29,30} A study using mouse models of asthma

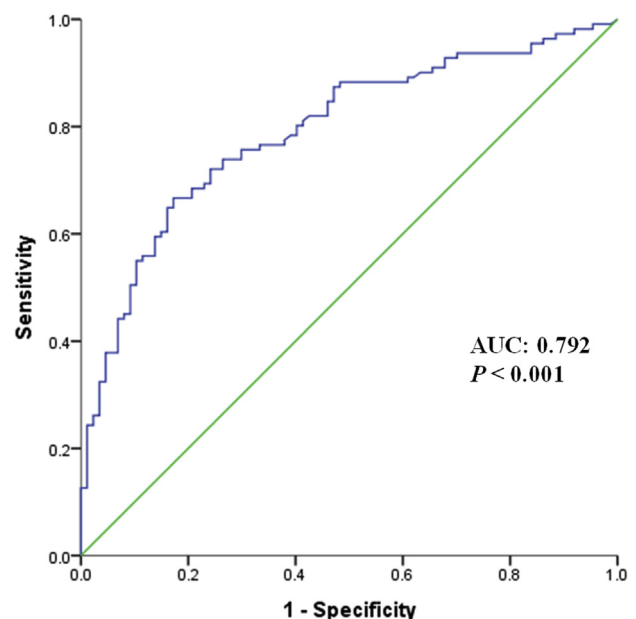


Figure 4. Receiver operating characteristic curve of serum dipeptidyl-peptidase 10 levels used to discriminate patients with aspirin-exacerbated respiratory disease from normal control subjects. AUC, area under the curve.

suggested a positive correlation of YKL-40 with T-helper cell type 2 and inflammation induced by interleukin-3 by inducing the accumulation of, and decreasing apoptosis by, inflammatory cells.³¹ There also was a strong correlation of the *CHI3L1* gene polymorphism with serum YKL-40 levels, asthma, and abnormal lung function.³² An examination of DPP10 levels during the L-ASA BPT showed no significant changes before vs after the L-ASA BPT (data not shown). This indicates that DPP10 might not be involved in acute inflammation triggered by aspirin exposure in patients with AERD but could affect chronic and persistent eosinophilic inflammation, a central feature of AERD.^{3–5,33} These findings suggest that DPP10 might represent chronic eosinophilic inflammation in the airways of patients with AERD.

Considering the biological role of DPP10 in persistent eosinophilic inflammation in patients with AERD, 3 observations were made. First an unknown peptidase activity of DPP10 could affect the activities of cytokines or chemokines that are important in persistent eosinophilic inflammation. Second, its interaction with voltage-gated potassium channels, which are ubiquitously expressed in smooth muscle and inflammatory cells in the airways,³⁴ could have an influence on airway hyperreactivity and remodeling by modulating the electrophysiologic properties of cells.^{15,35,36} Third, DPP10 could conjugate to a signaling pathway by modulating intracellular Ca^{2+} concentrations, leading to activation of inflammatory pathways. However, at present, no detailed evidence regarding the functional role of DPP10 in the pathogenesis of AERD exists.

To the authors' knowledge, this represents the first study to describe a potential role of DPP10 in AERD with its prognostic significance. However, this study does have some limitations. First, this study was limited by the retrospective nature of the evaluations. To clarify a potential biomarker of DPP10 for predicting the AERD phenotype, a prospective study should be performed. Second, the rs17048175 SNP was targeted for a case–control association study based on a previous finding in a GWAS. A preselection bias to elucidate the clinical relevance from the association results might be present; therefore, replication studies in other populations should be performed. To exclude a false-positive association, other candidate SNPs detected in the initial GWAS require validation with replication studies. Third, this study could not verify a functional evaluation of DPP10 in the pathogenesis of AERD. Therefore, the biological relevance of DPP10 in the pathogenesis of AERD remains to be clarified.

In conclusion, the present results suggest that a genetic variant of DPP10 could affect its expression, induce eosinophilic inflammation, and contribute to the susceptibility to AERD.

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