

Influence of Peroxisome Proliferator-activated Receptor (PPAR α) P12Ala Polymorphism as a Shared Risk Marker for Both Gastric Cancer and Impaired Fasting Glucose (IFG) in Japanese

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Abstract Activation of peroxisome proliferator-activated receptor (PPAR α) has been shown to inhibit the proliferation of gastric cancer cells. A common polymorphism at codon 12 of this gene (Pro12Ala) has been shown to confer protection against diabetes and colorectal cancer. We investigated the influence of PPAR α gene P12Ala polymorphism on the risk of gastric cancer and on the severity of Helicobacter pylori-induced gastritis as well as impaired fasting glucose (IFG) in Japanese. About 215 patients with gastric cancer (GC) and 201 patients without GC enrolled in this study. P12Ala polymorphism of PPAR α was investigated by PCR-RFLP in all of the subjects. The gastritis score of noncancerous antral mucosa was calculated by the updated Sydney system. The diagnosis of IFG was based on repeated evidence of serum fasting glucose (SFG) concentration of greater than or equal to 110 mg/dl. The P12Ala genotype of PPAR α showed a significantly higher frequency in GC patients than in controls (OR = 2.94; 95%CI = 1.13–7.66). Among 151 gastric cancer subjects, the atrophy and metaplasia scores of the antral mucosa adjacent to cancer showed a tendency to be higher in those with the P12Ala allele. Our study suggests that the PPAR α Pro12Ala polymorphism may be a shared risk marker of both IFG and gastric cancer in Japanese.

Keywords Gastric cancer
Peroxisome proliferator-activated receptor (PPAR)
Polymorphism
Impaired fasting glucose (IFG)

Introduction

Gastric cancer remains a significant worldwide health burden. Although the incidence of and mortality due to non-cardiac gastric cancer have been decreasing over the last few decades, it still remains second only to lung cancer as the leading cause of cancer mortality worldwide [1]. Helicobacter pylori infects the human stomach and causes chronic mucosal inflammation. Although, it has been classified as a carcinogen [2], there is marked variation in the extent of gastric inflammation among H. pylori-infected patients, and only a small percentage of them actually develop gastric cancer. This suggests that genetic factors may also play an important role in gastric carcinogenesis.

The peroxisome proliferator-activated receptors (PPARs) are ligand-dependent transcription factors that are members of the nuclear receptor superfamily. At least three different PPAR subtypes, α , β , and γ have been described [3]. PPAR α is highly expressed in adipocytes and is responsible for the regulation of adipocyte differentiation and glucose homeostasis, but it has also been suggested to act as a regulator of cell proliferation and the inflammatory

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response [6]. When activated by specific ligands, PPAR forms heterodimers with retinoid X receptor (RXR), which regulate the expression of target genes by binding to the peroxisome proliferator-responsive element (PPRE). PPAR also has been demonstrated in other tissues, including the colon, stomach, small intestine, liver, and pancreas [9]. Recently, it was reported that PPAR activation can inhibit gastric mucosal inflammation and apoptosis induced by *H. pylori* [11]. These findings suggest that PPAR may play a significant role in suppressing gastric mucosal inflammation and tumorigenesis by gastric epithelial cells.

Studies on the PPAR gene (PPARG) have identified a number of polymorphisms, including one that causes an amino acid substitution, Pro12Ala [7]. This substitution may significantly alter the conformation of PPAR protein, and thus may influence its activity. The PPAR Pro12Ala allele has been reported to show decreased binding to the promoter element and demonstrates weaker transactivation of responsive promoters in vitro [8].

Some authors have reported that the PPAR Pro12Ala polymorphism confers protection against diabetes and colorectal cancer [4, 18]. Concerning the effect of PPAR Pro12Ala polymorphism on gastric carcinogenesis, however, one recent study found that the PPAR Pro12Ala allele increases the risk of gastric cancer in China [9]. In the present study, we investigated the influence of PPAR Pro12Ala polymorphism on the risk of gastric cancer as well as diabetes or impaired fasting glucose (IFG) in Japanese. We also investigated its association with various subtypes and clinicopathologic features of gastric cancer. Furthermore, we investigated the effect of this polymorphism on the histologic severity of *H. pylori*-induced gastritis.

GC were observed irrespective of *H. pylori* infection status. GC was diagnosed histologically and was classified according to Lauren's classification [20]. Detailed information was obtained about the stage, anatomical location, venous and lymphatic invasion, lymph node metastasis, distant metastasis, and peritoneal dissemination. Patients who had severe systemic disease and had received non-steroidal anti-inflammatory drugs were excluded from this study. The Ethics Committee of Fujita Health University School of Medicine approved the protocol and written informed consent was obtained from all of the subjects.

