Original Article
Allergy Asthma Immunol Res. 2009 October;1(1):30-35.
doi: 10.4168/aair.2009.1.1.30
pISSN 2092-7355 • eISSN 2092-7363

AAIR
Allergy, Asthma & Immunology Research

Association analysis of peroxisome proliferator-activated receptors gamma gene polymorphisms with asprin hypersensitivity in asthmatics

Sun-Hee Oh[1], Se-Min Park[1], Jong-Sook Park[1], An-Soo Jang[1], Yong-Mok Lee[2], Soo-Taek Uh[2], Young Hoon Kim[3], In-Seon Choi[4], Mi-Kyeong Kim[5], Byung Lae Park[6], Hyoung-Doo Shin[6,7,**], Choon-Sik Park[1,*]

[1]*Genome Research Center for Allergy and Respiratory Disease, Soonchunhyang University, Bucheon Hospital, Bucheon, Korea*
[2]*Division of Allergy and Respiratory Disease, Soonchunhyang University, Seoul Hospital, Seoul, Korea*
[3]*Division of Allergy and Respiratory Disease, Soonchunhyang University, Chunan Hospital, Chunan, Korea*
[4]*Department of Allergy, Chonnam National University Medical School and Research Institute of Medical Sciences, Gwangju, Korea*
[5]*Department of Internal Medicine, Chungbuk National University, College of Medicine, Cheongju, Korea*
[6]*Department of Genetic Epidemiology, SNP Genetics, Inc., Seoul, Korea*
[7]*Department of Life Science, Sogang University, Seoul, Korea*

Purpose: Peroxisome proliferator-activated receptors (PPARs) are transcriptional factors activated by ligands of the nuclear hormone receptor superfamily. The activation of PPARγ regulates inflammation by downregulating the production of Th2 type cytokines and eosinophil function. In addition, a range of natural substances, including arachidonate pathway metabolites such as 15-hydroxyeicosatetranoic acid (15-HETE), strongly promote *PPARG* expression. Therefore, genetic variants of the *PPARG* gene may be associated with the development of aspirin-intolerant asthma (AIA). We investigated the relationship between single nucleotide polymorphism (SNP) of the *PPARG* gene and AIA. **Methods:** Based on the results of an oral aspirin challenge, asthmatics (n=403) were categorized into two groups: those with a decrease in FEV_1 of 15% or greater (AIA) or less than 15% (aspirin-tolerant asthma, ATA). We genotyped two single nucleotide polymorphisms in the *PPARG* gene from Korean asthmatics and normal controls (n=449): *+34C>G* (Pro12Ala) and *+82466C>T* (His449His). **Results:** Logistic regression analysis showed that *+82466C>T* and haplotype 1 (CC) were associated with the development of aspirin hypersensitivity in asthmatics (*P*=0.04). The frequency of the rare allele of *+82466C>T* was significantly higher in AIA patients than in ATA patients in the recessive model [*P*=0.04, OR=3.97 (1.08–14.53)]. In addition, the frequency of *PPARG* haplotype 1 was significantly lower in AIA patients than in ATA patients in the dominant model (OR=0.25, *P*=0.04). **Conclusions:** The *+82466C>T* polymorphism and haplotype 1 of the *PPARG* gene may be linked to increased risk for aspirin hypersensitivity in asthma.

Key Words: peroxisome proliferator-activated receptors gamma; aspirin; asthma; gene; polymorphism

INTRODUCTION

Peroxisome proliferator-activated receptors (PPARs) are transcriptional factors activated by ligands of the nuclear hormone receptor superfamily. This superfamily is divided into the steroid receptor family and the thyroid, vitamin D, and retinoid (or non-steroid) receptor family.[1] Three different PPAR subtypes have been identified: PPARα (PPARA), PPARγ (*PPARG*), and PPARδ (PPARD, which is also called PPARβ). *PPARG* (MIM #601487), located on chromosome 3p25, plays an important role in regulating adipocyte differentiation and lipid metabolism[2] as well as cell turnover.[3] However, the production of immune-modulating cytokines in various cell types was reported

