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• *RAPID COMMUNICATION* •

No relationship between IL-1B gene polymorphism and gastric acid secretion in younger healthy volunteers

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Abstract

AIM: To investigate the influence of IL-1B-511 gene polymorphism on IL-1B mRNA expression and gastric acid output in individual with or without *Helicobacter pylori (H pylori)* infection.

METHODS: IL-1B mRNA expression and gastric acid secretion in 117 health volunteers were assayed using semi-quantitative RT-PCR and gastric juice assay, respectively. Pepsinogen (PG) I and II of 255 subjects (including 117 health volunteers) were also examined.

RESULTS: T/T genotype individuals with *H pylori* infection had a more decreased PG I/II ratio. In gastric antrum mucosa, the individuals with *H pylori* infection had higher IL-1B expression than those without *H pylori* infection, but there was no obvious difference among each genotype. In gastric corpus, the individuals with *H pylori* infection had a significantly higher IL-1B expression than those without *H pylori* infection. IL-1B-511T/T genotype was markedly higher as compared with the other two genotypes. Both maximal acid output and basic acid output were similar among each genotype in IL-1B-511 gene locus, regardless of *H pylori* infection.

CONCLUSION: IL-1B-511 T allele does not decrease gastric acid output, although it has a stimulated influence on IL-1B expression. Consequently, the pathway, through which IL-1B plays a central role in gastric cancer development, might not depend on low acid, but on the other regulation mechanisms.

Key words: IL-1; Polymorphism; Stomach neoplasm; Gastric acid; *Helicobacter pylori* (*H pylori*)

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INTRODUCTION

Gastric cancer development is a multifactor and multi-step process. Clinical and epidemiological studies have suggested that environmental effects and dietary habits, such as smoking, alcohol consumption, low intake of fruits or vegetables and *Helicobacter pylori (H pylori)* infection, were the primary causes for the occurrence of carcinogenesis[1,2]. Furthermore, decades of researches have built up a variety of evidence that genetic risk factors also play an important role in cancer development[3]. Recently, through a case-control study, El-Omar *et al*[4] discovered that there was a strong relationship between IL-1 gene polymorphism and gastric cancer in the Polish population. The association between IL-1B-511 T allele and gastric carcinoma or atrophic gastritis was discovered by Machado *et al*[5] and Furuta *et al*[6] respectively. The results of several studies are in agreement with ours on Chinese population[7].

The epidemiological studies mentioned above were based on a hypothesis that IL-1B-511 and -31 gene polymorphisms contributed to stomach cancer development through T allele upregulating IL-1B mRNA expression, and then inhibiting directly gastric acid secretion. Low gastric acid was reported as a risk factor for cancer, because it resulted in a change of the colonized place of *H pylori* from gastric antrum to the corpus[8,9]; unfortunately, corpus-predominant gastritis with bacterial overgrowth was at increased risk of atrophic gastritis (with several biomarkers, such as pepsinogen (PG)I, II or I/II ratio)[6,10] and even gastric cancer. Both increased intragastric pH value and *H pylori* infection could significantly enhance N-nitroso compounds concentration, which is a putative promoter of carcinogenesis and tumor progression[11]. Svendsen *et al*[12] discovered 5 gastric cancer patients among 114 patients with low gastric acid secretion in a long-term follow-up (mean 8.4 years) study. However, this model was only supported by animal studies[4,13]. It is unknown now whether IL-1B gene polymorphism increased IL-1β protein level and resulted in human hypochlorhydria and atrophic gastritis *in vivo*. In the present study, we investigated the effects of IL-1B-511 genetic polymorphism on IL-1β mRNA expression and gastric acid secretion in the gastric mucosa of human beings with or without *H pylori* infection.

MATERIALS AND METHODS

Subjects

A total of 255 students (121 females and 132 males) from the Sun Yat-Sen University of Medical Sciences were enrolled in this study (Table 1). All subjects belonged to the ethnic group of Han and their age ranged from 19 to 24 years (mean 21.4±1.5 years). None of them had the histories of systemic lupus erythematosis, diabetes mellitus, rheumatoid arthritis, and inflammatory bowel disease. None of the subjects had received treatment for *H pylori* infection. Subjects with a family history of gastric cancer were also excluded.

