

Association between Pro12Ala Polymorphism of Peroxisome Proliferator-Activated Receptor-Gamma 2 and Myocardial Infarction in the Chinese Han Population

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Summary

Background: Peroxisome proliferator-activated receptor-gamma 2 (PPAR-gamma 2) is a nuclear receptor that plays an important role in adipocyte differentiation, energy metabolism, and homeostasis. The Pro12Ala polymorphism of PPAR-gamma 2 is associated with decreased risk of diabetes mellitus. Presumably, it may have a protective effect on myocardial infarction (MI).

Hypothesis: The purpose of the study was to explore the association between the Pro12Ala polymorphism and the risk of MI in the Chinese population.

Methods: The Pro12Ala polymorphism was detected by polymerase chain reaction-restriction fragment length polymorphism among 844 subjects, including 218 patients with MI and 626 controls. Clinical parameters such as fasting serum total cholesterol, triglycerides, and plasma glucose were detected by autoanalyzer assay. Waist circumference, weight, height, and blood pressure (BP) were measured and body mass index (BMI) was calculated.

Results: The frequencies of the Ala allele in the MI and control groups were 0.053 and 0.032, respectively. There was a significant difference in genotype and allele frequency distribution between the two groups (after adjustment for age, gender, BP, fasting plasma glucose, total cholesterol, triglycerides, and smoking, odds ratio [OR] = 2.51, 95% confidence interval

[CI]: 1.26–5.00, $p = 0.009$). In the group with MI, the difference in frequency of the Ala allele in women (0.241) compared with that of men (0.056) was significant (OR = 4.29, 95% CI: 1.96–9.37, $p < 0.001$). There was no relationship between the Pro12Ala polymorphism and waist circumference, weight, BMI, BP, or triglycerides ($p > 0.05$).

Conclusions: Our study suggests that Pro12Ala polymorphism is associated with increased risk of MI.

Key words: peroxisome proliferator-activated receptor-gamma 2, polymorphism, myocardial infarction

Introduction

The peroxisome proliferator-activated receptor (PPAR) is a member of the nuclear hormone receptor family, and consists of three subtypes: PPAR-alpha, PPAR-beta, and PPAR-gamma. In humans, alternative use of promoters and different splicing of PPAR-gamma results in three different isoforms: PPAR-gamma 1, PPAR-gamma 2, and PPAR-gamma 3. The PPAR-gamma 2 that is primarily expressed in white and brown adipose tissue can induce the differentiation of preadipocytes into adipocytes, regulate lipid and fatty acid metabolism, and enhance insulin sensitivity. It has been reported that the PPAR-gamma 2 agonists thiazolidinediones (TZDs) can inhibit the expression of tumor necrosis factor-alpha (TNF-alpha), interleukin-1beta (IL-1beta), interleukin-6 (IL-6);¹ decrease hypertriglyceridemia; ameliorate endothelial dysfunction;² and inhibit vascular smooth muscle cell (VSMC) proliferation and migration.³ Recent work has shown that the Pro12Ala polymorphism of the PPAR-gamma 2 gene is associated with higher insulin sensitivity and decreased risk of type 2 diabetes mellitus (DM).⁴ Diabetes mellitus is a coronary heart disease (CHD) risk equivalent. Presumably, the Pro12Ala polymorphism can reduce the development and progression of myocardial infarction (MI). However, data on the risk of MI were scarce and controversial. To investigate the association between Pro12Ala polymorphism and MI, we performed a case-control study in patients with MI and in healthy subjects.

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Received: March 1, 2006

Accepted with revision: March 28, 2006

Subjects and Methods

Subjects

The study groups comprised 844 subjects of the Chinese Han population in Hubei, including 218 patients with MI and 626 controls. All subjects underwent standardized evaluation including physical examination, clinical diagnosis, laboratory tests, and questionnaire on family history, diet, physical activity, tobacco smoking, and alcohol consumption. Cases in the group with MI had a history of MI or were newly diagnosed by the elevated molecular markers of cardiac injury, cardiac enzymes, and electrocardiogram ambulatory changes, or confirmed by angiography. This study group consisted of 160 men and 58 women, with a mean age of 64.95 ± 10.79 years. The control group consisted of healthy subjects, including 346 men and 280 women with a mean age of 62.10 ± 8.23 years. Written informed consent was obtained from all participants.