Correspondence to: Choon-Sik Park, M.D., Ph.D.*, Division of Allergy and Respiratory Medicine, Department of Internal Medicine, Soonchunhyang University Bucheon Hospital, 1174 Jung-dong, Wonmi-gu, Bucheon 420-021, Korea.
Tel: +82-32-621-5105; Fax: +82-32-621-5016; E-mail: mdcspark@unitel.co.kr
Hyoung-Doo Shin, M.D., Ph.D.**, Department of Life Science, Sogang University, 1 Shinsu-dong, Mapo-gu, Seoul 121-742, Korea.
Tel: +82-2-705-8615; Fax: +82-2-2026-4299; E-mail: hdshin@sogang.ac.kr
Received: June 26, 2009; Accepted: August 31, 2009
• There are no financial or other issues that might lead to conflict of interest.

to downregulate the expression of *PPARG*, and block adipocyte differentiation. It is well established that a variety of natural substances, including arachidonate pathway metabolites such as 15-hydroxyeicosatetranoic acid (15-HETE), strongly promote *PPARG* expression.[3-5] Stimulation of the *PPARG* ligand significantly inhibited the downregulation of eosinophil function.[6] *PPARG* expression is associated with the inflammatory and remodeling responses in the asthmatic airway.[7]

Among the sub-phenotypes of asthma, aspirin-intolerant asthma (AIA) refers to the development of bronchoconstriction in asthmatic individuals following the ingestion of aspirin or other non-steroidal anti-inflammatory drugs. This syndrome is characterized by the 'aspirin triad' of aspirin hypersensitivity, bronchial asthma, and nasal polyposis.[8] Most clinical investigators now include chronic hyperplastic eosinophilic sinusitis (CHES) as a fourth hallmark of aspirin-exacerbated respiratory disease (AERD).[9] As is true for other asthmatic individuals, the airways of patients with AIA show signs of persistent inflammation, with marked eosinophilia, epithelial disruption, cytokine production, and upregulation of inflammatory molecules.[10] Although the pathogenesis of AIA has not been elucidated completely, multiple points of overproduction or underproduction of critical mediators in the metabolism of arachidonic acid, including leukotrienes, lipoxins, thromboxane, and prostaglandins, probably account for the susceptibility to aspirin.[10] In addition, the levels of proinflammatory, immune cytokines and chemokines, including IL-2, IL-3, IL-4, IL-5, IL-13, GM-CSF, and eotaxin, are increased in the airways and systemic circulation in AIA.[11,12] The production of these molecules is regulated by various transcription factors, including *PPARG*. Therefore, genetic variants of the *PPARG* gene may be associated with the development of asthma or aspirin intolerance in asthmatics.

Recently, Palmer et al.[13] reported that *PPARG* gene polymorphisms are associated with a risk for asthma exacerbation in Caucasian populations. We also reported that the homozygous haplotype combination of *+34C>G* (Pro12Ala) was associated with an increased risk for asthma exacerbation.[13] To our knowledge, however, no study has analyzed the potential associations of the two common polymorphisms of the *PPARG* gene [*+34C>G* (Pro12Ala) and *+82466C>T* (His449His)] with the risk for aspirin intolerance in asthmatics.