Table 1 Relationship between IL-1B-511 genotypes and *H pylori* status

Loci	Genotype	*H pylori*+ (*n*=96)	*H pylori*– (*n*=159)	Total (*n*=255)
IL-1B-511	C/C	34	63	97
	C/T	46	75	121
	T/T	16	21[1]	37 (14.1%)
IL-1B-31	C/C	72	120	192
	C/T	22	37	59
	T/T	2	2[2]	4 (1.6%)

[1]*H pylori*+ *vs H pylori*–: x^2=0.6; [2]*H pylori*+ *vs H pylori*–: x^2=0.3

After genotyping of IL-1B gene and test of *H pylori* antibody IgG, 117 subjects were randomly selected for the second step study on IL-1B-511 locus, but IL-1B-31 T/T genotype frequency is too low to be researched (Tables 1 and 2). Three biopsy specimens were collected from the antrum (two specimens for RNA extraction and another one for urease test) and two biopsy specimens from corpus for RNA extraction. In each genotypical group, no statistical difference in *H pylori* prevalence, sex, and age was observed (Table 2).

Table 2 Common characteristics of 117 subjects (*n*, mean±SD)

	IL-1B-511 genotype (*n* =117)		
	T/T (*n* =37)	C/T (*n* =40)	C/C (*n* =40)
H pylori+	14	15	18[1]
Sex (F/M)	16/21	18/22	19/21[2]
Age (yr)	21.9±1.5	22.1±1.6	22.3±1.6[3]

[1]x^2=0.6; [2]x^2=0.1, [3]F=1.4

Examination of pepsinogen I and II

Using ELISA assay, PG I and II of 255 subjects were examined. Blood samples were obtained after 10-h fasting, and then coagulated at room temperature for 30 min to extract serum. Finally, the ELISA assay was performed according to the manufacturer's instructions (Orion Diagnostica Company). All analysis was done in duplicate and with an internal standard. The mean absorbance (A_{450}) of each specimen was tested at 450 nm.

DNA extraction

DNA was isolated from peripheral blood using the NaI method[14]. Briefly, heparinized whole blood (100 mL) was added to twofold volume of 6 mol/L NaI and fourfold volume of chloroform:isoamyl alcohol (24:1) and centrifuged at 5 000 r/min for 5 min. The aqueous layer was removed and isopropanol was added to the pellet to deposit DNA (centrifugation at 5 000 r/min for 5 min). Extracted DNA was rinsed 2-3 times with 700 mL/L alcohol and resuspended in 40 μL TE buffer (pH 8.0).

Genotyping of IL-1B-511 and -31 loci polymorphism

Polymorphism of IL-1B-511 and -31 that encodes IL-1B was genotyped by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP)

A fragment containing the AvaI polymorphic site at position -511 of the IL-1B gene was amplified using PCR. The oligonucleotides, 5'-GCCTGAACCCTGCATACCGT-3' and 5'-GCCAATAGCCCTCCCTTCT-3', flanking this region were used as primers. AluI polymorphic site at position -31 was amplified using primers: 5'-AGAAGCTTCCACCAATACTC-3' and 5'-ACCACCTAGTTGTAAGGAAG-3'. PCR was carried out as described previously by Zeng *et al*[7] PCR fragments were separated by electrophoresis on 30 g/L agarose with ethidium bromide staining. The C allele was designated, if two bands of 92 and 63 bp were obtained, and T allele was designated, if a single band of the undigested 155 bp was obtained. The genotype was designated as follows: C/C, 2 bands of 92 and 63 bp; C/T, 3 bands of 155, 92, and 63 bp; T/T, a single band of 155 bp.

Detection of IL-1B mRNA expression

The biopsy specimens (5-10 mg) were mixed with 1 000 μL TRIzol (Invitrogen) and then homogenized for RNA extraction. RNA was resuspended in 40 μL TE buffer (RNase-free).

RNA solution (5 μL) was diluted 10-fold and $A_{260}/_{280}$ ratio was examined. The total RNA was calculated as follows: $RNA_{total}=A_{260}\times40\times N$.

IL-1B amplification was performed using the primers: IL-1B primers, P1 5'-gatgaagtgctccttccaggac-'3, P2 5'-tggagcaacaagtggtgttctcca-'3 (480 bp); and GAPDH primers, P1 5'-cacagtccatgccatcactg-'3, P2 5'-tactccttggaggccatgtg-'3 (480 bp).