Fasting serum total cholesterol (TC), triglycerides (TG), and fasting plasma glucose (FPG) were measured with an autoanalyzer (Hitachi, Tokyo, Japan). Waist circumference (WC), weight, height, and blood pressure (BP) were measured at the same time. The body mass index (BMI) was calculated.

DNA Extraction and Genotyping Analysis

The genomic DNA of all subjects was isolated from peripheral blood leukocytes and then frozen at -20°C . The PPAR-gamma 2 gene was amplified by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). The sequences of the primers were designed according to the document,⁵ forward primer: 5'-GCCAATTCAAGCCCAGTC-3'; reverse primer: 5'-GATATGTTTGCAGACAGTGTATCAGTGAAGGAATCGCTTTCCG-3'. The reverse primer contained one nucleotide mismatch (underlined), which made it possible to use the restriction enzyme HpaII (Fermentas, Inc., Hanover, Md., USA) for the detection of the Pro12Ala polymorphism. The conditions for PCR were as follows: PCR in a 25 μl reaction mixture containing the primers 0.4 μM , MgCl₂ 1.8 mM, KCl 2.5 mM, dNTP 200 μM , Taq polymerase 1.5 u and genomic DNAs 0.2 μg . The reaction mixtures were incubated at 94°C for 5 min, followed by 30 cycles of denaturation at 94°C for 45 s, annealing at 55.6°C for 45 s, and extension at 72°C for 40 s, with a final extension of 7 min at 72°C . The PCR products were 267 bp. After determination under ultraviolet radiation, the PCR products were digested with HpaII (locus, C'CGG). The digestion mixtures included HpaII 2 u, buffer 8 μl ; PCR products 10 μl were incubated at 37°C overnight, then resolved by 2.5% ethidium bromide (EB)-stained agarose gel electrophoresis (100 V, 1 h).

Statistical Analysis

Statistical analysis was performed with the Statistical Package for Social Sciences SPSS 11.0 (SPSS Inc., Chicago, Ill., USA). Clinical parameters were expressed as mean \pm standard

deviation (SD). The proportions of genotypes or alleles were compared by chi-square analysis. Differences in clinical parameters between the two groups were evaluated by *t*-test. Logistic regression analysis was used to estimate the OR and 95% CI. A *p* value of <0.05 was considered statistically significant.

Results

The PPAR-Gamma 2 Gene Pro12Ala Polymorphism

The expected PCR products after digestion were three genotypes: Pro/Pro, Pro/Ala, and Ala/Ala. 224 bp, 43 bp for normal Pro/Pro homozygotes; 267 bp, 224 bp, and 43 bp for Pro/Ala heterozygotes; 267 bp for Ala/Ala homozygotes (Fig. 1). The genotype distribution of the PPAR-gamma 2 gene Pro12Ala polymorphism was in Hardy-Weinberg equilibrium.

The results showed that the Pro/Pro was the main genotype of the PPAR-gamma 2 gene in the Chinese Han population in Hubei. The frequencies of Pro/Pro, Pro/Ala, and Ala/Ala genotypes between MI and control groups were 0.894, 0.106, 0.000, and 0.939, 0.058, 0.030, respectively, and those of Pro and Ala alleles in the MI and control groups were 0.947, 0.053, and 0.968, 0.032, respectively (Table I). The total 12Ala allele frequency in both groups was 0.037. There was a significant difference in PPAR-gamma 2 genotype and allele frequencies distribution between MI and control groups (after adjustment for age, gender, BP, FPG, TC, TG, and smoking, OR = 2.51, 95% CI: 1.26–5.00, $p = 0.009$). In the MI group, the difference in frequency of the Ala allele in women (0.241) compared with that of men (0.056) was significant (OR = 4.29, 95% CI: 1.96–9.37, $p < 0.001$). However, in the control group, there was no difference in allele frequency distribution between genders ($p = 0.630$) (Table II).

