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Association of peroxisome proliferator-activated receptor-gamma gene polymorphisms with the development of asthma

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Summary
Background: The peroxisome proliferator-activated receptors (PPAR) are the nuclear hormone receptor superfamily of ligand-activated transcriptional factors. PPAR-gamma (PPARG) activation downregulates production of Th2 type cytokines and *eosinophil* function. Additionally, treatment with a synthetic PPARG ligand can reduce lung inflammation and IFN-gamma, IL-4, and IL-2 production in experimental allergic asthma. In patients with asthma, *PPARG* gene expression is known to be associated with the airway inflammatory and remodeling responses. Thus, genetic variants of *PPARG* may be associated with the development of asthma.
Methods: We genotyped two single nucleotide polymorphisms on the *PPARG* gene, $+34C>G$ (Pro12Ala) and $+82466C>T$ (His449His), in Korean subjects (839 subjects with asthma and 449 normal controls).
Results: Association analysis using logistic regression analysis showed that $+82466C>T$ and haplotypes 1(CC) and 2(CT) were associated with the development of asthma ($p = 0.01$–0.04). The frequency of *PPARG-ht2* was significantly lower in the patients with asthma compared to the normal controls in codominant and dominant models ($p = 0.01$, $p_{corr} = 0.03$ and $p = 0.02$, $p_{corr} = 0.03$, respectively). Conversely, the frequency of *PPARG-ht1* was significantly higher in

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the patients with asthma compared to the normal controls in the codominant model [$p = 0.04$, OR: 1.27 (1.01−1.6)]. In addition, the rare allele frequency of $+82466C > T$ was significantly lower in patients with asthma in comparison to normal controls in the codominant model (OR: 0.78, $p = 0.04$). Thus, polymorphism of the *PPARG* gene may be linked to an increased risk of asthma development.

Introduction

The peroxisome proliferator-activated receptors (PPAR) are the nuclear hormone receptor superfamily of ligand-activated transcriptional factors, which include receptors for steroids, thyroid hormone, vitamin D, and retinoic acid.[1] Three subtypes of PPAR are known, PPAR-alpha, PPAR-delta, and PPAR-gamma (PPARG). *PPARG* (MIM# 601487), located on chromosome 3p25, was originally characterized as a regulator of adipocyte differentiation and lipid metabolism,[2] and of cellular turnover.[3] In addition, PPARG activation has been known to downregulate the synthesis and release of immune modulating cytokines from various cell types.[4] That a range of naturally occurring substances, including the metabolites of arachidonate pathway, such as 15-hydroxyeicosatetranoic acid (15-HETE), or Th2 cytokines, such as IL-4, are potent inducers of *PPARG* expression has been well established.[5] In contrast, stimulation of the PPARG ligand was found to significantly inhibit production of the Th2 type cytokines and downregulate eosinophil functions.[6,7] Additionally, treatment with a synthetic PPARG ligand can reduce lung inflammation and IFN-gamma, IL-4, and IL-2 production in experimental allergic asthma.[8] In subjects with asthma, *PPARG* expression is known to be associated with the airway inflammatory and remodeling responses.[9] Thus, genetic variants of the *PPARG* gene may be associated with the development of asthma.

Recently, Palmer et al. reported that *PPARG* gene polymorphisms were associated with the risk of asthma exacerbation in Caucasian populations.[10] The homozygous haplotype combination of $+34C > G$ (Pro12Ala) was associated with an increased risk for asthma exacerbation.[10] However, to the best of our knowledge, no previous study has analyzed potential associations between the two common polymorphisms of the *PPARG* gene, $+34C > G$ (Pro12Ala) and $+82466C > T$ (His449His), with the risk of asthma.

Materials and methods

Subjects

The subjects were recruited from the Asthma Genome Research Center, which consists of Soonchunhyang University hospitals in Bucheon, Seoul, and Chunan, Korea. All of the subjects were Korean. A clinical history was obtained for each patient using a physician-administered questionnaire.[11] And the patients with asthma had compatible clinical symptoms and physical characteristics.[12] Each patient showed airway reversibility [as documented by inhalant bronchodilator-induced improvement of more than 15% of forced expiratory volume in 1 s (FEV_1)] and/or airway hyperreactivity of less than 10 mg/ml of methacholine. Normal controls ($n = 449$) were recruited from spouses of the patients or members of the general population who answered negatively to a screening questionnaire regarding respiratory symptoms.[11] The controls 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.[13] Atopy was defined as one or more positive reactions (>3 mm in diameter or greater than histamine reaction of 1 mg/ml) on the skin prick test. Total IgE was measured using the UniCAP system (Pharmacia Diagnostics, Uppsala, Sweden). The subjects with diabetes mellitus were excluded because the *PPARG* polymorphism was reported to be associated with the development of diabetes mellitus in Korea.[14] All subjects gave written informed consent to participate in the study, and the protocols were approved by the local ethics committees.

Genotyping of the single nucleotide polymorphism (SNPs) on the *PPARG* gene

For genotyping of polymorphic sites, amplifying primers and probes were designed for TaqMan® (Table 1) and the single

Table 1 Primer sequence for genotyping of SNPs on *PPARG* gene.

Approaches	Loci	Region	Primer sequence	Orientation	Location
Variant Screening					
	$+34C > G$	Exon3	GTTATGGGTGAAACTCTGGGAGATT	Forward	−3/+22
			GCAGACAGTGTATCAGTGAAGGAAT	Reverse	+44/+68
			ATTGACCCAGAAAG	VIC	+23/+41
			ATTGACGCAGAAAG	FAM	
	$+82466C > T$	Exon8	CAGAAAATGACAGACCTCAGACAGA	Forward	+824271/+82442
			CGTCTTCTTGATCACCTGCAGTAG	Reverse	+82463/+82486
			CTGCACGTGTTCCG	VIC	+82449/+82462
			CTGCACATGTTCCG	FAM	