Assessment of diabetes or impaired fasting glucose (IFG)

The diagnosis of impaired fasting glucose was based on repeated evidence of serum fasting glucose (SFG) concentration of greater than or equal to 110 mg/dl. Meanwhile, the patients who had a SFG concentration < 110 mg/dl were considered as non-IFG.

Histological examination

Biopsy specimens were obtained from the uninvolved mucosa of the gastric antrum adjacent to cancer for assessment of gastritis. The extent of neutrophil infiltration, mononuclear cell infiltration, atrophy, and metaplasia was assessed according to the updated Sydney system, with each factor being scored from 0 (normal) to 3 (marked).

Detection of *H. pylori* infection

The *H. pylori* infection status was determined on the basis of histology, culture, the rapid urease test (RUT), and antibodies to *H. pylori*. Infection was diagnosed when at least one of these four tests was positive.

Materials and methods

Study population

We studied 416 patients attending the Gastroenterology Division of Fujita Health University Hospital (Aichi, Japan) from January 2005 to January 2006. The 416 patients contained 215 patients with gastric cancer (GC) who had a mean age of 64.7 (29-93) years and a male:female (M:F) ratio of 153:62 and 201 non-cancer patients who had a mean age of 63.1 (30-90) years and a M:F ratio of 122:79. Non-cancer patients underwent endoscopic examination for the complaint of abdominal discomfort and were diagnosed as having gastric ulcer, duodenal ulcer, gastritis or normal appearances. Gastric and duodenal ulcer patients were selected from *H. pylori*-positive subjects. Meanwhile, the

Genotyping

Genomic DNA was extracted from frozen normal gastric biopsy tissues or peripheral blood cells using the standard phenol/chloroform method. Then PPAR Pro12Ala polymorphism was determined by the polymerase chain reaction-restriction fragment length polymorphism technique, as described previously [21]. The forward primer was 5'-ctgatgtcttgactcatggg-3' and the reverse primer was 5'-ggaagacaactacaagagc-3'. PCR was carried out in a

reaction volume of 25 μ l containing 20 μ g of genomic DNA, 1 \times reaction buffer, 0.125 mmol/l deoxynucleotide triphosphates, 10 pmol of each primer, and 0.6 units of Taq polymerase (Toyobo, Osaka, Japan). DNA was denatured at 95 C for 5 min, followed by 35 cycles of 95 C for 30 s, 53 C for 30 s, and 72 C for 40 s, with final extension at 72 C for 7 min. Then digestion with 5 units of Hga-I (New England Biolabs, Inc., Beverly, MA) was employed to analyze PPARc Pro12Ala polymorphism, yielding products of 295 bp (Pro) and 178 + 117 bp (Ala). Digestion was performed overnight at 37 C, the products were separated on a 3% agarose gel, and were stained with ethidium bromide for visualization. Genotypes were determined by two independent investigators who were blinded to patient data.

Statistical analysis

The χ^2 test was used for comparison of PPARc genotype frequencies between the GC and control groups. The odds ratio (OR) and 95% confidence interval (CI) were calculated by logistic regression with adjustment for age, sex, and H. pylori infection status. For the comparison of PPARc genotype frequencies between the IFG and non-IFG patients, logistic regression with adjustment for age and sex was performed. Differences of gastritis scores between the two PPARc genotypes (Ala carriers and Pro/Pro) were examined by the Mann-Whitney U test. A probability value of less than 0.05 was considered statistically significant in all analyses.

Results

Study population

A total of 416 subjects including 215 GC and 201 non-cancer patients participated in this study. The characteristics of the subjects are summarized in Table 1. There were no significant differences between the two groups with respect to the age distribution, but male sex and H. pylori infection were significantly more common in the GC group. The main endoscopic diagnoses in the control group were gastric ulcer in 39 patients (19.4%), duodenal ulcer in 16 patients (8%), gastric + duodenal ulcer in four patients (2%), and gastritis in 142 patients (70.6%). SFG concentration was measured in 396 of all 416 patients and 165 patients with IFG who had a mean age of 66.5 (33–93) years and a male:female (M:F) ratio of 112:52, as well as 232 non-IFG patients who had a mean age of 62.4 (29–90) years and a M:F ratio of 146:86 were identified. There were no significant differences between IFG patients and non-IFG

