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Association between PPARγ2 Pro12Ala polymorphism and myocardial infarction and obesity in Han Chinese in Hohhot, China

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ABSTRACT. Activation of the peroxisome proliferator-activated receptor γ (PPARγ) improves insulin sensitivity and inhibits atherosclerosis. Whether PPARγ2 Pro12Ala polymorphism affects myocardial infarction is not clearly understood. We investigated a possible association of PPARγ2 Pro12Ala polymorphism with obesity and myocardial infarction in Han Chinese in Hohhot, Inner Mongolia, China. We included 121 subjects with myocardial infarction and 137 healthy controls in our study. Triglycerides, total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol were measured. The following information was recorded for each subject: age, gender, body height, body weight, systolic blood pressure, and diastolic blood pressure; the body mass index was calculated. PCR-RFLP was used to examine the Pro12Ala polymorphism. There were significant differences in clinical characteristics between myocardial infarction patients and healthy controls, except for diastolic blood

pressure and triglycerides. The PP, PA/AA genotype frequencies were 88.4 and 11.6% in myocardial infarction patients and 95.6 and 4.4% in controls, respectively (P = 0.031). Individuals with the A allele had a significantly higher risk of myocardial infarction. The A allele was not an independent risk factor for obesity. We conclude that PPARγ2 Pro12Ala polymorphisms are associated with increased risk for myocardial infarction in Han Chinese in Hohhot.

Key words: Peroxisome proliferator-activated receptor γ; PCR-RFLP; Cardiovascular disease; Body mass index

INTRODUCTION

Myocardial infarction (MI) is the leading cause of death for both men and women worldwide (McDermott, 2007). Insulin resistance, atherosclerosis and dyslipidemia are important factors contributing to MI. The incidence of MI is increasing each year; however, the etiology of the disease is not clearly explained. The molecular mechanism of MI can be elucidated with a thorough study of the genetics of the disease.

Peroxisome proliferator-activated receptors (PPARs) were found by Issemann and Green (1990). PPARs are members of the type II nuclear hormone receptor superfamily, which consists of three subtypes (PPARα, β/δ, and γ). PPARγ highly expressed in adipose tissue and colon and moderately expressed in liver, heart and kidney. The PPARγ is a transcription factor that belongs to the same family as the steroid and thyroid hormone receptors. The human PPARγ gene is located on chromosome 3p25 and produces 3 different molecules (PPARγ1, PPARγ2, and PPARγ3) by alternative mRNA splicing. There are additional 28 amino acids on the N-terminal of PPARγ2, which are coded by exon B. PPARγ2 is mainly found in adipose tissue, where it plays roles in regulating target genes, metabolism of fat and sugar, insulin resistance, obesity, cell differentiation and proliferation, inflammation, and atherosclerosis (Hsueh and Bruemmer, 2004). Activation of PPARγ2 increases insulin sensitivity (Miyazaki et al., 2001), anti-atherosclerosis (Hu et al., 2010), anti-inflammation (Wang et al., 2005), and anti-oxidation (Ren et al., 2009), improves high blood pressure and dyslipidemia, and reduces the risk of cardiovascular disease (Tavares et al., 2005). A cytosine to guanine substitution in exon B of the PPARγ2 gene results in a change of proline (Pro) to alanine (Ala). The Ala variant has lower affinity for the response element and a lower capacity for activating target genes by about 50% (Tamori et al., 2002). It has been shown that insulin sensitivity, inflammation, dyslipidemia have an important role in MI (Holvoet, 2008). Therefore, based on the current studies, we hypothesized that PPARγ2 Pro12Ala polymorphism may be associated with MI. In this study, we investigated the correlation between PPARγ2 Pro12Ala polymorphism and MI in Han Chinese in Inner Mongolia to provide data to help elucidate the mechanism of MI.