Comparisons of Clinical Baseline Parameters between the Two Groups (Table III)

As shown in the Table III, the level of FPG in the MI group was significantly higher than that in the control group ($p =$

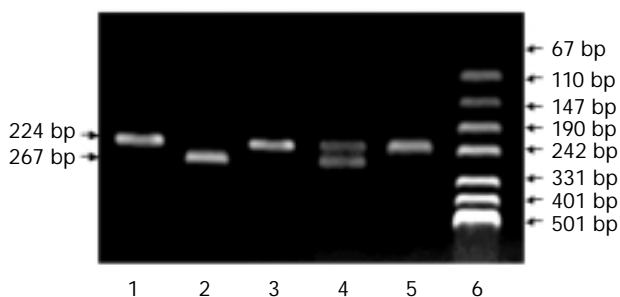


FIG. 1 Electrophoresis results of PPAR-gamma 2 gene Pro12Ala polymorphism digested by HpaII. Lanes 1, 3, 5 for normal Pro12Pro homozygotes; lane 2 for Ala12Ala homozygotes; lane 4, for Pro12Ala heterozygotes; lane 6 for marker.

TABLE I Peroxisome proliferator-activated receptor-gamma 2 genotype and allele frequencies in myocardial infarction (MI) and control groups

Groups	n	Genotypes (%) ^a			Alleles (%) ^a	
		Pro/Pro	Pro/Ala	Ala/Ala	Pro	Ala
MI	218	89.4 (n = 195)	10.6 (n = 23)	0 (n = 0)	94.7	5.3
Controls	626	93.90 (n = 588)	5.8 (n = 36)	0.3 (n = 2)	96.8	3.2

^a p < 0.05 by chi-square test.

TABLE II Pro12Ala polymorphism and clinical parameters of the two groups

Variables	MI			Controls		
	PP (n = 195)	PA+AA (n = 23)	p Value	PP (n = 588)	PA+AA (n = 38)	p Value
Men (%)	151 (94.4)	9 (5.6)	—	333 (94.3)	20 (5.7)	—
Women (%)	44 (75.9)	14 (24.1) ^a	0.000	255 (93.4)	18 (6.6)	0.630
Age (years)	64.17 ± 11.58	65.21 ± 12.34	0.689	59.46 ± 7.88	60.00 ± 8.83	0.691
WC (cm)	88.23 ± 11.40	86.81 ± 13.72	0.433	85.35 ± 10.10	86.56 ± 12.35	0.650
Weight (kg)	66.87 ± 11.28	60.76 ± 11.40 ^b	0.021	64.12 ± 10.54	65.87 ± 12.63	0.871
BMI (kg·m ⁻²)	24.16 ± 3.54	24.52 ± 3.59	0.622	24.43 ± 3.33	24.91 ± 4.58	0.736
SBP (mmHg)	129.39 ± 24.65	135.27 ± 24.48 ^b	0.046	131.5 ± 20.41	129.45 ± 21.2	0.452
DBP (mmHg)	79.08 ± 14.51	81.98 ± 14.78	0.579	81.16 ± 10.57	80.21 ± 9.80	0.660
FPG (mmol·l ⁻¹)	7.80 ± 3.04	6.60 ± 4.26 ^b	0.005	5.54 ± 1.53	5.16 ± 1.80	0.253
TC (mmol·l ⁻¹)	4.26 ± 1.15	4.82 ± 1.14 ^b	0.037	4.46 ± 1.09	4.58 ± 1.28	0.325
TG (mmol·l ⁻¹)	1.53 ± 0.98	1.49 ± 0.60	0.410	1.62 ± 1.22	1.58 ± 1.02	0.594

^a p < 0.05 by chi-square test.

^b vs. PP, p < 0.05.

Abbreviations: WC = waist circumference, BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, FPG = fasting plasma glucose, TC = total cholesterol, TG = triglycerides, MI = myocardial infarction.

0.003). There were no significant differences in any other clinical baseline parameters between the MI and control groups (p > 0.05). However, WC and BMI in both groups were slightly increased according to the normal criteria in China (men: WC < 85 cm, women: WC < 80 cm, BMI < 24 kg·m⁻²), which implied that these subjects were slightly overweight.

