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Original Article

Association of peroxisome proliferator-activated receptor-gamma gene polymorphisms and gene-gene interaction with asthma risk in a Chinese adults population

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Abstract: Aims: To investigate the association between single nucleotide polymorphism (SNP) of peroxisome proliferator-activated receptors γ (PPAR γ) and additional gene-gene interactions on asthma risk. Methods: A total of 882 subjects (602 males, 280 females), with a mean age of 61.3±14.8 years old, including 430 asthma patients and 452 normal subjects were selected in this study, including the genotyping of polymorphisms. Logistic regression was performed to investigate association between SNP and asthma. Generalized MDR (GMDR) was used to analysis the interaction among four SNP. Results: Asthma risk was significantly lower in carriers of Ala allele of the rs1805192 polymorphism than those with Pro/Pro (Pro/Ala+ Ala/Ala *versus* Pro/Pro, adjusted OR (95% CI)=0.70 (0.51-0.94). In addition, we also found a significant association between rs10865710 and asthma, asthma risk was significantly lower in carriers of G allele of the rs10865710 polymorphism than those with CC (CG+ GG *versus* CC, adjusted OR (95% CI)=0.68 (0.55-0.95). There was a significant three-locus model (P=0.0107) involving rs1805192, rs10865710 and rs709158, indicating a potential gene-gene interaction among rs1805192, rs10865710 and rs709158. Overall, the three-locus models had a cross-validation consistency of 10 of 10, and had the testing accuracy of 60.72% after covariates adjustment. Conclusions: Our results support an important association of rs1805192 and rs10865710 with asthma, and additional interaction among rs1805192, rs10865710 and rs709158.

Keywords: Asthma, PPAR γ, interaction, SNP

Introduction

Asthma is one of common disorders of the airway. The burden of asthma appears to be increasing world-wide and both morbidity and mortality from asthma have increased in many parts of the world, making it a global health concern. Asthma is defined as a chronic inflammatory disease of the airway that is characterized by increased responsiveness to a multiplicity of stimuli [1]. Although genetic and environmental factors may play a role in the development of asthma, the exact pathogenesis of asthma is not clearly understood.

Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear receptor super family containing transcription factors regulating gene expression. More recently, PPARs have been shown to implicate diverse conditions such as atherosclerosis, inflammatory response, obesity, diabetes, immune response, and aging [2, 3]. They are ubiquitously expressed through whole body, and three subtypes, encoded by separated genes, have been identified, namely PPAR α, PPAR β/δ, and PPAR γ. PPAR γ has been the most extensively studied receptor among the three PPAR subtypes. PPAR γ was initially identified as a transcription factor involved in fat cell differentiation, and recently, accumulating evidence indicates that PPAR γ affects cell cycle, differentiation, and apoptosis [4]. Activation of PPAR γ could down regulate the synthesis and release of immunomodulatory cytokines from various cell types, and participate in the regulation of

Table 1. Description for 5 SNPs and Probe sequence used for Taqman fluorescence probe analysis

SNP ID	SNP	Position	Exon/Intron	Nucleotide substitution	Probe sequence
rs709158	Intron A>G	12403176	Intron_2	A>G	5'-AGATACGGGGGAGGAAATTCACTGG[A/G] TTTTACAATATATTTTTCAAGGCAA-3'
rs10865710	C681G	12293198	Intron	C>G	5'-TTGGCATTAGATGCTGTTTTGTCTT[C/G] ATGGAAAATACAGCTATTCTAGGAT-3'
rs1805192	Pro12Ala	12361238	Exon_B	C>G	5'-ACCTCAGACAGATTGTCACGGAACA[C/T] GTGCAGCTACTGCAGGTGATCAAGA-3'
rs4684847	Intron C>T	12326337	Intron_3	C>G	5'-ATTTATTTAAATCATCTCTAATTCT[C/T] ACAACTCCGAAAAGATAAGAAAACA-3'
rs3856806	C161T	12415557	Exon-6	C>T	5'-GGTTGACACAGAGATGCCATTCTGG[C/G] CCACCAACTTTGGGATCAGCTCCGT-3'

inflammatory processes [5, 6], so PPAR γ is one of the potential candidates in the treatment of inflammatory diseases, such as asthma. However, less study focused on the association between PPAR γ single nucleotide polymorphism (SNP) and asthma in human study, so the aim of this study was to investigate the association between SNP of PPAR γ and additional gene-gene interactions on asthma risk.