Table 1 Characteristics of subjects

	Gastric cancer (GC) cases	Patients without GC	P
Subjects (n)	215	201	
Sex [male/female (%/%)]	153/62 (71/29)	122/79 (61/39)	0.03
Mean age \pm SD (years)	64.7 \pm 11.9	63.1 \pm 12.6	0.46
H. pylori infection positive ratio (%)	85.1	70.6	0.0005

^a χ^2 test, ^b Mann-Whitney U test

Table 2 Characteristics of subjects

	IFG cases	Patients without IFG	P
Subjects (n)	164	232	
Sex [male/female (%/%)]	112/52 (68/32)	146/86 (63/37)	0.27
Mean age \pm SD (years)	66.5 \pm 11.6	68.9 \pm 10.45	0.001
GC patients/without GC	89/75	115/117	0.36

^a χ^2 test, ^b Mann-Whitney U test

of patients with respect to sex and occurrence of GC, but age distribution was significantly higher in the IFG patients (Table 2).

PPARc Pro12Ala polymorphism was investigated in all 416 subjects. The frequency of Pro12Ala polymorphism in the non-cancer patients did not deviate significantly from that expected under the Hardy-Weinberg equilibrium and also did not show any significant difference from the genotype distribution revealed by other studies performed in Japanese populations ($\chi^2 = 0.08, P = 0.77$) [23]. There were no subjects homozygous for the Ala12 allele of the PPARc gene. First, we compared the prevalence of Pro12Ala polymorphism between IFG patients and non-IFG patients by logistic regression analysis and found that the Pro12Ala genotype held a lower risk of IFG (age and sex adjusted OR = 0.33; 95%CI = 0.13–0.83) (Table 1). In contrast, comparison of the genotype frequency between the GC and control groups showed that the PPARc Pro12Ala genotype was associated with a significantly higher risk of gastric cancer (OR = 2.43; 95%CI = 1.04–5.67) (Table 4). To investigate whether the PPARc Ala12 allele influenced the clinicopathologic features of gastric cancer, the tumor location, stage, Lauren's classification, lymphatic and venous invasion, lymph node metastasis, peritoneal dissemination, and distant metastasis were included in a stratified analysis. Among these

Table 3 Association between PPAR γ polymorphism and risk of IFG

Variables (n)	Genotype		Pro/Pro vs. Pro/Ala	
	Pro/Pro	Pro/Ala	OR (95%CI)	P
Patients without IFG (201)	209	23	Reference	
IFG (215)	158	6	0.33 (0.13-0.83)	0.02

Data are adjusted for sex and age

clinicopathologic features, we found that PPAR γ Pro12Ala polymorphism increased the risk of non-cardiac gastric cancer (OR = 2.39; 95%CI = 1.02-5.65), lower third gastric cancer (OR = 3.56; 95%CI = 1.31-9.71), advanced cancer (OR = 2.93; 95%CI = 1.13-7.58), and Lauren's intestinal cancer (OR = 2.94; 95%CI = 1.13-7.66). We also found that the Ala12 allele tended to increase the risk of venous invasion (OR = 3.12; 95%CI = 0.98-9.93) and lymph node metastasis (OR = 2.38; 95%CI = 0.89-6.40) (Table 5), but there was no association between this allele and peritoneal dissemination or distant metastasis. In the control group, there were no significant genotype differences among the patients with gastric ulcer, duodenal ulcer, and gastritis (data not shown).

Effect of PPAR γ polymorphism on the severity of gastritis in noncancerous gastric mucosa adjacent to cancer

Among all 21 subjects with 12Ala allele and randomly selected age, sex matched 130 subjects with homozygous for the Pro12 allele, the atrophy and metaplasia scores of the antral mucosa showed a tendency to be higher in those possessing the 12Ala allele (Table 6), but the neutrophil infiltration and mononuclear cell infiltration scores did not show any correlation between the 12 Ala carriers and subjects homozygous for the Pro12 allele.

Discussion

In two Japanese populations, the frequency of the common polymorphism of PPAR γ Ala12 allele was shown to be significantly lower in individuals with type 2 diabetes than in normal subjects [14, 15]. In addition, the same genotype

was also associated with reduced risk of colorectal cancer [17, 18], suggesting that this allele may confer protection against diabetes and colorectal cancer. In our study, we have also shown the frequency of Ala12 allele was significantly lower among IFG patients. This indicates that the Ala12 allele may be associated with lower risk of both diabetes and IFG. Meanwhile, in agreement with a recent study performed in China [9], we found that the Ala12 allele is associated with the risk of gastric cancer in a Japanese population. The Ala12 allele frequency was significantly higher in patients with gastric cancer than in controls. In 1998, Deeb et al. reported that Pro12Ala polymorphism of PPAR γ was associated with reduced transactivation activity [13]. Activation of PPAR γ has been shown to inhibit cell growth and to induce the apoptosis of gastric cancer cells [10]. Although we did not investigate the effect of PPAR γ polymorphism on PPAR γ activity in human gastric epithelial cells, it is possible that the polymorphism might have altered the activity of PPAR γ . Thus, it seems reasonable for the 12Ala allele to be a risk factor for gastric cancer.