MATERIAL AND METHODS

Subjects

All subjects gave informed consent. One hundred and twenty one MI patients (72

males and 49 females, ranging from 51-80 years) with an average age of 65.28 ± 7.89 years old were enrolled. All patients were diagnosed according to the criteria of the World Health Organization, which include chest pain plus either electrocardiogram (ECG, elevated or depressed ST, or abnormal Q wave) or elevated levels of cardiac enzymes (Rose and Blackburn, 1982). Individuals with complicated diabetes and other metabolic diseases, severe liver and kidney dysfunction or cancers were excluded from the study. One hundred and thirty seven healthy controls (79 males and 58 females, ranging from 45-85 years) with an average age of 63.15 ± 10.32 years old were selected by routine physical examination. The controls excluded those with cardiovascular and cerebrovascular diseases, diabetes, and liver and kidney dysfunction by medical history, physical examination, laboratory tests, ECG, X-ray, and ultrasound examination. All the subjects did not take lipid-lowering drugs for 2 months. Our study was approved by the Inner Mongolia Medical College Affiliated Hospital Ethics Committee.

Body mass index (BMI) was calculated by weight (kg) divided by square height (m^2). According to the situation in China (Liu et al., 2001), BMI < 26 was considered as non-obesity, BMI ≥ 26 as obesity. Blood pressure (systolic blood pressure (SBP) and diastolic blood pressure (DBP)) was measured three times for each subjects and the average was used. Blood samples were drawn after an overnight fast. Total plasma cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were measured according to standardized methods (Beckman Coulter Unicel DxC 800 Synchron Clinical Systems; Beckman Coulter Company, Fullerton, CA, USA). Hyperlipemia was diagnosed as TG > 150 mg/dL (1.7 mM) and/or TC > 220 mg/dL (5.72 mM) and/or LDL-C > 140 mg/dL (3.64 mM).

DNA isolation and TaqMan PCR

Genomic DNA was extracted by a kit (TIANamp Blood DNA kit, TIANGEN, Beijing, China). The PPARγ2 Pro12Ala polymorphism (rs1801282) was analyzed using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). PCR was performed in a volume of 25 µL including 10.1 µL ddH_2O, 12.5 µL 2X Taq Master Mix (Promega), 0.2 µL primer [sense 5'-CCAATTCAAGCCCAGTCCTTTC-3' and antisense 5'-CAGTGAAGGAATCGCTT TCCG-3' (Issemann and Green, 1990)] and 2 µL template DNA. The reaction conditions were as follows: initial denaturation at 95°C for 5 min, followed by 35 cycles of denaturation at 94°C for 40 s, annealing at 55°C for 50 s, and extension at 72°C for 1 min; with a final extension at 72°C for 7 min. PCR products were digested with *Bst*U-I (New England BioLabs, Beijing, China) in a 60°C water bath for 2 h. Digestion products (7 µL) were electrophoresed using a 4% agarose gel at 120 V for 1 h and analyzed with a Gel-Pro imaging instrument.

Sequencing

To confirm that the detection of this C→G nucleotide substitution by PCR-RFLP analysis was reproducible, we also performed PCR-based direct sequencing analysis. The genotype of each study subject was determined blindly without knowledge of clinical status. PP and AA genotypes were selected and re-amplified, and the DNA sequences were verified by direct sequencing (United States ABI Prism 3700 DNA analyzer 377; Applied Biosystems, Foster City, CA, USA).

Statistical analysis

All clinical and biochemical data were expressed as mean ± standard deviation. The comparison of average clinical data between groups was performed by the independent sample *t*-test. The chi-square test was used to compare genotype and allele frequencies between groups and to determine whether individual variants were in accord with Hardy-Weinberg equilibrium. Dualistic logistic regression was used to investigate the risk factor of myocardial infarction and obesity. The factors with $P < 0.05$ in univariate regression were further analyzed in multivariate logistic regression. Statistical analysis was performed by the SPSS 13.0 software. Statistical significance was established at $P < 0.05$.

RESULTS

The clinical characteristics of MI patients and healthy controls are shown in Table 1. The age and gender of two groups were well matched. There was a significant difference in clinical characteristics between MI patients and healthy controls except DBP and TG.