MATERIALS AND METHODS

Subjects

The subjects were recruited from the Asthma Genome Research Center, comprising Soonchunhyang Bucheon, Seoul, and Chunan Hospitals, and Chunnam and Chungbuk University Hospitals in Korea. All of the subjects were Korean. A clinical history was obtained for each patient, using a physician-administered questionnaire that included the history of aspirin hypersensitivity. The asthmatics had compatible clinical symptoms and physical characteristics (Global Initiative for Asthma).[14] All patients had a history of dyspnea and wheezing during the previous 12 months plus one of the following: 1) >15% increase in FEV_1 or >12% increase plus 200 mL following inhalation of a short-acting bronchodilator; 2) <10 mg/mL PC_{20} methacholine; or 3) >20% increase in FEV_1 following 2 weeks of treatment with inhaled steroids and long-acting bronchodilators. The asthmatics had experienced no exacerbation of asthma or any respiratory tract infection in the 6 weeks preceding the oral aspirin challenge (OAC). Based on the results of the OAC, the asthmatics (n=403) were categorized into two groups: those with a decrease in FEV_1 of 15% or greater (AIA, n=60), and those with a decrease of less than 15% [aspirin-tolerant asthma (ATA), n=343]. The oral provocation test was performed with increasing doses of aspirin (10-450 mg Astrix; Mayne Pharma, Melbourne, Australia) using a modification of a previously described method.[15,16] Aspirin-intolerance bronchospasm, as reflected by the rate (%) of FEV_1 decline, was calculated as the difference between the pre-challenge and post-challenge FEV_1 values divided by the pre-challenge FEV_1. Subjects who developed skin manifestations were labeled as positive responders (n=60). Normal controls (n=449) were recruited from among spouses of the patients or members of the general population who answered negatively to a screening questionnaire regarding respiratory symptoms.[17] The normal controls had no history of aspirin intolerance and had FEV_1 values >80% predicted, PC_{20} methacholine >10 mg/mL, and normal findings on simple chest radiograms. Skin prick tests were performed with 24 common aeroallergens (Bencard, Brentford, UK). Atopy was defined as one or more positive reactions (>3 mm in diameter) on the skin prick test. Total IgE was measured using a UniCAP system (Pharmacia Diagnostics, Uppsala, Sweden). Subjects with diabetes mellitus were excluded because the *PPARG* polymorphism is reported to be associated with the development of diabetes mellitus in Koreans.[18] All subjects gave written informed consent to participate in the study, and the protocol was approved by the local ethics committees.

Genotyping the SNPs in the *PPARG* gene

The amplifying primers and probes used to genotype the polymorphic sites by the single base method were as described previously.[19] Primer Express (Applied Biosystems, Foster City, CA, USA) was used to design the PCR primers and MGB TaqMan probes. One allelic probe was labeled with FAM dye; and the other, with fluorescent VIC dye. PCR was performed in TaqMan Universal Master Mix, without uracil-N-glycosylase (Applied Biosystems), containing 900 nM TaqMan MGB-probe and 200 nM primer. The reaction was performed in a 384-well plate in a total reaction volume of 5 μL, using 20 ng of genomic DNA. The plate was heated in a thermal cycler (PE 9700; Applied Biosystems) for 2 min at 50°C and then for 10 min at 95°C, followed by 40 cycles of 95°C for 15 sec and 60°C for 1 min. The fluores-

cence intensity of each reaction was determined using a Prism 7900 HT detector (Applied Biosystems), and the fluorescence data were analyzed by automated software (SDS 2.1).

Statistical analysis

We applied the widely used Lewontin's D' (|D'|) and R^2 measures of linkage disequilibrium to all pairs of biallelic loci.[20] Haplotype associations were estimated using HaploScore (http://www.biostat.wustl.edu/genetics/geneticssoft/), which computes score statistics to test for associations between a given haplotype and a wide variety of traits, including binary, ordinal, quantitative, and Poisson parameters. The genetic effects of the haplotypes were analyzed in the same way as the SNPs. The distributions of the *PPARG* SNP genotypes and haplotypes among the subjects with asthma and the normal subjects were analyzed with logistic regression models that controlled for age (continuous value), gender (male=0, female=1), atopy status (non-atopy=0, atopy=1), body mass index (BMI; continuous value), and smoking status (nonsmoker=0, ex-smoker=1, smoker=2) as covariates. The data were managed and analyzed using SPSS ver. 10.0 (SPSS, Chicago, IL, USA). A value of $P \leq 0.05$ was regarded as statistically significant.

RESULTS

Characteristics of the study subjects

We recruited 403 subjects from the asthma cohort. The clinical characteristics of the study subjects are summarized in Table 1. The maximum fall in FEV_1 during the 5-hr follow-up period after aspirin challenge was used as the value for the aspirin-induced fall in FEV_1. Aspirin-induced declines in FEV_1 ranged from -15% to 68%. The log transformed PC_{20} methacholine values for the asthmatics were significantly lower among those with AIA than among those with ATA (P=0.013, Table 1).

