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BRIEF ARTICLE

HOGG1 polymorphism in atrophic gastritis and gastric cancer after *Helicobacter pylori* eradication

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Abstract

AIM: To investigate the association between Ser326Cys human oxoguanine glycosylase 1 (hOGG1) polymorphism and atrophic gastritis and gastric cancer after *Helicobacter pylori* (*H. pylori*) eradication.

METHODS: A total of 488 subjects (73 patients with gastric cancer, 160 with atrophic gastritis after *H. pylori* eradication and 255 controls) were prospectively collected. Polymerase chain reaction-restriction fragment length polymorphism analysis was performed to distinguish hOGG1 Ser326Cys polymorphism. Statistical analysis was conducted by two-sample *t* test for continuous variables and χ^2 test for categorical variables. Logistic regression models were used to find the risk factors for gastric cancer and atrophic gastritis.

RESULTS: Neither the hOGG1 Ser/Cys nor the Cys/Cys genotype was associated with gastric cancer. Compared with the Ser/Ser genotype, odds ratio (OR) for Ser/Cys was 0.96, (95% CI: 0.51-1.84) and OR for Cys/Cys was 1.1 (95% CI: 0.48-2.1). No association was detected between hOGG1 polymorphism and Lauren type of gastric cancer (P = 0.61) either. However, Ser/Cys and Cys/Cys were significantly associated with atrophic gastritis with OR: 1.76 for Ser/Cys (95% CI: 1.03-3.0) and 2.38 for Cys/Cys (95% CI: 1.34-4.23). After controlling for age, gender, smoking and alcohol, there were still significant associations with OR: 2.05 for Ser/Cys (95% CI: 1.14-3.68) and 2.76 for Cys/Cys (95% CI: 1.47-5.18).

CONCLUSION: HOGG1 polymorphisms (Cys/Cys and Ser/Cys) are associated with atrophic gastritis. No significant association is detected between hOGG1 polymorphisms (Cys/Cys or Ser/Cys) and gastric cancer.

Key words: Human oxoguanine glycosylase 1 polymorphism; Atrophic gastritis; Gastric cancer

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INTRODUCTION

Gastric carcinoma develops in the following sequence: superficial gastritis, atrophic gastritis, intestinal metaplasia, dysplasia and cancer according to Correa's model[1]. *Helicobacter pylori* (*H. pylori*) infection is an important cause of chronic atrophic gastritis. The tissue damage and cell destruction are either caused by direct release of cytotoxins, lipase and phospholipase or indirectly by reactive oxygen species (ROS) released from polymorphonuclear leucocytes[2]. ROS is thought to be one of the pathogeneses for both atrophic gastritis and cancer[3]. However, the mechanism is still unclear for atrophic gastritis developing in *H. pylori* negative patients.

Oxygen-free radicals (OFR) are generated in small amounts in the course of normal metabolic reactions. However, OFR can react with complex cellular molecules such as fats, proteins, or DNA and cause further damage to them. Some oxidative DNA lesions are pro-mutagenic and oxidative damage has been proposed to play a role in the development of certain cancers[4,5]. Hydroxyl radicals are important for DNA damage. This radical is so reactive that it can damage all components of the DNA molecule: the purine and pyrimidine bases as well as the deoxyribose backbone[6]. One of the most common lesions formed by ROS modifications is 8-Hydroxy-2'-deoxyguanosine (8-OHdG). A specific DNA glycosylase/apurinic (AP) lyase, 8-hydroxy-2'-deoxyguanosine-glycosylase/apruinic lyase (ogg1), which catalyses the release of 8-OHdG and the cleavage of DNA at the AP site was found in *Escherichia coli* and yeast[4,5]. The human homologue of this gene, hOGG1 has been identified[6,7]. The gene product of hOGG1 can exhibit greatest specificity and activity for 8-OHdG:dC and is inactive against 8-oxodeoxyguanosine:dA[8,9]. HOGG1 has also been shown to excise 2,6-dianimo-4-hydroxy-5-formamidopyrimidine residues in a similar manner to its yeast homologue[10]. A C/G polymorphism at position 1245 in the 1α-specific exon 7 of the hOGG1 results in an amino acid substitution from serine to cysteine in codon 326. A number of hOGG1 polymorphisms have been described and a Ser/Cys substitution in exon 7 is highly prevalent[8,9,11,12]. The hOGG1 protein encoded by the wild-type 326Ser allele exhibited substantially higher DNA repair activity than the 326Cys. Some studies have suggested that the Ser326Cys hOGG1polymorphism may be associated with increased risk for lung[8], stomach[9], orolaryngeal[11,12], bladder[13] as well as gallbladder cancers[14] The aim of this study was to investigate the association between hOGG1 genotype and gastric cancer as well as atrophic gastritis.