RT-PCR amplification was performed in a volume of 50 μL containing 2× AccessQuick™ Master mixture (Promega Company). The final PCR aliquot (10 μL) was analyzed by electrophoresis on 30 g/L agarose with ethidium bromide staining.

Measurement of gastric acid secretion

Gastric acid secretion was detected in 117 subjects following pentagastrin injection. For this, all subjects received no medication (e.g. antiacid, etc.) for 24 h and no food for 12 h before the test. On the morning of the test, a tube was passed into the stomach through the nose. The tube was securely fastened and subjects were made to lie

on their left-side. The gastric juices were then collected by applying continuous suction (at 30-50 mmHg below atmospheric pressure) to the tube.

Statistical analyses

Hardy–Weinberg equilibrium at individual loci was assessed using χ^2 test in the statistics program SPSS (version 12.0, Chicago, IL, USA). Comparison of genotype frequencies between cases and controls was assessed by χ^2 test. ANOVA or *t*-test was used for analysis of means. All *P* values were two-sided and considered statistically significant at $P<0.05$.

RESULTS

Analysis of pepsinogen I and I/II ratio in different IL1-1B-511 genotypes

In *H pylori*-positive cases, T/T genotype individuals had markedly decreased PGI/II ratio as compared with the other genotypes ($F = 3.7$, $P = 0.03$). On the contrary, no significant difference in PGI/II ratio was observed among the genotypical groups without *H pylori* infection. PGI level was similar in the three genotypes of infected subjects or non-infected subjects, although PGI level was lower in *H pylori*-positive subjects than that in negative subjects (Table 3).

Table 3 PG I and I/II ratio in different genotypes with or without *Helicobacter pylori* (*H pylori)* infection (mean±SD)

		IL-1B-511 genotype		
		C/C (*n* = 97)	C/T (*n* = 121)	T/T (*n* = 37)
H pylori+	PGI	38.5 ± 6.7	40.3 ± 7.2	38.0 ± 6.7
(*n*=96)	PGI/II	4.9 ± 0.4	5.0 ± 0.4	4.7 ± 0.31
H pylori–	PGI	23.6 ± 4.3	24.0 ± 5.0	23.5 ± 3.5
(*n*=159)	PGI/II	5.0 ± 0.3	4.9 ± 0.3	4.9 ± 0.4

$F = 3.7$, $P = 0.03$ ($P_{T/TvsC/T} = 0.008$, $P_{T/TvsC/C} = 0.04$).

Relationship between IL-1B-511 gene polymorphism and IL-1B mRNA expression

In *H pylori*-negative individuals, the levels of IL-1B mRNA expression were markedly decreased in the gastric antrum, and similar among each genotype. However, in *H pylori*-positive subjects, IL-1β mRNA expression was significantly increased, but there was no difference among C/C, C/T, or T/T genotype (Figures 1 and 2)

Furthermore, in the individuals without *H pylori*-infected corpus, no significant difference was detected in the expression of IL-1β mRNA among the genotype in IL-1B-511 single nucleotide polymorphism. In *H pylori* infection corpus, however, the level of IL-1β mRNA was higher. Individuals with T/T genotype had remarkably increased IL-1B mRNA than those with C/C or C/T genotype. No difference in IL-1B mRNA levels was observed between C/C and C/T genotypes. Meantime, we discovered a carrier of both IL-1B-511 T/T and –31 T/T genotypes, which had the highest IL-1B gene expression among all the subjects (Figures 1 and 2).

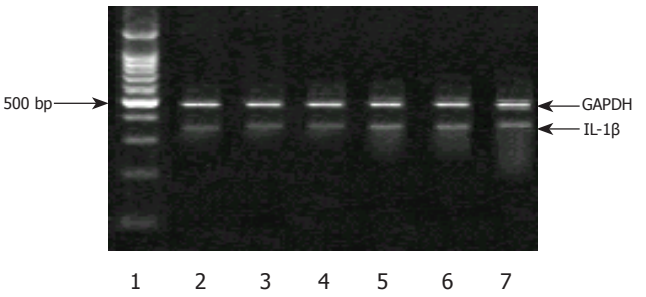

Figure 1 Expression of IL-1βmRNA in antrum Lane 1: a standard DNA ladder, lane 2: C/C genotype without *H pylori* infection, lane 3: C/T genotype without *H pylori* infection, lane 4: T/T genotype without *H pylori* infection, lane 5: C/C genotype with *H pylori* infection, lane 6: C/T genotype with *H pylori* infection, lane 7: T/T genotype with *H pylori* infection.