PPARG polymorphisms and the risk for aspirin intolerance in asthmatics

Two SNPs, *+34C>G* (P12A) on exon 3 and *+82466C>T* (H449H) on exon 8, in the PPARG gene were genotyped for the association study. The minor allele frequencies (MAFs) of these two SNPs in the Korean population were 0.042 (*+34C>G*) and 0.168 (*+82466C>T*) (Table 2). The genotype distributions of the two SNPs were in Hardy-Weinberg equilibrium for all subjects (P> 0.05, Table 2). Four haplotypes were constructed, and two haplotypes with a frequency >0.05 were used for the analysis. Using

Table 1. The clinical profiles of the study subjects

Description	Normal controls	ATA	AIA	*P* value
Number	449	343	60	–
Age (yr [range])	44 (5-80)	48 (14-77)	45.5 (17-72)	0.375
Duration (yr [range])	–	3 (1-60)	5 (1-40)	0.383
Onset of age (yr [range])	–	41 (1-76)	38.5 (1-67)	0.186
Sex (Male, %)	40.31	33.53	35	0.824
Smoker (%)	17.16	13.12	10	0.127
Atopy (%)	35.15	56.01	58.33	0.738
FVC (% predicted)	94.24±0.59	85.19±0.93	85.03±2.26	0.95
FEV_1 (% predicted)	104.14±0.72	83.31±1.17	79.23±2.85	0.181
log (PC_{20} methacholine [mg/mL])	1.39±0.002	0.31±0.04	0.06±0.1	0.013
BMI (kg/m^2)	23.81±0.16	24.47±0.18	23.92±0.37	0.221
Blood eosinophil (%)	2.37±0.1	6.2±0.36	6.56±0.69	0.23
log transformed total IgE (IU/mL)	1.66±0.03	2.14±0.04	2.24±0.07	0.269
Rate of FEV_1 decline after aspirin challenge (%)	–	3.74±0.27	25.42±2.09	<0.0001

Values are mean±S.E. ATA and AIA represent aspirin-tolerant asthma and aspirin-intolerant asthma, respectively.
P values are obtained using T test or χ^2 test between AIA and ATA.

Table 2. The frequencies, heterozygosity and Hardy-Weinberg Equation of SNPs on *PPARG* gene in the study population

Loci	rsSNP	Region	Amino acid change	Genotype				Frequency	Heterozygosity	HWE
				C/C	C/R	R/R	N			
+34C>G	rs1801282	Exon4	Pro12Ala	784	65	3	852	0.042	0.076	0.192
+82466C>T	rs3856806	Exon10	His446His	594	230	28	852	0.168	0.270	0.327

C/C, C/R and C/C represent common allele, heterozygosity and rare allele.
**P* values of deviation from Hardy-Weinberg Equilibrium (HWE) in the study population.

multiple logistic regression models, both SNPs and the two haplotypes (*ht1* and *ht2*) were analyzed for associations with the risk for aspirin intolerance in the asthmatics (Table 3). The analysis revealed that *PPARG+82466C>T* was associated with aspirin intolerance in the recessive model, and there were more subjects homozygous for the rare alleles *PPARG+82466C>T* in the AIA group than in the ATA group in the recessive model (6.66% vs 2.04%, *P*=0.04, OR=3.97 [1.08-14.53]). In the haplotype analysis, there were fewer subjects with *ht1* in the AIA group than in the ATA group (93.33% vs 97.96%, *P*=0.04, OR=0.25 [0.07-0.92]) in the dominant model. The rate (%) of FEV_1 decline after aspirin challenge is the most important parameter for the diagnosis of aspirin intolerant asthmatics, and thus we used linear regression analysis to investigate the associations between the SNP (*+82466C>T*), haplotype 1, and percentage fall of FEV_1 following aspirin challenge. Haplotype 1 and *+82466C>T* showed the strongest association with the rate (%) of FEV_1 decline after aspirin challenge in the asthmatics. Asthmatics homozygous for the rare *+82466C>T* allele had a greater decline in FEV_1 after aspirin provocation than those with the common allele (*P*=0.0004, Fig. 1A). In the haplotype analysis, the decline in FEV_1 after aspirin provocation was greater in asthmatics lacking the *ht1* haplotype than in those with the haplotype (*P*=0.0004, Fig. 1B).