PPAR γ 12Ala allele has been shown to be associated with reduced risk of colorectal cancer and diabetes [14, 18]. Presence of the Pro12Ala variant polymorphism is reported to be associated with lower body mass index (BMI), improved insulin sensitivity, and a reduced risk for type 2 diabetes [14, 16]. Therefore, it is possible that PPAR γ is associated with risk for colorectal cancers through insulin-related mechanisms.

However, in the stomach, experimental studies have actually demonstrated that activation of PPAR gamma inhibited the growth of gastric cancer cells and suppressed the gastric mucosal inflammation [10, 11, 33]. Considering the function of PPAR gamma in the stomach, our result of PPAR gamma 12Ala allele, which is associated with reduced promoter activity, of increasing the risk of gastric cancer and gastric atrophy may suggest that gastric carcinogenesis may have different genetic background to colorectal carcinogenesis in some measure.

Next, we investigated the effect of PPAR γ Pro12Ala polymorphism on the characteristics of gastric cancer by stratified analysis, and found that the Ala12 allele was associated with a higher risk of non-cardiac, or lower third cancer and intestinal cancer. These results may be explained by both the anti-tumor effect [10, 24] and the anti-inflammatory effect [1, 25, 27] of PPAR γ . Correa et al. reported

Table 4 Association between PPAR γ polymorphism and risk of gastric cancer

Variables (n)	Genotype		Pro/Pro vs. Pro/Ala	
	Pro/Pro	Pro/Ala	OR (95%CI)	P
Patients without GC (201)	193	8	Reference	
Overall GC (215)	194	21	2.43 (1.04-5.67)	0.04

Data are adjusted for sex, age, and H. pylori infection status

Table 5 Association between PPARc polymorphism and clinicopathologic features of gastric cancer

Variables (n)	Genotype		Pro/Pro vs. Pro/Ala	
	Pro/Pro	Pro/Ala	OR (95%CI)	P
Patients without GC (201)	193	8	Reference	
Tumor location				
Cardia (6)	5	1	4.97 (0.48–51.40)	0.18
Non-cardia (209)	190	19	2.39 (1.02–5.65)	0.049
Upper third (17)	16	1	2.50 (0.27–23.11)	0.42
Middle third (101)	92	9	2.04 (0.74–5.65)	0.17
Lower third (87)	77	9	3.56 (1.31–9.71)	0.01
Staging				
Early (105)	96	9	2.03 (0.74–5.54)	0.17
Advanced (91)	80	11	2.93 (1.13–7.58)	0.03
Lauren's classification				
Intestinal type (124)	111	13	2.94 (1.13–7.66)	0.03
Diffuse type (90)	82	7	2.21 (0.79–6.21)	0.14
Lymphatic invasion				
Positive (97)	88	9	2.21 (0.80–6.08)	0.13
Negative (74)	67	7	2.39 (0.82–7.02)	0.11
Venous invasion				
Positive (50)	44	6	3.12 (0.98–9.93)	0.053
Negative (121)	111	10	1.93 (0.72–5.14)	0.19
Lymph node metastasis				
Positive (101)	89	12	2.38 (0.89–6.40)	0.08
Negative (114)	106	8	1.96 (0.72–5.34)	0.19
Peritoneal dissemination				
Positive (33)	29	4	3.19 (0.88–11.58)	0.08
Negative (182)	166	16	2.31 (0.96–5.58)	0.06
Distant metastasis				
Positive (19)	17	2	2.86 (0.55–14.82)	0.21
Negative (196)	177	19	2.36 (0.99–5.63)	0.053

All data are adjusted for sex, age, and *H. pylori* infection status

Table 6 Association between genotypes and histologic scores in noncancerous gastric antral mucosa adjacent to cancer

Genotype (n)	Pro/Pro(130)	Pro/Ala(21)	P
Neutrophil infiltration	0.85 ± 0.46	1.00 ± 0.32	0.14
Mononuclear cell infiltration	1.65 ± 0.62	0.9 ± 0.64	0.1
Atrophy	1.09 ± 0.76	1.4 ± 0.82	0.09
Intestinal metaplasia	1.42 ± 1.03	1.85 ± 0.46	0.08