MATERIALS AND METHODS

Subjects

This is a prospective case-control study in patients with atrophic gastritis and gastric cancer and healthy controls consecutively enrolled at Sir Run Run Shaw Hospital, China from April 2005 to March 2008.

All enrolled gastric cancer patients were histologically confirmed prior to operation and chemotherapy. Healthy controls were patients with normal endoscopic findings during the recruiting period. Gastric cancer patients were classified according to Lauren type. The inclusion criteria for atrophic gastritis were: endoscopically diagnosed atrophic gastritis according to Sydney system[15] and documented *H. Pylori* infection eradication for at least 1 year. *H. pylori* was confirmed to be negative in both histopathology and ^{13}C Urea breath test. The exclusion criteria for atrophic gastritis included newly diagnosed atrophic gastritis with *H. Pylori* infection or the *H. Pylori* which was eradicated within 1 year; the *H. Pylori* status was unknown or negative before diagnosis; patients with any kind of gastric operation history; and either histology or ^{13}C Urea breath test was considered to be positive for *H. pylori* infection.

Five biopsy specimens taken from the antrum, the angulus and the corpus of the stomach were embedded in paraffin wax, stained with haematoxylin-eosin and by Giemsa method. Mononuclear cell infiltration, polymorphonuclear cell infiltration, glandular atrophy, intestinal metaplasia, and the density of *H. pylori* were graded from 0 to 3, according to the updated Sydney system[15] by an experienced pathologist.

Each participant completed a self-structured questionnaire about alcohol and tobacco consumption. Alcohol drinking was defined as severe (a total amount of 20 g/d or more for 10 years), none (less than once a month) and mild (any amount in between). Smoking was defined as none, mild (less than 20 cigarettes per day) and severe (more than 20 cigarettes per day). The study was approved by the Sir Run Run Shaw Hospital Institutional Review Board. Each participant signed an informed consent form.

DNA genotyping assays

DNA was extracted from 10 mL whole blood according to the protocol of QIAamp DNA blood kit handbook. The basic method for detecting polymorphism was based on polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Generated fragments were separated by a 4% Metaphor agarose gel, stained with ethidium bromide. Puc19 DNA/*Msp* I (*Hpa* II) Marker, 23 (MBI Fermentas) or DNA Molecular Weight Marker Ⅷ (Roche Molecular Biochemicals, USA) were used. DNA was subject to PCR using fluorescent primers directed against the marker of hOGG1[8]. PCR protocols were presented in detail as follows: 20 pmol of primers (5'-ACTAGTCTCACCAGCCGTGAC-3' and 5'-TGGCCTTTGAGGTAGTCACAG-3') reacted with 1 mmol/L $MgCl_2$ and 2.5 U of *Taq* DNA polymerase in 50 μL systems. The PCR reaction began with denaturation at 95℃ for 14 min, and then was taken at 95℃, 1 min; 59.5℃, 1 min; and 72℃, 1 min for 30 cycles.