DISCUSSION

PPARs are receptors for steroids, thyroid hormone, vitamin D, and retinoic acid,[1] and they regulate adipocyte differentiation, lipid metabolism,[2] and cellular turnover.[3] Furthermore, polymorphisms of the *PPARG* gene have been associated with diabetes, obesity, and metabolic syndrome.[18,21-25] The two common polymorphisms of *PPARG* were reported to modify susceptibility to type II diabetes mellitus, obesity, and sub-phenotypes of metabolic syndrome in Koreans[18,21,22] and Caucasians.[23-26] Therefore, we excluded subjects with diabetes from the analysis and adjusted the results for the BMI.

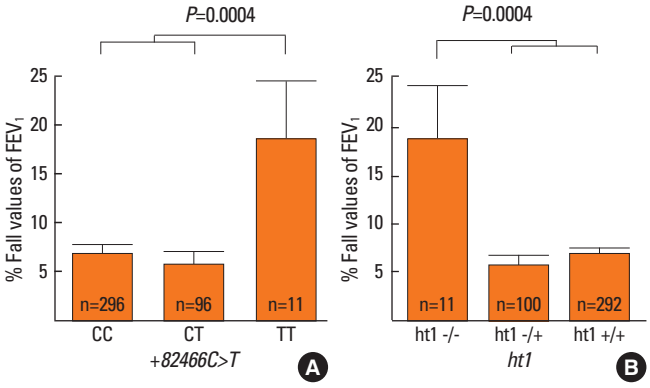

Fig. 1. The comparison of the rate of fall (%) of FEV_1 with aspirin provocation between subjects possessing the rare and common alleles by (A) *+82466C>T* and (B) haplotype 1 of *PPARG* gene. The *P* values were obtained by linear regression analysis, controlled for age (continuous value), gender (male=0, female=1), atopy status (non-atopy=0, atopy=1), smoking status (non-smoker=0, ex-smoker=1, smoker=2), and BMI (continuous value) as covariates.

Table 3. Comparisons of genotype and haplotype distributions of *PPARG* between the subjects with AIA and those with ATA

Loci	Position	rsSNP	Genotype	N (%)		Co-dominant		Dominant		Recessive	
				AIA	ATA	OR (95%CI)	*P* value	OR (95%CI)	*P* value	OR (95%CI)	*P* value
+34C>G	Exon4	rs1801282	C	55 (91.67%)	319 (93%)	1.38 (0.55±3.44)	0.49	1.14 (0.41±3.14)	0.8	–	–
			CG	4 (6.67%)	24 (7%)						
			G	1 (1.66%)	0 (0%)						
+82466C>T	Exon10	rs3856806	C	46 (76.67%)	250 (72.89%)	1.02 (0.59±1.75)	0.95	0.79 (0.41±1.51)	0.47	3.97 (1.08±14.53)	**0.04**
			CT	10 (16.67%)	86 (25.07%)						
			T	4 (6.66%)	7 (2.04%)						
ht1	–	–	–/–	4 (6.67%)	7 (2.04%)	0.89 (0.52±1.5)	0.65	0.25 (0.07±0.92)	**0.04**	1.09 (0.58±2.04)	0.79
			ht1/–	12 (20%)	88 (25.66%)						
			ht1/ht1	44 (73.33%)	248 (72.3%)						
ht2	–	–	–/–	48 (80%)	269 (78.43%)	1.03 (0.56±1.89)	0.93	0.9 (0.45±1.78)	0.75	3.48 (0.6±20.18)	0.16
			ht2/–	10 (16.67%)	70 (20.41%)						
			ht2/ht2	2 (3.33%)	4 (1.16%)						

ATA and AIA represent aspirin-tolerant asthma and aspirin-intolerant asthma, respectively. C/C, C/R and R/R represent common allele, heterozygosity and rare allele. The *P* values were obtained by logistic regression analysis, controlled for age (continuous value), sex (male=0, female=1), atopy status (non-atopy=0, atopy= 1) and smoking status (non-smoker=0, ex-smoker=1, smoker=2) and BMI (continuous value) as co-variables.
Bold faces mean the *P*<0.05.