Table 1. Comparison of clinical characteristics between myocardial infarction patients and controls.

	Control	MI	P
Males / females	137 (79/58)	121 (72/49)	
Age (years)	50.08 ± 15.01	53.47 ± 16.21	0.232
SBP (mmHg)	120.61 ± 12.33	134.14 ± 19.63	0.000*
DBP (mmHg)	73.91 ± 10.66	73.80 ± 11.68	0.937
BW (kg)	66.08 ± 11.13	72.65 ± 10.00	0.000*
BMI (kg/m^2)	23.44 ± 2.88	25.81 ± 2.82	0.000*
TG (mM)	1.60 ± 1.09	1.74 ± 0.11	0.143
TC (mM)	4.71 ± 0.85	5.93 ± 0.55	0.000*
LDL-C (mM)	2.74 ± 0.63	4.20 ± 0.35	0.000*
HDL-C (mM)	1.39 ± 0.43	0.16 ± 0.17	0.000*

The independent sample *t*-test was used to compare clinical characteristics between myocardial infarction patients and healthy controls. Data are reported as means ± standard deviations. *Indicates significant difference between groups. MI = myocardial infarction; SBP = systolic blood pressure; DBP = diastolic blood pressure; BW = body weight; BMI = body mass index; TG = triglycerides; TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol.

The DNA fragment of the PPAR-γ2 gene was 244 bp after PCR amplification. The expected sizes of the products after digestion with *Bst*U-I were the following: homozygous wild-type (PP) without a restriction site and an electrophoresis band of 244 bp; mutant homozygote (AA) with a restriction site in each DNA chain, resulting in electrophoresis bands of 223 and 21 bp; and heterozygote (PA) with restriction sites in one of the DNA chains, resulting in 3 electrophoresis bands at 244, 223, and 21 bp.

In the subjects we studied, the incidence of PPAR-γ2 gene P/P, P/A and A/A genotypes was 92.2, 6.2 and 1.6%, respectively; the incidence of PPAR-γ2 gene P and A alleles was 95.3 and 4.7%, respectively. We observed that the PPAR-γ2 Pro12Ala polymorphism genotype distribution was in accordance with Hardy-Weinberg expectations in each group (MI, $\chi^2 = 1.423$, $P = 0.491$; healthy controls, $\chi^2 = 0.079$, $P = 0.961$; obesity, $\chi^2 = 0.898$, $P = 0.638$; non-obesity, $\chi^2 = 3.517$, $P = 0.172$). It showed that the study groups were representative.

The PPAR-γ2 gene P/P, P/A and A/A genotype distributions were 88.4, 11.6 and 0.0%

in MI patients and 95.6, 1.5 and 2.9% in healthy controls, respectively. The P allele frequency in patients and healthy controls was 94.2 and 96.4%, and the A allele frequency was 5.8 and 3.6%, respectively. There was a significant difference in frequencies of PPAR-γ2 genotypes PP and PA/AA between MI patients and healthy controls (P = 0.031, Table 2). The frequency of PPAR-γ2 gene P/P, P/A and A/A genotype was 89.8, 7.9, and 2.3% in obesity and 93.5, 5.3 and 1.2% in non-obesity, respectively. The P allele frequency in obesity and non-obesity was 93.75 and 96.15% and the A allele frequency was 6.25 and 3.85%, respectively. There was no significant difference in distribution of PPAR-γ2 genotype frequency between obesity and non-obesity (P > 0.05, Table 2).

Table 2. Distribution of PPARγ2 Pro12Ala variant genotype and allele frequencies in subjects.