The hOGG1 PCR product (10 μL) was incubated with 2 U of *Fnu*4H I (New England Biolabs) overnight at 37℃, ended with 65℃ for 20 min. *Fnu*4H I (cuts cysteine alleles

Table 1 Clinical characteristics of subjects

	Total patients (*n* = 488)	Atrophic gastritis (*n* = 160)	Gastric cancer (*n* = 73)	Controls (*n* = 255)
Mean age (SD, yr)	48.6 (11.9)	51.4 (10.6)	59.6 (11.2)	43.6 (10.3)
Gender (%)				
Male	57.2	48.7	65.8	60.0
Female	42.8	51.3	34.2	40.0
Smoking (%)				
None	69.4	75.6	52.1	70.5
Mild/moderate	21.4	19.4	30.1	20.0
Severe	9.2	5.0	17.8	9.5
Alcohol (%)				
None	61.6	68.8	41.1	63.0
Mild/moderate	28.1	25.6	41.1	26.0
Severe	10.3	5.6	17.8	11.0
HOGG1 (%)				
Ser/Ser	24.5	16.7	28.8	28.2
Ser/Cys	47.0	35.3	25.8	46.7
Cys/Cys	28.5	48.0	45.4	25.1

HOGG1: Human oxoguanine glycosylase 1.

Table 2 Clinical characteristics of different grades of atrophic gastritis

	Grade 1 (*n* = 68)	Grade 2 (*n* = 68)	Grade 3 (*n* = 23)
Mean age (SD, yr)	51.3 (10.8)	51.1 (9.8)	52.9 (12.8)
Gender (%)			
Male	47.1	50.0	52.2
Female	53.9	50.0	47.8
Smoking (%)			
None	76.5	75.0	73.9
Mild/moderate	16.2	20.6	26.1
Severe	7.3	4.4	0.0
Alcohol (%)			
None	70.6	64.7	73.9
Mild/moderate	22.1	29.4	26.1
Severe	7.3	5.9	0.0
HOGG1 (%)			
Ser/Ser	18.2	15.1	13.0
Ser/Cys	62.1	36.4	43.5
Cys/Cys	19.7	48.5	43.5

HOGG1: Human oxoguanine glycosylase 1.

generated 123/124 and 169/170 bp fragments from primary 293 bp amplicon.

Quality control

(1) Blind the researchers to case control status; (2) include blanks in each plate in different well positions; (3) include multiple and duplicate control subjects in each plate in different well positions; (4) determine 10% as an acceptable amount of missing data and rerun assays if there is more missing data in either cases or controls; and (5) perform an Hardy-Weinberg Equilibrium test for each SNP before testing any hypothesis.

Statistical analysis

Statistical analysis was performed by SAS software (SAS Institute Inc, Version 9.1, Cary NC.). Discrete variables were analyzed by the Pearson χ^2 test and continuous variables by the Student's *t* test or generalized regression models. Logistic regression models were fitted to find the risk factors for gastric cancer and atrophic gastritis. For all analyses, significance was determined at a level of $P < 0.05$ (two-tailed).

RESULTS

Clinical characteristics in different groups

Totally, 488 subjects were included in this study (160 patients with atrophic gastritis, 73 with gastric cancer and 255 controls). All gastritis patients were *H. pylori* negative, which was confirmed by both histopathology and ^{13}C Urea breath test. The clinical characteristics of the subjects are summarized in Tables 1-3. Patients with gastric cancer were significantly older than those in the control group (59.6 ± 11.2 years *vs* 43.6 ± 10.3 years, $P < 0.0001$) and atrophic gastritis group (59.6 ± 11.2 years *vs* 51.4 ± 10.6 years, $P < 0.0001$). Gastric cancer group had a significantly higher ratio of males than atrophic gastritis group (65.8% *vs* 48.7%, $P = 0.02$).

Table 3 Clinical characteristics of different grades of intestinal metaplasia

	Grade 1 (*n* = 44)	Grade 2 (*n* = 76)	Grade 3 (*n* = 40)
Mean age (SD, yr)	50.7 (9.5)	51.4 (11.2)	51.9 (10.1)
Gender (%)			
Male	47.7	48.7	50.0
Female	52.3	51.3	50.0
Smoking (%)			
None	86.4	71.1	72.5
Mild/moderate	6.8	25.0	22.5
Severe	6.8	3.9	5.0
Alcohol (%)			
None	77.3	60.5	75.0
Mild/moderate	15.9	32.9	22.5
Severe	6.8	6.6	2.5
HOGG1 (%)			
Ser/Ser	13.9	18.6	15.8
Ser/Cys	53.5	42.7	52.6
Cys/Cys	32.6	38.7	31.6

HOGG1: Human oxoguanine glycosylase 1.