In addition to their metabolic effects, PPARs/RXRs heterodimerize with various receptors, and these heterodimers regulate the transcription of genes involved in allergic inflammation and airway remodeling.[7] A notable finding in our study was that the SNP *PPARG+82466C>T* was associated with aspirin intolerance. There were more subjects homozygous for the rare *PPARG+82466C>T* allele with AIA than with ATA in the recessive model (Table 3). In the haplotype analysis, there were significantly fewer subjects with *ht1* in the AIA group than in the ATA group. Based on linear regression analysis, the decline in FEV_1 after aspirin challenge in asthmatics homozygous for the rare *+82466C>T* allele was 2.5 times that in asthmatics with the common allele. In the haplotype analysis, the decline in FEV_1 after aspirin provocation was greater in asthmatics without the *ht1* haplotype than in those with the haplotype. These results suggest that a rare *PPARG+82466C>T* allele and haplotype 1 are predisposing factors for aspirin intolerance in asthmatics.

Some eicosanoids activate *PPARG*; these include 13-hydroxyoctadecadienoic acid,[27] 15-hydroxyeicosatetraenoic acid (15-HETE), and 15-deoxy-12,14 prostaglandinJ2 (15d-PGJ 2),[28] a prostaglandin D2 metabolite. The accumulation of 15-HETE after aspirin-stimulation of peripheral leukocytes from patients with AIA may activate *PPARG* to modulate airway inflammation.[29] As metabolites of the arachidonate pathway, such as 15-HETE and 15d-PGJ 2, regulate transcription and endogenous ligands for the *PPARG* gene, changes in these mediators in AIA may be responsible for the change in the amount of PPAR-r in the target organ of aspirin hypersensitivity. Therefore, altered synthesis of 15-HETE and 15d-PGJ 2 in AIA may activate *PPARG* differently from the activation in ATA. In addition, the *PPARG* agonist rosiglitazone upregulates both the mRNA expression of two lipoxygenase enzymes (platelet-type 12-lipoxygenase and 15-lipoxygenase) and the secretion of their eicosanoid products, 12- and 15-HETE. The rosiglitazone-induced increase in *PPARG* mRNA expression is blocked entirely by the lipoxygenase (LO) inhibitor baicalein and is restored by the addition of exogenous 12-HETE.[30] In the process of lipoxin formation, aspirin acetylation does not totally inhibit the catalysis of COX-2, and this can affect the production of 12-HETE, 15-HETE, and 13-HODE. Previously, we observed that the alleles of the ALOX5 and ALOX5AP promoters cannot be considered prominent risk factors for the development of AIA. However, a genetic variant involving a tandem repeat (GGGCGG; Sp1-binding motif) in the ALOX5 promoter is associated with the severity of airway hyper-responsiveness in AIA patients.[31] Therefore, genetic polymorphism of the rare *PPARG+82466C>T* allele may contribute to the development of aspirin intolerance via a functional change in the gene, such as an altered response to the LO products or altered induction of the two LO enzymes. The molecular mechanism by which the rare *PPARG+82466C>T* allele, which does not change the encoded protein, modulates the phenotype is even less clear. It is possible that these variants are in linkage disequilibrium with other functional variants, although the *PPARG* locus has been the focus of intense scrutiny as a candidate for diabetes and related traits, and no such variant has been found.

In summary, we genotyped two SNPs in the *PPARG* gene, *+34C>G* (Pro12Ala) and *+82466C>T* (His449His), and examined the association of each with the development of aspirin intolerance in asthmatics. Association analysis showed that *PPARG+82466C>T* and *PPARG* haplotypes were associated with the development of aspirin intolerance. Therefore, the *+82466C>T* polymorphism in the coding region of the *PPARG* gene may confer aspirin hypersensitivity via the regulation of gene expression. This information may be useful in the development of new strategies for the diagnosis and control of aspirin intolerance. Further studies are required to define the molecular mechanisms by which common variation at the *PPARG* locus modulates aspirin hypersensitivity, and to determine whether this suggests treatment strategies in asthmatics with different *PPARG* genotypes.