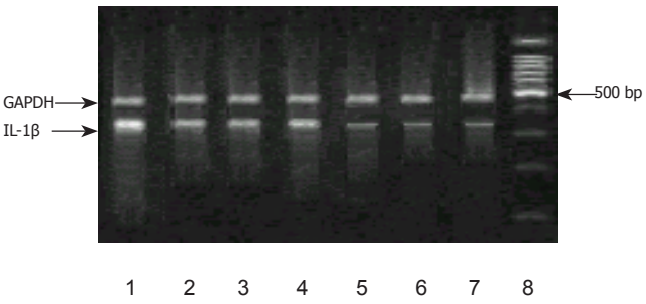

Figure 2 Expression of IL-1βmRNA in corpus. Lane 8: a standard DNA ladder, lane 7: C/C genotype without *H pylori* infection, lane 6: C/T genotype without *H pylori* infection, lane 5: T/T genotype without *H pylori* infection, lane 4: C/C genotype with *H pylori* infection, lane 3: C/T genotype with *H pylori* infection, lane 2: T/T genotype with *H pylori* infection, lane 1: T/T genotype of -511 and -31 with *H pylori* infection.

IL-1B-511 genotype and gastric fluid analysis

In basic condition (basic acid output), gastric acid secretion was similar between *H pylori*-negative and -positive subjects (5.1±1.0 *vs* 5.2±1.1 mmol/h, $t = 0.48$), and also among three different genotypes (six groups comparison, $F = 0.2$, Figure 3). After a pentagastrin stimulation, there was no significant difference for maximal acid output between *H pylori*-negative and -positive subjects (18.3±2.3 *vs* 18.4±2.0 mmol/h, $t = 0.1$), and among three different genotypes (six groups comparison, $F = 0.7$, Figure 4).

pH values of basic gastric juice and stimulated gastric fluid were 4.8±1.1 and 1.4±0.4, respectively. There was a slight increased pH value in *H pylori* infection subjects. Nevertheless, the individuals with T/T genotype did not show a much weaker ability to secrete hydrogen ion (Figure 5, $F = 0.13$ and 0.35).

DISCUSSION

Several studies revealed that hypochlorhydria induced

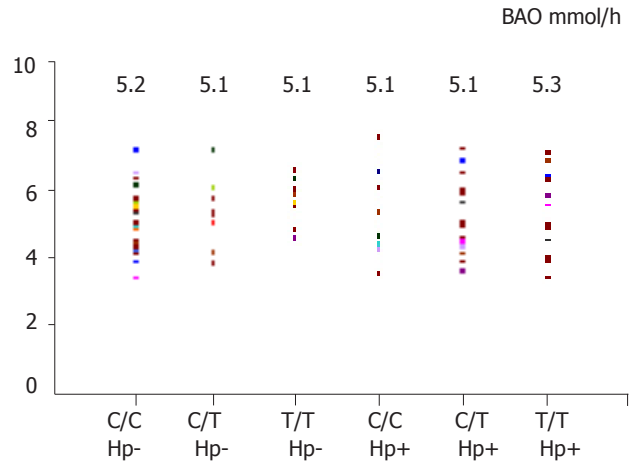

Figure 3 BAO in different genotype or *H pylori* status

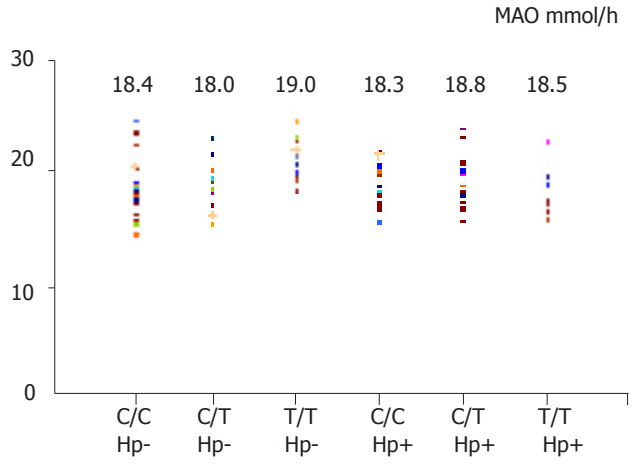

Figure 4 MAO in different genotypes or *H pylori* status

by overexpression of IL-1B was regarded as a bridge to link IL-1 gene polymorphism to gastric cancer[4–7]. The ability of mucosa to secrete gastric acid has been considered as a critical factor to decide clinical outcomes and bacterial description of *H pylori* infection[14,15]. *H pylori* implanted predominantly in the antrum mucosa, a