HOGG1 genotype in different groups

The hOGG1 genetic polymorphism was determined using PCR and RFLP (Figure 1). As shown in Table 4, neither the hOGG1 Ser/Cys nor the Cys/Cys genotype was associated with gastric cancer, compared with the Ser/Ser genotype (OR: 0.96 for Ser/Cys, 95% CI: 0.51-1.84 and OR: 1.1 for Cys/Cys, 95% CI: 0.48-2.1). No association was detected between hOGG1 polymorphism and Lauren type of gastric cancer ($P = 0.61$) either. Ser/Cys and Cys/Cys were significantly associated with atrophic gastritis (OR: 1.76, 95% CI: 1.03-3.0 and OR: 2.38, 95% CI: 1.34-4.23). After controlling for age, gender, smoking and alcohol, there were still significant associations, with OR: 2.05 for Ser/Cys, 95% CI: 1.14-3.68 and 2.76 for Cys/Cys, 95% CI: 1.47-5.18.

There was no statistically significant association be-

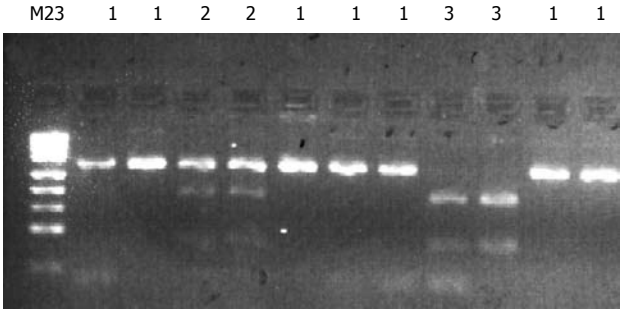

Figure 1 Selected genotyping assays. The human oxoguanine glycosylase 1 genetic polymorphism was determined using polymerase chain reaction and restriction fragment length polymorphism. 1: Genotype Ser/Ser in 293 bp; 2: Genotype Cys/Ser in 293/169/124 bp; 3: Genotype Cys/Cys in 169/124 bp; M23: Marker 23, PUC19DNA/*Msp* Ⅰ (*Hpa* Ⅱ) Marker, 23 (Fermentas life science Co.).

Table 4 Odds ratios for association of genotypes and gastric cancer/atrophic gastritis

HOGG1 subtypes	Gastric cancer *vs* control		Atrophic gastritis *vs* control	
	OR (95% CI)	Adjusted OR (95% CI)[1]	OR (95% CI)	Adjusted OR (95% CI)[1]
Ser/ser	1	1	1	1
Ser/Cys	0.96 (0.51-1.84)	1.29 (0.57-2.93)	1.76 (1.03-3.0)	2.05 (1.14-3.68)
Cys/Cys	1.1 (0.48-2.10)	1.22 (0.48-3.14)	2.38 (1.34-4.23)	2.76 (1.47-5.18)

[1]Adjusted for age, gender, other risk factors such as alcohol and smoking. HOGG1: Human oxoguanine glycosylase 1; OR: Odds ratios.

tween intestinal dysplasia and hOGG1 polymorphism (P = 0.75). HOGG1 Cys/Cys group had statistically significantly higher rate of moderate and severe atrophic gastritis than Ser/Cys and Ser/Ser group (P = 0.03). Smoking was a risk factor for gastric cancer (mild smoking 35% *vs* 20% and moderate smoking 15% *vs* 9.45%, P = 0.02), but not a risk factor for atrophic gastritis. Alcohol was a risk factor for gastric cancer (mild drinking 37.5% *vs* 26% and moderate smoking 17.5% *vs* 11%, P = 0.03), but not a risk factor for atrophic gastritis.

DISCUSSION

The exact mechanism by which oxidative stress contributes to the development of aging and carcinogenesis is still unclear. The importance of oxidative damage in chronic gastritis, either in the presence or absence of *H. pylori*, has been confirmed by various studies[2,16,17]. It is shown in the present study that there are different ratios of oxidative repair enzyme gene polymorphism between atrophic gastritis patients and healthy controls. This difference implies that the accumulation of oxidative DNA damage plays a role in atrophic gastritis. A characteristic pattern of modifications can be described both chemically and structurally for ROS-induced DNA damage as follows: modification of all bases, production of base-free sites, deletions, frame shifts, strand breaks, DNA-protein cross-links, and chromosomal rearrangements[18].