ACKNOWLEDGMENTS

This work was supported by a grant from the Korea Health 21 R&D Project, (A010249), and the DNA samples were generously provided by the Soonchunhyang University Bucheon Hospital Biobank, a member of the National Biobank of Korea, supported by the Ministry of Health, Welfare, and Family Affairs, Republic of Korea.

REFERENCES

1. Mangelsdorf DJ, Thummel C, Beato M, Herrlich P, Schütz G, Umesono K, Blumberg B, Kastner P, Mark M, Chambon P, Evans RM. The nuclear receptor superfamily: the second decade. Cell 1995;83:835-9.
2. Tontonoz P, Hu E, Spiegelman BM. Stimulation of adipogenesis in fibroblasts by PPAR gamma 2, a lipid-activated transcription factor. Cell 1994;79:1147-56.
3. Chinetti G, Griglio S, Antonucci M, Torra IP, Delerive P, Majd Z, Fruchart JC, Chapman J, Najib J, Staels B. Activation of proliferator-activated receptors alpha and gamma induces apoptosis of human monocyte-derived macrophages. J Biol Chem 1998;273:25573-80.
4. Jiang C, Ting AT, Seed B. PPAR-gamma agonists inhibit production of monocyte inflammatory cytokines. Nature 1998;391:82-6.
5. Huang JT, Welch JS, Ricote M, Binder CJ, Willson TM, Kelly C, Witztum JL, Funk CD, Conrad D, Glass CK. Interleukin-4-dependent production of PPAR-gamma ligands in macrophages by 12/15-lipoxygenase. Nature 1999;400:378-82.
6. Ueki S, Matsuwaki Y, Kayaba H, Oyamada H, Kanda A, Usami A, Saito N, Chihara J. Peroxisome proliferator-activated receptor gamma regulates eosinophil functions: a new therapeutic target for allergic airway inflammation. Int Arch Allergy Immunol 2004;134 Suppl 1:30-6.
7. Benayoun L, Letuve S, Druilhe A, Boczkowski J, Dombret MC, Mechighel P, Megret J, Leseche G, Aubier M, Pretolani M. Regula-