Group	Obesity		Myocardial infarction	
	Obese (N = 88)	Non-obese (N = 170)	MI (N = 121)	Control (N = 137)
Genotype				
PP	79 (89.8%)	159 (93.5%)	107 (88.4%)	131 (95.6%)
PA	7 (7.9%)	9 (5.3%)	14 (11.6%)	2 (1.5%)
AA	2 (2.3%)	2 (1.2%)	0 (0.0%)	4 (2.9%)
P	0.285	0.031		
Allele				
P	165 (93.75%)	327 (96.15%)	228 (94.2%)	264 (96.4%)
A	11 (6.25%)	13 (3.85%)	14 (5.8%)	10 (3.6%)
P	0.215	0.250		

Data are reported as numbers with frequencies in parentheses. Because there were too fewer individuals with AA genotype, AA genotype was combined with PA genotype in the chi-square test. MI = myocardial infarction.

We investigated the difference in clinical characteristics between individuals with PP and PA/AA genotypes in all subjects, MI patients, healthy controls, obesity and non-obesity, respectively. We found that the level of TC was significantly higher in PP subjects than in PA/AA subjects (P = 0.006, Table 3). A high level of TC was also found in MI patients and non-obese subjects with PP genotype (P = 0.007 and 0.039, respectively, Table 4, 5). There was a much lower level of HDL-C in non-obesity with PA/AA genotype than in non-obesity with PP genotype (P = 0.022, Table 5). There was no significant difference in clinical characteristics between healthy control and obesity with PP and PA/AA genotype.

Table 3. Comparison of clinical characteristics between PP and PA/AA genotype carriers in all subjects.

	PP	PA/AA	P
Number (258)	238	20	
Age (years)	64.11 ± 9.28	63.25 ± 14.55	0.753
BW (kg)	68.90 ± 11.27	72.30 ± 8.32	0.188
BMI (kg/m^2)	24.49 ± 3.12	25.35 ± 2.61	0.230
SBP (mmHg)	126.29 ± 17.09	130.25 ± 18.44	0.323
DBP (mmHg)	73.45 ± 10.40	74.25 ± 10.31	0.741
TG (mM)	1.69 ± 0.87	1.57 ± 0.46	0.558
TC (mM)	5.24 ± 0.93	5.84 ± 0.99	0.006*
LDL-C (mM)	3.39 ± 0.90	3.78 ± 0.71	0.063
HDL-C (mM)	1.34 ± 7.82	0.51 ± 0.61	0.637

The independent sample *t*-test was used to compare clinical characteristics between PP and PA/AA genotype carriers. Data are reported as means ± standard deviations. *Indicates significant difference between groups. BW = body weight; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; TG = triglycerides; TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol.

Table 4. Comparison of clinical characteristics between PP and PA/AA genotype carriers in myocardial infarction patients.

	PP	PA/AA	P
Number (121)	107	14	
Age (years)	63.36 ± 14.75	64.67 ± 21.46	0.551
BW (kg)	72.73 ± 10.28	72.07 ± 7.87	0.818
BMI (kg/m^2)	25.83 ± 2.90	25.67 ± 2.18	0.844
SBP (mmHg)	134.34 ± 19.56	132.64 ± 20.86	0.763
DBP (mmHg)	73.71 ± 11.81	74.50 ± 11.06	0.813
TG (mM)	1.73 ± 0.11	1.75 ± 0.14	0.614
TC (mM)	5.40 ± 0.48	6.18 ± 0.92	0.007*
LDL-C (mM)	4.21 ± 0.34	4.09 ± 0.43	0.228
HDL-C (mM)	1.28 ± 11.68	0.14 ± 0.75	0.718

The independent sample *t*-test was used to compare clinical characteristics between PP and PA/AA genotype carriers. Data are reported as means ± standard deviations. *Indicates significant difference between groups. BW = body weight; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; TG = triglycerides; TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol.

Table 5. Comparison of clinical characteristics between PP and PA/AA genotype carriers in non-obesity group.