Materials and methods

Subjects

This was a hospital based case-control study. Participants were consecutively recruited from asthma patients who received treatment between January 2011 and November 2013 from the First Affiliated Hospital of Chengdu Medical College. We excluded participants with diabetes, CVD, missing data and participants with BMI <18.5 kg/m^2, because PPAR γ was also associated with these diseases. A total of 882 subjects (602 males, 280 females), with a mean age of 61.3±14.8 years old, including 430 asthma patients and 452 normal subjects were selected in this study, including the genotyping of polymorphisms. Informed consent was obtained from all participants.

Body measurements

Data on demographic information, lifestyle risk factors for all participants were obtained using a standard questionnaire administered by trained staffs. Body weight, height, waist circumference were measured, and body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. Waist circumference (WC) was measured two times at 1 cm above the umbilicus at minimal respiration by trained observers; the mean of the two WC measurements was utilized in the analysis. Cigarette smokers were those who self-reported smoking cigarettes at least once a day for 1 year or more. Alcohol consumption was expressed as the sum of milliliters of alcohol per week from wine, beer, and spirits. Blood samples were collected in the morning after at least 8 hours of fasting.

All plasma and serum samples were frozen at -80°C until laboratory testing. Plasma glucose was measured using an oxidase enzymatic method. The concentrations of HDL cholesterol and triglycerides were assessed enzymatically using an automatic biochemistry analyzer (Hitachi Inc., Tokyo, Japan) and commercial reagents. All analysis was performed by the same lab.

Genomic DNA extraction and genotyping

We selected SNPs within the PPAR γ gene, which have been reported associations with asthma and minor allele frequency (MAF) greater than 1%. 5 SNP of PPAR γ were selected for genotyping in the study: rs1805192, rs10865710, rs709158, rs4684847 and rs3856806. Genomic DNA from participants was extracted from EDTA-treated whole blood, using the DNA Blood Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. All SNPs were detected by Taqman fluorescence probe. ABI Prism7000 software and allelic discrimination procedure was used for genotyping of fore-mentioned four SNP. 25 μl reaction mixture including 1.25 ul SNP

Table 2. General characteristics of study participants in case and control group

Variables	Asthma cases group (n=430)	Control group (n=452)	*p-values*
Age (years)	57.2±14.0	56.6±14.2	0.528
Males N (%)	202 (47.0)	222 (49.1)	0.579
Smoke N (%)	177 (41.2)	154 (34.1)	0.035
Alcohol consumption N (%)	181 (42.1)	178 (39.4)	0.455
High fat diet N (%)	174 (40.5)	169 (37.4)	0.382
Low fiber diet N (%)	187 (43.5)	178 (39.4)	0.243
WC (cm)	83.7±9.8	82.1±9.3	0.013
BMI (kg/m^2)	24.4±6.7	23.2±6.2	0.006

Note: means± standard deviation for age, WC, BMI.

Genotyping Assays (20×), 20 ng DNA, 12.5 μl Genotying Master Mix (2×), initial denaturation for 10 min and 95°C, denaturation for 15 s and 92°C, annealing and extension for 90 s and 60°C, 50 cycles. Probe sequences of all SNPs were shown in **Table 1**.