tion of peroxisome proliferator-activated receptor gamma expression in human asthmatic airways: relationship with proliferation, apoptosis, and airway remodeling. Am J Respir Crit Care Med 2001;164:1487-94.
8. Samter M, Beers RF Jr. Concerning the nature of intolerance to aspirin. J Allergy 1967;40:281-93.
9. Stevenson DD, Sanchez-Borges M, Szczeklik A. Classification of allergic and pseudoallergic reactions to drugs that inhibit cyclooxygenase enzymes. Ann Allergy Asthma Immunol 2001;87:177-80.
10. Szczeklik A, Stevenson DD. Aspirin-induced asthma: advances in pathogenesis, diagnosis, and management. J Allergy Clin Immunol 2003;111:913-21
11. Bachert C, Wagenmann M, Hauser U, Rudack C. IL-5 synthesis is upregulated in human nasal polyp tissue. J Allergy Clin Immunol 1997;99:837-42.
12. Min JW, Jang AS, Park SM, Lee SH, Lee JH, Park SW, Park CS. Comparison of plasma eotaxin family level in aspirin-induced and aspirin-tolerant asthma patients. Chest 2005;128:3127-32.
13. Palmer CN, Doney AS, Ismail T, Lee SP, Murrie I, Macgregor DF, Mukhopadhyay S. PPARG locus haplotype variation and exacerbations in asthma. Clin Pharmacol Ther 2007;81:713-8.
14. National Asthma Education and Prevention Program. Expert panel report: guidelines for the diagnosis and management of asthma update on selected topics. J Allergy Clin Immunol 2002;110:S141-S219.
15. Kim TH, Chang HS, Park SM, Nam BY, Park JS, Rhim T, Park HS, Kim MK, Choi IS, Cho SH, Chung IY, Park BL, Park CS, Shin HD. Association of angiotensin I-converting enzyme gene polymorphisms with aspirin intolerance in asthmatics. Clin Exp Allergy 2008;38:1727-37.
16. Cormican LJ, Farooque S, Altmann DR, Lee TH. Improvements in an oral aspirin challenge protocol for the diagnosis of aspirin hypersensitivity. Clin Exp Allergy 2005;35:717-22.
17. Ferris BG. Epidemiology Standardization Project (American Thoracic Society). Am Rev Respir Dis 1978;118:1-120.
18. Moon MK, Cho YM, Jung HS, Park YJ, Yoon KH, Sung YA, Park BL, Lee HK, Park KS, Shin HD. Genetic polymorphisms in peroxisome proliferator-activated receptor gamma are associated with Type 2 diabetes mellitus and obesity in the Korean population. Diabet Med 2005;22:1161-6.
19. Oh SH, Park SM, Lee YH, Cha JY, Lee JY, Shin EK, Park JS, Park BL, Shin HD, Park CS. Association of peroxisome proliferator-activated receptor-gamma gene polymorphisms with the development of asthma. Respir Med 2009;103:1020-4.
20. Hedrick PW. Gametic disequilibrium measures: proceed with caution. Genetics 1987;117:331-41.
21. Kim KS, Choi SM, Shin SU, Yang HS, Yoon Y. Effects of peroxisome proliferator-activated receptor-gamma 2 Pro12Ala polymorphism on body fat distribution in female Korean subjects. Metabolism 2004;53:1538-43.
22. Rhee EJ, Oh KW, Lee WY, Kim SY, Oh ES, Baek KH, Kang MI, Kim SW. Effects of two common polymorphisms of peroxisome proliferator-activated receptor-gamma gene on metabolic syndrome. Arch Med Res 2006;37:86-94.
23. Doney AS, Fischer B, Cecil JE, Boylan K, McGuigan FE, Ralston SH, Morris AD, Palmer CN. Association of the Pro12Ala and C1431T variants of PPARG and their haplotypes with susceptibility to Type 2 diabetes. Diabetologia 2004;47:555-8.
24. Altshuler D, Hirschhorn JN, Klannemark M, Lindgren CM, Vohl MC, Nemesh J, Lane CR, Schaffner SF, Bolk S, Brewer C, Tuomi T, Gaudet D, Hudson TJ, Daly M, Groop L, Lander ES. The common PPARgamma Pro12Ala polymorphism is associated with decreased risk of type 2 diabetes. Nat Genet 2000;26:76-80.
25. Ardlie KG, Lunetta KL, Seielstad M. Testing for population subdivision and association in four case-control studies. Am J Hum Genet 2002;71:304-11.
26. Buzzetti R, Petrone A, Ribaudo MC, Alemanno I, Zavarella S, Mein CA, Maiani F, Tiberti C, Baroni MG, Vecci E, Arca M, Leonetti F, Di Mario U. The common PPAR-gamma2 Pro12Ala variant is associated with greater insulin sensitivity. Eur J Hum Genet 2004;12:1050-4.
27. Nagy L, Tontonoz P, Alvarez JG, Chen H, Evans RM. Oxidized LDL regulates macrophage gene expression through ligand activation of PPARgamma. Cell 1998;93:229-40.
28. Forman BM, Tontonoz P, Chen J, Brun RP, Spiegelman BM, Evans RM. 15-Deoxy-delta 12, 14-prostaglandin J2 is a ligand for the adipocyte determination factor PPAR gamma. Cell 1995;83:803-12.
29. Kowalski ML, Ptasinska A, Bienkiewicz B, Pawliczak R, DuBuske L. Differential effects of aspirin and misoprostol on 15-hydroxyeicosatetraenoic acid generation by leukocytes from aspirin-sensitive asthmatic patients. J Allergy Clin Immunol 2003;112:505-12.
30. Limor R, Sharon O, Knoll E, Many A, Weisinger G, Stern N. Lipoxygenase-derived metabolites are regulators of peroxisome proliferator-activated receptor gamma-2 expression in human vascular smooth muscle cells. Am J Hypertens 2008;21:219-23.
31. Kim SH, Bae JS, Suh CH, Nahm DH, Holloway JW, Park HS. Polymorphism of tandem repeat in promoter of 5-lipoxygenase in ASA-intolerant asthma: a positive association with airway hyperresponsiveness. Allergy 2005;60:760-5.