Scores shown are mean ± SD. Mann-Whitney U test

that gastric atrophy and metaplasia following severe inflammation are an especially strong risk factor for developing the intestinal type of gastric cancer [28, 29]. We have also showed that the Ala12 allele is associated with the risk of more advanced stage. Similarly, Ala12 allele also tended to be associated with a higher risk of Uemura et al. also reported that severe gastric atrophy, venous invasion and lymph node metastasis, possibly due to corpus-predominant gastritis, and intestinal metaplasia are strong risk factors for the development of intestinal-type gastric cancer [30]. For example, PPARc ligands suppress angiogenesis by strong induction of apoptosis in endothelial cells [31, 32]. PPARc Pro12Ala polymorphism may influence both the anti-tumor and anti-inflammatory actions of PPARc, as also been shown to inhibit peritoneal of PPARc and thus may modify the risk of developing metastasis by gastrointestinal cancer cells [33], while a intestinal gastric cancer, which frequently arises from a decrease of PPARc activity has been found in some cancers with metastasis [34, 35]. Thus, PPARc may play a key role in suppressing the progression and metastasis of gastric

cancer, so that PPAR γ Pro12Ala polymorphism may also over all non-cancer patients did not deviate from the frequency of healthy controls reported in previous studies. So we considered the group of patients was appropriate as the control subjects in this study.

12Ala allele would be associated with the risk of these complications. However, no correlation was observed between the 12Ala allele and the risk of such complications, possibly because the number of patients with peritoneal dissemination and distant metastasis in this study was small, suggesting that further investigation is needed in a larger population.

We also showed that the PPAR γ Pro12Ala allele is associated with the severity of gastric mucosal atrophy and intestinal metaplasia. Among 151 gastric cancer subjects, the atrophy and metaplasia scores of the antral mucosa showed a tendency to be higher in those possessing the 12Ala allele. Gastric mucosal atrophy and intestinal metaplasia are caused by chronic exposure to inflammation induced by *H. pylori* infection. PPAR γ has an anti-inflammatory effect by regulating the expression of various genes associated with inflammation, and such an effect also occurs in persons with *H. pylori*-related gastritis. Solimani et al. reported that PPAR γ activation by administration of ciglitazone led to a dose-dependent reduction in the severity of mucosal inflammation elicited by *pylori* LPS [27]. Rajnish et al. also reported that two PPAR γ agonists (15dPG $_2$ and BRL-49653) significantly attenuated *pylori*-induced apoptosis, while co-treatment with PPAR γ agonists blocked the ability of *pylori* to activate nuclear factor (NF)- κ B and increase the level of IL-8, a target of (NF)- κ B [11]. Because of the important role that PPAR γ plays with respect to the inflammatory response in *pylori*-induced gastritis, PPAR γ Pro12Ala polymorphism, associated with PPAR γ activity, may also be important for determining the severity of gastric mucosal atrophy. However, we did not find any association between PPAR γ Pro12Ala polymorphism and acute or chronic inflammation. Progression of atrophic gastritis is terminated by the development of extensive intestinal metaplasia, so patients with severe atrophic gastritis and intestinal metaplasia often have mild, but not severe inflammation. However, it should be noted that they had had long-term prior exposure to severe mucosal inflammation.

Regarding the histological differences in gastritis, it has been suggested that patients with gastric ulcer have more severe gastric mucosal atrophy and have increased risk of gastric cancer compared to those with duodenal ulcer [36, 37]. But in this study, frequencies of PPAR γ genotypes were not significantly different among patients with gastric ulcer, duodenal ulcer, and gastritis. In addition, when patients with peptic ulcer were included in non-cancer patients, the frequency of PPAR γ Pro12Ala polymorphism reduced risk of IFG, but in contrast, the same genotype was also associated with more severe gastric mucosal atrophy, with intestinal metaplasia, and with an increased risk of gastric cancer, especially the intestinal type, non-cardiac cancer, lower third cancer, and advanced cancer, venous invasion, and lymph node metastasis, suggesting that the PPAR γ Pro12Ala polymorphism may be a shared risk factor for both IFG and gastric cancer. However, we only investigated PPAR γ polymorphism in a limited region of Japan. Since the PPAR γ gene polymorphism shows variations in different ethnic groups [39], further studies will be needed in a larger and ethnically diverse population to confirm the influence of this gene on gastric carcinogenesis as well as developing IFG.

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