Statistical analysis

The mean and SD for normally distributed continuous variables, and percentages for categorical variable, were calculated and compared. The genotype and allele frequencies were obtained by direct count. The categorical data were analyzed using χ^2 test. Further, continuous variables were analyzed using Student's t test or one-way analysis of variance. Hardy-Weinberg equilibrium (HWE) was performed by using SNP Stats (available online at http://bioinfo.iconcologia.net/SNPstats). Logistic regression was performed to investigate association between SNP and EH using gender, age, smoking and alcohol status, WC and BMI as covariates in the model. Generalized MDR (GMDR) [7] was used to analysis the interaction among four SNP, cross-validation consistency, the testing balanced accuracy, and the sign test, to assess each selected interaction were calculated.

Results

A total of 882 subjects (602 males, 280 females), with a mean age of 61.3±14.8 years old, were selected, including 430 asthma patients and 452 normal subjects. Participants characteristics stratified by cases and controls are shown in **Table 2**. Age, gender, alcohol consumption, high fat diet and low fiber diet were not significantly different between cases and controls. The rate of smoking and the mean of WC and BMI were higher in asthma patients than that in control group subjects.

All genotypes were distributed according to Hardy-Weinberg equilibrium (All *p* values more than 0.05). There were significant differences in alleles and genotypes distributions in rs1805192 and rs10865710 between asthma patients and controls (**Table 3**). Logistic regression analysis showed a significant association of rs1805192 variants genotypes with decreased asthma risk, after adjustment for gender, age, smoking and alcohol status, WC and BMI. Asthma risk was significantly lower in carriers of Ala allele of the rs1805192 polymorphism than those with Pro/Pro (Pro/Ala+ Ala/Ala *versus* Pro/Pro, adjusted OR (95% CI)=0.70 (0.51-0.94). In addition, we also found a significant association between rs10865710 and asthma, asthma risk was significantly lower in carriers of G allele of the rs10865710 polymorphism than those with CC (CG+ GG *versus* CC, adjusted OR (95% CI)=0.68 (0.55-0.95).

We employed the GMDR analysis to investigate the impact of the interaction among 5 SNP in PPAR γ, after adjustment for covariates including gender, age, smoking and alcohol status, WC and BMI. **Table 4** summarizes the results obtained from GMDR analysis for two to five locus models. There was a significant three-locus model (P=0.0107) involving rs1805192, rs10865710 and rs709158, indicating a potential gene-gene interaction among rs1805192, rs10865710 and rs709158. Overall, the three-locus models had a cross-validation consistency of 10 of 10, and had the testing accuracy of 60.72%.

In order to obtain the odds ratios and 95% CI for the joint effects of rs1805192, rs10865710 and rs709158 on asthma, we conducted interaction analysis between 3 SNP by using logistic regression. We found that subjects with Pro/Ala or Ala/Ala-CG or GG-AG or GG genotype have lowest asthma risk, compared to subjects with Pro/Pro-CC-AA genotype, OR (95% CI) was 0.26 (0.12-0.57), after covariates adjustment (**Table 5**).