	PP	PA/AA	P
Number (169)	158	11	
Age (years)	55.87 ± 15.54	61.27 ± 11.82	0.260
SBP (mmHg)	125.00 ± 16.91	130.18 ± 20.91	0.335
DBP (mmHg)	72.54 ± 11.17	73.27 ± 8.95	0.833
TG (mM)	1.61 ± 0.84	1.52 ± 0.42	0.737
TC (mM)	5.40 ± 0.48	6.18 ± 0.92	0.039*
LDL-C (mM)	3.24 ± 0.84	3.57 ± 0.80	0.216
HDL-C (mM)	0.97 ± 0.69	0.47 ± 0.62	0.022*

The independent sample *t*-test was used to compare clinical characteristics between PP and PA/AA genotype carriers. Data are reported as means ± standard deviations. *Indicates significant difference between groups. SBP = systolic blood pressure; DBP = diastolic blood pressure; TG = triglycerides; TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol.

Univariate logistic regression showed that a high level of SBP, MBI, TG, TC, and LDL-C and low level of HDL-C and PPAR-γ2 A allele (OR = 2.857, 95%CI = 1.062-7.687, P = 0.038) was a risk factor of MI. However, in multivariate logistic regression, only MBI, TG, TC, and PPAR-γ2 A allele was a risk factor of MI (OR = 2.684, 95%CI = 1.037-6.951, P = 0.042, Table 6). Univariate logistic regression showed that a high level of SBP, DBP, TG, TC, and LDL-C and low level of HDL-C and PPAR-γ2 A allele (OR = 3.437, 95%CI = 1.116-10.589, P = 0.031) was a risk factor of obesity. However, in multivariate logistic regression, DBP and HDL-C but not the PPAR-γ2 A allele (OR = 2.651, 95%CI = 0.825-8.517, P = 0.102, Table 7) was a risk factor of obesity.

Table 6. Multivariate logistic regression analysis of risk factors of myocardial infarction.

Risk factor	OR	95%CI	P
BMI	1.967	1.461-2.648	<0.000
PA/AA genotype	2.684	1.037-6.951	0.042
TG	2.470	1.471-4.147	0.001
TC	10.414	6.163-17.595	0.000

BMI = body mass index; TG = triglycerides; TC = total cholesterol; OR = odds ratio; 95%CI = 95% confidence intervals.

Table 7. Multivariate logistic regression analysis of risk factors of obesity.

Risk factor	OR	95%CI	P
DBP	4.895	1.032-23.214	<0.046
PA/AA genotype	2.651	0.825-8.517	0.102
HDL-C	3.532	2.070-6.028	0.000

DBP = diastolic blood pressure; HDL-C = high-density lipoprotein cholesterol; OR = odds ratio; 95%CI = 95% confidence intervals.

DISCUSSION

The PPAR-γ2 Pro12Ala polymorphism was first discovered by Yen et al. (1997). The incidence of PPAR-γ2 Pro12Ala polymorphism varied in different ethnic groups. The frequency of A allele was 10, 3 and 2% in Mexican- and African-Americans and Nauruns, respectively (Kagawa et al., 2002; Wei et al., 2006; Black et al., 2008). Our study found that the incidence of the A allele was 3.6% in healthy controls, which was lower than that in Caucasians (11-13%) (Schaffler et al., 2001; Kolehmainen et al., 2003), but was similar to that in a population of East Asia such as Koreans (3.5%) (Kim et al., 2004), Chinese (4.2%) (Pan et al., 2009) and Japanese (4.1%) (Mori et al., 2001).

Association between PPAR-γ2 and diseases has been intensively studied. Several polymorphisms have been found, including Pro12Ala, C161T, Pro115Gln, Pro467Leu, Val290Met and C-689T. The most common polymorphism is Pro12Ala. Regarding the association of the PPAR-γ2 Pro12Ala polymorphism and type 2 diabetes and MI, controversial data have been published. Deeb et al. (1998) reported that individuals with allele A showed reduced risk of developing type 2 diabetes by 75%. The analysis of 6 studies revealed that individuals with allele A had reduced the risk of developing type 2 diabetes by 21% (Altshuler et al., 2000). On the contrary, no association between PPAR-γ2 Pro12Ala polymorphism and type 2 diabetes was also found (Stefanski et al., 2006). Ridker et al. (2003) found that PPAR-γ2 Pro12Ala polymorphism was associated with MI, while Zafarmand et al. (2008) reported that PPAR-γ2 Pro12Ala polymorphism was not a risk factor of MI. The controversial results may due to differences in ethnic groups, regions, number of samples, and environment.