TABLE III Comparison of clinical baseline parameters between the two groups

Variables	MI	Controls	p Value
Age (years)	64.95 ± 10.79	62.10 ± 8.23	0.060
WC (cm)	88.15 ± 11.74	85.81 ± 10.65	0.091
Weight (kg)	64.13 ± 11.32	64.85 ± 10.42	0.542
BMI (kg·m ⁻²)	24.21 ± 3.54	24.57 ± 3.32	0.910
SBP (mmHg)	130.82 ± 24.66	131.10 ± 20.41	0.458
DBP (mmHg)	80.22 ± 14.52	81.02 ± 10.57	0.671
FPG (mmol·l ⁻¹)	7.52 ± 3.75	5.30 ± 1.98 ^a	0.003
TC (mmol·l ⁻¹)	4.41 ± 1.15	4.48 ± 1.23	0.785
TG (mmol·l ⁻¹)	1.51 ± 0.95	1.61 ± 1.45	0.210

^a vs. MI, p < 0.05.

Abbreviations as in Table II.

Relationship between Pro12Ala Polymorphism and Clinical Parameters in the Two Groups (Table II)

As shown in Table II, in the MI group, several significant differences in clinical parameters were observed between subjects with and without the Pro12Ala polymorphism. The levels of serum TC and systolic blood pressure (SBP) were higher in patients with than in those without the Ala allele (p < 0.05). The levels of FPG and weight were higher in patients with than in those without Pro allele (p < 0.05). We found no significant differences in WC, BMI, TG, or diastolic blood pressure (DBP) between patients with and without the Pro12Ala polymorphism. Similarly, in the control group, we failed to find any differences in clinical parameters between subjects with and without Ala allele.

Discussion

The PPAR-gamma gene, which is located on chromosome 3, can induce the transcription of target genes after ligand-dependent activation or in a ligand-independent manner. Several genetic variants in the PPAR-gamma gene have been described, the most prevalent being the missense mutation in the PPAR-gamma 2 codon 12 of exon B, involving a C→G substi-

tution at nucleotide 34 that resulted in the exchange of alanine for proline in the position of the PPAR- γ 2 protein. The nonconservative substitution of proline for alanine may cause a conformational change in the protein and lead to a reduction in the transcriptional activity of PPAR- γ 2.

The results of our study show that the frequency of the Ala allele in the MI group was significantly higher than that in the control group. The frequency of the Ala allele in the control group was consistent with that of the Han population in Beijing and Guangdong in China and that of Japanese,⁴ whereas the frequency of the Ala allele was significantly lower than that in Uygur population (10.4%) of Xinjiang in China and that in Americans.⁶ These data indicate that there is an ethnic difference in Pro12Ala genotype and allele frequency distribution.

We found no evidence that the Ala allele was associated with a decreased risk of MI; however, our results suggest that the Ala allele is associated with increased risk of MI in the Chinese Han population. This result is consistent with previous research that suggests that U.S. men and women with the 12Ala allele and a BMI ≥ 25 kg·m² have a significantly increased risk of MI,⁷ in spite of being free of cardiovascular disease at baseline. In contrast to our study, other research shows that Pro12Ala polymorphism is associated with a reduced risk of the incidence of MI in initially healthy men.⁶ The former study was carried out by a nested case-control design in a prospective cohort investigation among 121,700 female and 51,529 U.S. male health professionals, with a follow-up of 8 and 6 years, respectively. Furthermore, the latter was carried out by a nested case-control design in a prospective cohort of 14,916 initially healthy American men, with a follow-up of 13.2 years. In our case-control study, the participants with MI were enrolled strictly, but our patients were accompanied by an increased mean level of serum FPG. Control subjects with cardiovascular, hepatic, and renal diseases were excluded by physical examination and laboratory tests. We believe that the design of this research is reasonable and that all the data are powerful and believable. On the other hand, these studies involved various ethnicities and different baseline conditions such as increased BMI, FPG, and there were gender differences between the subjects who were suffering from MI; this could have contributed to the disparate effects.