One of the most common lesions formed by ROS

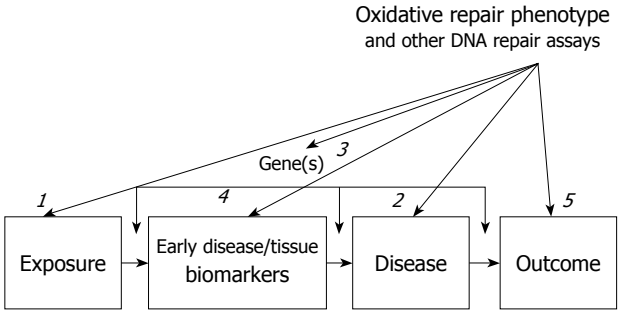

Figure 2 Categories in the molecular epidemiology of oxidative repair[34].

modifications is 8-OHdG. Among the polymorphisms found, the C/G polymorphism at position of 1245 in the 1 a-specific exon 7 of the hOGG1 gene, which results in amino acid substitution from serine (Ser) to cysteine (Cys) in codon 326 is highly prevalent[19,20]. The proportion of homozygous *C* (Ser326) individuals is different from one to another ethnic group, from 12% in Chinese, 25.8% in Micronesians, 27.7% in Japanese, 39.9% in Australian Caucasian, 24%-57.1% in Germans, 63.7% in Hungarians to 74.5% in Melanesians[21]. Although there are some contradictory results about the polymorphisms in hOGG1 affection repair function and carcinogenesis, most of these researches showed that the Cys allele was associated with cancer[22], such as esophageal[23], lung[24], gastric[25], prostate[26], nasopharyngeal cancers[22,27,28]. Only limited researches found that in Caucasian populations, Ser326 confers risk to prostate cancer[20]. Similar to our result, some studies found that Ser326Cys polymorphism has no contribution to gastric cancer and lung cancer[21,29]. Similar results were also found in breast cancer and colorectal cancer[30-32]. We did not evaluate other sequence variants, such as 11657A/G or 7143A/G, which was found to be associated with prostate cancer[14].

Oxidative DNA damage has been proposed to be related to a series of diseases. To understand the role of DNA repair activity, accurate, reproducible and specific phenotype assays should be developed and tested in human populations in molecular epidemiology studies. As presented by Caporaso[33] in 2003 (Figure 2), there are five categories of questions that can be addressed in a molecular epidemiology study.

In the first category, the exposure to alcohol and tobacco are interesting targets for gastric cancers. Both alcohol drinking and smoking can cause oxidative damage, their roles should be further studied. The present study showed that both alcohol and smoking were risk factors for gastric cancer. It was found that nicotine, at 0.8 μmol/L, the very low sub-micromolar level occurring in the tissues of smokers, may increase oxidative stress, induces apoptosis, and enhance the ability of NaDOC to activate the 153 kDa growth arrest and DNA damage promoter[34]. Some studies revealed that a frequent drinking habit elevated the odds ratio (OR) for stomach cancer in Cys/Cys compared with Ser/Ser and Ser/Cys carriers, suggesting that the hOGG1 Ser(326)Cys polymorphism may alter the impact

of some environmental factors on stomach cancer development[35].