Our study found that PPAR-γ2 Pro12Ala polymorphism was an independent risk factor of MI. Foam cell differentiation, inflammation and cell proliferation play key roles in the formation of atherosclerosis plague. Studies have demonstrated that PPAR-γ has a role in anti-inflammation (Bouhlel et al., 2007). It was reported that PPAR-γ2 inhibits the formation of plague. PPAR-γ2 induced release of fat from foam cell by improving transcription of liver X receptor and activating ATP binding cassette transporter A1 (Akiyama et al., 2002). PPAR-γ2 inhibits the proliferation of vascular smooth muscle cells by decreasing expression of MMP-9 and angiotensin II type I receptor (Ji et al., 2009; Moran et al., 2009). Multiple functions of PPAR-γ2 have shown protection from developing MI. The low activity of the protein may result in metabolic disorders, inflammation and atherosclerosis. Therefore, PPAR-γ2 Pro12Ala polymorphism may play an important role in MI.

PPAR-γ2 has been found in white adipose tissue, and is involved in the differentiation of adipocytes and metabolism of fat (Iwai et al., 2011). Therefore, we investigated the association between PPAR-γ2 Pro12Ala polymorphism and obesity. Many studies have indicated that PPAR-γ2 Pro12Ala polymorphism is correlated with obesity, insulin resistance and

hyperlipidemia. Beamer et al. (1998) found that PPAR-γ2 Pro12Ala polymorphism was associated with high level of body weight, BMI and waistline in 169 obese Caucasians (average BMI = 36.5 kg/m^2), Meirhaeghe et al. (2000) reported that PPAR-γ2 Pro12Ala polymorphism correlated with obesity and blood fat. On the contrary, PPAR-γ2 Pro12Ala polymorphism was found to be associated with low body weight and high insulin sensitivity in 333 Finns (Deeb et al., 1998). There was no relation found between PPAR-γ2 Pro12Ala polymorphism and obesity and distribution of fat in 215 Japanese (Mori et al., 1998).

Our result did not reveal an association between PPAR-γ2 Pro12Ala polymorphism and obesity. The level of BMI and body weight was higher in individuals with PA/AA genotype than in individuals with PP genotype, but without significant difference. Kim et al. (2004) found that individuals with A allele had higher body weight, BMI and waist-to-hip ratio ($P < 0.05$). Meta-analysis of 30 independent studies revealed that individuals with A allele had higher BMI (Masud and Ye, 2003). The incidence of A allele was associated with obesity in middle-aged males from Spain (Beamer et al., 1998), in Java (Danawati et al., 2005), and among Caucasians (Beamer et al., 1998). We investigated the controversial result more carefully, and found that the differences in results may be due to small sample of our study, different criterion (BMI) to define obesity, different distribution of A allele and BMI between different ethnic groups. The incidence of A allele was correlated with BMI in a population with BMI > 27, while not in a population with BMI < 27 (Masud and Ye, 2003). Additionally, PPAR-γ2 Pro12Ala polymorphism was not associated with obesity in France (Ghoussaini et al., 2005) and Japan (Yamamoto et al., 2002). In out study, Logistic regression showed that PPAR-γ2 Pro12Ala polymorphism was not a risk factor of obesity in our local region.

We found that PPAR-γ2 Pro12Ala polymorphism was a risk factor of MI. In our study, we excluded MI patients with complicated diabetes, which eliminated the influence of diabetes on our results. Meanwhile, we did not find an association between PPAR-γ2 Pro12Ala polymorphism and obesity and blood pressure, which also eliminated the influence of metabolic syndrome on our results. However, our subjects were selected from Han Chinese in Hohhot, not representative of the Chinese population, which was a limitation in our results. Therefore, further study with different ethnic groups, large samples and other genetic polymorphisms will better reveal the association between PPAR-γ2 Pro12Ala polymorphism and MI and obesity.

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