The PPAR- γ 2 gene is an important modulating factor that can exert impact on lipid and glucose metabolism; the Pro12Ala variation may cause lipid metabolism disorder. Our results showed that the 12Ala allele was associated with an increased level of serum TC in the MI group but not in the control group. As a result of the reduction in transcriptional activity, Pro12Ala variation reduced the activation of lipoprotein lipase (LPL)⁸ and the level of serum adiponectin concentration,⁹ while increasing the level of leptin.¹⁰ Simultaneously, the variation of Pro12Ala increased the levels of serum TC, TG, and low-density lipoprotein (LDL) cholesterol,^{11,12} while decreasing the level of serum high-density lipoprotein (HDL) cholesterol. However, our studies showed no relationship between polymorphism and TG in either group.

In our study, the average level of serum FPG in subjects with MI was significantly higher than that in healthy subjects;

this indicates that DM plays an important role in MI. A further analysis showed that the average level of serum FPG of 12Ala allele carriers was significantly lower than that in noncarriers in the MI group. The result is consistent with a prior report that implied that the Ala allele is more sensitive to insulin and is associated with a reduced risk of DM.¹³ There was no difference in level of FPG among control subjects with and without the 12Ala allele. In addition, the relationship between polymorphism and SBP and weight was found in subjects with MI rather than in controls. However, the average SBP was in normal range (< 140 mmHg), and the BMI of Ala carriers with MI was not different from the Pro carriers and was also found to be the same in control group. This result is not consistent with the study of Memisoglu *et al.*, which indicated that there is an interaction between Pro12Ala polymorphism and dietary fat intake in relation to BMI.¹⁴ Thus, further observation of the impact of Pro12Ala polymorphism on SBP and BMI is necessary. These results suggest that the impact of Pro12Ala polymorphism on MI have various aspects, and that the effects may be modulated by the complex interactions between a variety of genetic and environmental factors.

It is interesting that the 12Ala allele was primarily observed in women in the MI group, probably due to the increased storage of white fat. Nevertheless, the distribution of 12Ala allele frequency in male subjects with MI did not differ from that in the male controls. Furthermore, there was no difference in 12Ala allele frequency distribution between genders in the control group. The question is whether there were other metabolic disorders in female patients with MI and the Ala allele. Our analyses found that these patients had significantly higher levels of FPG (7.30 ± 5.59 vs. 6.26 ± 4.58) and TC (5.31 ± 0.93 vs. 4.59 ± 1.17) than male patients with MI and the Ala allele, which implies that there were more severe metabolic disorders in women than in men with the Ala allele. Obviously, the data predict that women with the Ala allele are at increased risk of atherosclerosis and have a high susceptibility for MI.

We also observed the relationship between Pro12Ala polymorphism and other traditional cardiovascular risk factors such as smoking, age, and alcohol intake in both groups. In our study, no such relationship was found.

It has been reported that both heterozygous PPAR- γ 2 deficiency and the agonists TZDs can ameliorate lipid and glucose metabolic disorders, as well as insulin resistance (IR) by various pathways.¹⁵ Notably, treatment with agonists TZDs led to the decrease of levels of free fatty acids (FFA), TC, TG, upregulation of the level of insulin-sensitizing hormone-adiponectin,¹⁶ and downregulation of the levels of leptin and resistin. Thiazolidinediones may also decrease the injury of ischemia/reperfusion, reduce the size of MI,¹⁷ and reduce the risk of restenosis of percutaneous transluminal coronary angioplasty.¹⁸ It may be a novel way to treat MI.

Study Limitation

The principal limitation in our study was that the Ala allele was in a low-frequency variant, and that the group of study pa-

tients with Ala allele was small; thus, our research needs a larger sample size for further confirmation of the study results.

Conclusions

The result of our study suggests that Pro12Ala polymorphism of the PPAR-gamma 2 gene is associated with an increased risk of MI in the Chinese Han population, and that there is a gender difference in Pro12Ala polymorphism frequency distribution in the MI group; this could be important for clinical diagnosis and gene therapy. Whether the Pro12Ala polymorphism of the PPAR-gamma 2 gene has the same impacts on MI in other populations will need to be clarified in the future.

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