Table 3. Genotype and allele frequencies of 5 SNP between case and control group

SNPs	Genotypes and Alleles	Frequencies N (%)		*OR (95% CI)*[a]	*P*-values	*HWE test*
		Control (n=430)	Case (n=452)			
rs1805192	ProPro	218 (50.7)	262 (58.0)	1.00	<0.001	0.461
	ProAla	174 (40.5)	173 (38.3)	0.97 (0.82-1.32)		
	AlaAla	38 (8.8)	17 (3.7)	0.60 (0.42-0.90)		
	ProAla+AlaAla	212 (49.3)	190 (42.0)	0.70 (0.51-0.94)	0.018	
	Pro	610 (70.9)	697 (77.1)		0.003	
	Ala	250 (29.1)	207 (22.9)			
rs709158	AA	225 (52.3)	257 (56.8)	1.00	0.372	0.436
	AG	176 (40.9)	170 (37.6)	0.96 (0.81-1.28)		
	GG	29 (6.7)	25 (5.5)	0.91 (0.56-1.11)		
	AG+GG	205 (47.7)	195 (43.1)	0.86 (0.53-1.22)	0.192	
	A	626 (72.8)	684 (75.7)		0.168	
	G	234 (27.2)	220 (24.3)			
rs10865710	CC	220 (51.2)	256 (56.6)	1.00	0.012	0.989
	CG	169 (39.3)	175 (38.7)	0.98 (0.79-1.22)		
	GG	41 (9.5)	21 (4.6)	0.53 (0.42-0.91)		
	GG+CG	210 (48.8)	196 (43.4)	0.68 (0.55-0.95)	0.038	
	C	609 (70.8)	687 (76.0)		0.015	
	G	251 (29.2)	217 (24.0)			
rs4684847	CC	222 (51.6)	252 (55.8)	1.00	0.431	0.383
	CG	178 (41.4)	174 (38.5)	0.95 (0.73-1.26)		
	GG	30 (7.0)	26 (5.7)	0.89 (0.49-1.42)		
	GG+CG	208 (48.4)	200 (44.2)	0.93 (0.60-1.25)	0.236	
	C	622 (72.3)	678 (75.0)		0.202	
	G	238 (27.7)	226 (25.0)			
rs3856806	CC	224 (52.1)	255 (56.4)	1.00	0.436	0.191
	CT	180 (41.9)	172 (38.1)	0.96 (0.76-1.20)		
	TT	26 (6.0)	25 (5.5)	0.97 (0.53-1.35)		
	TT+CT	206 (47.9)	197 (43.6)	0.96 (0.58-1.23)	0.225	
	C	628 (73.0)	682 (75.4)		0.245	
	T	232 (27.0)	222 (24.6)			

[a]Adjusted for gender, age, smoke and alcohol status, BMI, WC.

Discussion

In this study, we found that there were significant differences in alleles and genotypes distributions in rs1805192 and rs10865710 between asthma patients and controls, and minor allele of the rs1805192 and rs10865710 polymorphisms were associated with lower asthma risk. To date, PPAR γ has been the most extensively studied receptor among the three PPAR subtypes and in the last few years growing evidence indicates that PPAR γ plays an important role in controlling immune and inflammatory responses. In addition, PPAR γ agonist was also reported that it has a modest effect in the allergen challenge model in asthma [8]. However, to our knowledge, this is the first study to investigate the association between PPAR γ polymorphisms and asthma in Chinese populations. Mueller [9] et al. indicated that ligands for PPAR γ may be efficacious in treating allergic asthma and have recently been implicated as the targets of cellular inflammatory and immune response [10, 11]. Given its anti-inflammatory and immunomodulatory properties, PPAR γ has been used in the treatment of inflammatory diseases, including asthma [12]. Benayoun et al. [13] reported that PPAR γ protein is expressed in human subjects who were asthmatic and found elevated expression

Table 4. Best gene-gene interaction models, as identified by GMDR

Locus no.	Best combination	Cross-validation consistency	Testing accuracy	*p*-values[a]
2	rs1805192 rs10865710	8/10	0.5669	0.1719
3	rs1805192 rs10865710 rs709158	10/10	0.6072	0.0010
4	rs1805192 rs10865710 rs709158 rs4684847	8/10	0.5399	0.0547
5	rs1805192 rs10865710 rs709158 rs4684847 rs3856806	7/10	0.5587	0.1719

[a]Adjusted for gender, age, smoke and alcohol status, BMI, WC.