Oxidative damage is a crucial step of *H. pylori* pathogenicity, being mechanistically related to the link between *H. pylori* infection and gastric carcinoma[36,37]. Many studies showed *H. pylori*-related oxidative DNA damage using various methodological approaches[16,38-43]. The severity of inflammation and damage associated with *H. pylori* infection is dependent on the ability of mucosal cells to counteract the increased load of reactive oxygen species[44]. *H. pylori* infection with increased oxidative damage to DNA occurred in the early stage of gastritis. The oxidative DNA damage is more apparent in gastric mucosa with severe disease than with chronic gastritis[3]. Both bacterial factors and the host response may be involved in the oxidative damage[44,45]. Patients with hOGG1 Cys/Cys genotype have a lower ability to clear ROS which contributed to the high level of DNA damage and led to epithelial cell death[43]. Farinati *et al*[46] and Konturek *et al*[47] showed that hOGG1 1245C-->G polymorphism was common in both gastric cancer and atrophic gastritis patients, but very rare in controls, and correlated more closely with 8-OHdG levels than did *H. pylori* infection or cagA status. The present study suggested that apoptosis induced by *H. pylori* may be one of the earliest events in the onset and progression of atrophic gastritis. *H. pylori* infection induced an up-regulation of Bax and down-regulation of Bcl-2 apoptosis[46]. Once the apoptosis begins, it does not depend on the existence of *H. pylori* but associated with the host capacity of DNA repair. van der Hulst *et al*[48] followed 155 cases of gastritis after *H. pylori* eradication for 1 year, and also could not find the improvement of atrophy and intestinal metaplasia. Forbes followed 54 cases of gastritis for 7 years, among them 32 cases received *H. pylori* eradication therapy, but the outcome of atrophy and intestinal metaplasia was the same between the two groups[49]. The current study found that some patients had improvement of atrophy and intestinal metaplasia after 1 year of *H. pylori* eradication and some had no improvement. Those patients might have deficiency in oxidative damage repair which was caused by either *H. pylori* infection or other exterior injury, such as alcohol or tobacco due to antioxidative enzyme polymorphism[46]. The present scientific consensus is that the *H. pylori* oncogenic role is mediated by the chronic active inflammation it elicits in the gastric mucosa. Although the ultimate basic mechanism of carcinogenesis is unknown, strongly suggestive evidences showed that oxidative stress played a pivotal role in the process[39]. We found that alcohol and tobacco rather than interior hOGG1 polymorphism were risk factors for gastric cancer.

In conclusion, Ser326Cys hOGG1 polymorphism plays an important role in atrophic gastritis after eradication of *H. pylori* for 1 year. However, no association was found between this polymorphism and gastric cancer, although it could be secondary to a not large enough sample size. Smoking and alcohol are risk factors of gastric cancer regardless of different kinds of Ser326Cys HOGG1 polymorphism. More prospective studies are needed to confirm our findings and further reveal the causal relationship between Ser326Cys hOGG1 polymorphism and atrophic gastritis/gastric cancer.

COMMENTS

Background

Although oxidation injury caused by *Helicobacter pylori* (*H. pylori*) is the mechanism of atrophic gastritis and gastric cancer, a large proportion of atrophic gastritis can not be reversed after *H. pylori* eradication. The defect of anti-oxidation barrier might be related to the occurence of atrophic gastritis and gastric cancer. The polymorphism of human oxoguanine glycosylase 1 (hOGG1) is thought to be closely related with the repairing level of DNA oxidation injury.

Research frontiers

hOGG1 is one of the most important antioxidative enzymes. Among several *hOGG1* gene polymorphisms, the Ser→Cys polymorphism at position 326 is related to decreased repair function. However, the association between hOGG1 polymorphism and gastric cancer or atrophic gastritis in post-*H. pylori* eradication patients remains unclear.

Innovations and breakthroughs

This is the first study to report that hOGG1 polymorphisms (Cys/Cys and Ser/Cys) are associated with atrophic gastritis patients after *H. pylori* eradication. No significant association was detected between hOGG1 polymorphisms (Cys/Cys or Ser/Cys) and gastric cancer.

Applications

The results from this study may hypothesize some different pathways involved in the gastric cancer and atrophic gastritis after *H. pylori* eradication with different hOGG1 polymorphisms. Biological approaches will be adopted to disclose the detailed mechanism in molecular pathway and gene sets level.

Peer review

The authors examined the association between HOGG1 polymorphism and atrophic gastritis and gastric cancer in post-*H. pylori* eradication patients. It was shown that hOGG1 polymorphisms (Cys/Cys and Ser/Cys) were associated with atrophic gastritis in a Chinese population with post-*H. pylori* eradication. No significant association was detected between hOGG1 polymorphisms (Cys/Cys or Ser/Cys) and gastric cancer. The results are interesting and may hypothesize the different underlying pathways leading to the outcomes in this population.

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