Table 5. Interaction analysis for 3-locus models by using logistic regression

rs1805192	rs10865710	rs709158	OR (95% CI)[a]	*P*-values
ProPro	CC	AA	1.00	-
ProPro	CC	AG or GG	0.95 (0.67-1.64)	0.627
ProPro	CG or GG	AA	0.92 (0.51-1. 69)	0.574
ProPro	CG or GG	AG or GG	0.61 (0.30-1.23)	0.216
AlaAla or AlaAla	CC	AA	0.81 (0.50-0.88)	<0.001
AlaAla or AlaAla	CC	AG or GG	0.45 (0.26-0.86)	<0.001
AlaAla or AlaAla	CG or GG	AA	0.44 (0.25-0.95)	0.012
AlaAla or AlaAla	CG or GG	AG or GG	0.26 (0.12-0.57)	<0.001

[a]Adjusted for gender, age, smoke and alcohol status, BMI, WC.

three SNP carriers than that in homozygous carriers. In the correlation analysis, the rs709158 was not associated with asthma, however, in the interaction analysis, the minor allele of this SNP can significantly affect asthma risk when accompanied with minor allele of rs1805192 and rs10865710. These findings indicate that a minor gene (even when its main effects are close to nil) can have a strong effect on obesity, due to the presence of gene-gene interaction.

in the bronchial submucosa, the airway epithelium, and smooth muscle cells compared with control subjects. Similarly, Patel et al. [14] reported that human airway smooth muscle cells expressed PPAR γ, and that exposure of these cells to PPAR γ ligands could inhibit their secretion of granulocyte macrophage colony stimulating factor as well as granulocyte colony stimulating factor. Palmer et al. [15] conducted a study in children and young adults, the results suggested that common genetic variation at the PPARG locus may play an important role in modulating the long-term control of asthma.

Asthma was a complex phenotype, which could be influenced by many types of gene, the most of which were minor SNP. So it is necessary to investigate the synergetic effect among several PPAR γ SNPs on risk of asthma. In this study, we employ the GMDR method to investigate the interaction among 5 SNPs of PPAR γ on risk of asthma, the results indicated that there was a significant interaction among rs1805192, rs10865710 and rs709158, subjects with Pro/Ala or Ala/Ala-CG or GG-AG or GG genotype have lowest asthma risk, compared to subjects with Pro/Pro-CC-AA genotype, the risk of asthma was 0.26 times in the mutation allele of

Several underlying mechanism of minor allele of induced decreased asthma risk was reported in previous studies [16-20]. Kim et al. [16] reported that expression of PPAR γ was increased by ovalbumin inhalationand the increased IL-10 levels in lung tissues after ovalbumin inhalation were further increased by the administration of rosiglitazone, pioglitazone, or AdPPAR γ. Levels of IL-4, IL-5, and ovalbumin-specific IgE were also increased after ovalbumin inhalation, and the increased levels were significantly reduced by the administration of the PPAR γ agonists or AdPPAR γ. These findings suggest that a protective role of PPAR γ in the pathogenesis of the asthma is partly mediated through an IL-10-dependent mechanism, to reduce airway hyper responsiveness and activation of eosinophils that are increased by induction of asthma [17-19]. Lee et al. [17] indicated the administration of PPAR γ agonists or AdPPAR γ up-regulated phosphatase and tensin homologue deleted on chromosome ten (PTEN) expression in allergen-induced asthmatic lungs and they demonstrate a protective role of PPAR γ in the pathogenesis of the asthma phenotype through regulation of PTEN expression. An animal study [20] suggested that the therapeutic effect of rosiglitazone in neutro-

philic asthma is partially due to the role of the PPAR γ pathway in regulating T cell proliferation and differentiation.

Till now, to our knowledge, this is the first study involved in the gene-gene interaction of PPAR γ on asthma risk. How, the limitations of this study should be considered. Firstly, although the number of study participants met the requirement for analysis, the present sample size was relatively small. Interaction analysis should be conducted for gene-gene interaction with others gene, including PTEN or IL-10 gene, also interaction with others environmental risk factors should be investigated in the future studies, such as diet behavior or smoking and so on.

In conclusion, we found a significant association between rs1805192 and rs10865710 and decreased asthma risk, and we also obtained a significant interaction among rs1805192, rs10865710 and rs709158, based on this Chinese hospital based case-control study.

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Disclosure of conflict of interest

None.

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