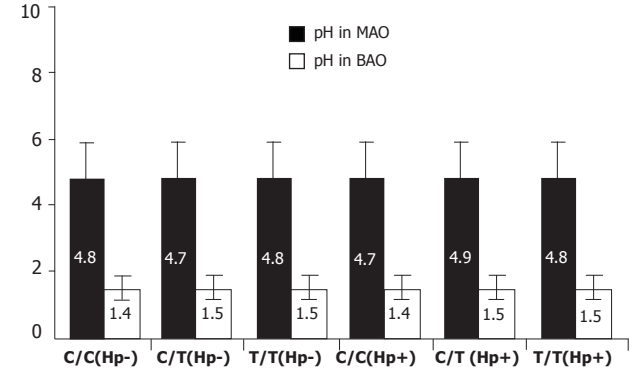

Figure 5 pH value of BAO and MAO in different genotypes or *H pylori* status.

place with a higher pH value, contrarily increased acid environment of corpus mucosa that resulted from a large number of B lymphocytes provides a habitat for *H pylori* to grow. However, for some special individuals with genetic hypochlorhydria, *H pylori* has a chance to migrate from antrum to the corpus. As a result, a large ulcer area resulted in a decreased acid level, which accumulates gastric atrophy or stomach carcinoma development[9]. Schepp *et al*[16] reported that rat parietal cells express IL-1 receptors mediating inhibition of H+ production. The antisecretory effect of IL-1B may contribute to hypoacidity secondary to acute *H pylori* infection or during chronic colonization by *H pylori* preferring the fundic mucosa. Another study reported that the efficacy of IL-1B to inhibit parietal cell H+ production was 100-fold and 6 000-fold higher as compared to proton pump inhibitors and H2 antagonists, respectively[17]. Recently, it has been identified that IL-1B exerts a potent function of gastric acid secretion through the other molecules and protein kinase pathway[18,19].

Until recently, however, no research has provided unambiguous and direct proofs suggesting that lower acid output resulted from higher IL-1B level in the human body except from a rodent model.

In this study, we discovered that T/T genotype individuals infected with *H pylori* had a more decreased PGI/II ratio as compared with the other genotypes, which is partly consistent with the results reported by Furuta *et al*[6] suggesting that IL-1B-511 gene polymorphism might be a risk factor for gastric carcinoma. IL-1B mRNA expression in subjects without *H pylori* infection was not remarkable, and was similar in each genotype, showing that there might be a very low level of IL-1B mRNA expression in normal mucosa. In contrast, the results are more complex in *H pylori*-positive individuals. There was a remarkable upregulation in the antrum, but no relationship with genotype was observed. In the corpus mucosa, however, the level of IL-1B mRNA was markedly higher than that in the antrum mucosa. Furthermore, IL-1B-511 T/T genotype individual had a mild increased IL-1B mRNA level as compared with C/T and C/C genotype. So, these results indicated that this mutation of IL-1B-511 C→T might upregulate IL-1B mRNA expression in corpus but not in the antrum, as these results are consistent to the results reported by Hwang *et al*[20]

The association of IL-1B-31 locus and IL-1B expression is not investigated because genetically mutated subject is too small (about 1%) to be collected. Fortunately, we found one female subject with *H pylori* positive and IL-1B-511 T/T and -31 T/T genotypes simultaneously had a markedly increased IL-1B mRNA level in corpus but not in the antrum. These results suggested a cooperative effect between –511 and –31 locus in IL-1B mRNA expression. These findings are also in agreement with the previous results reported by El-Omar *et al*[4] and Hwang *et al*[20]

We discovered that in basic or pentagastrin stimulation condition, gastric acid secretion was similar between *H pylori*-negative and -positive subjects. Acid secretion function did not show a marked heterogeneity among

three different genotypes of IL-1B-511. This data denoted that higher IL-1B level does not make a strong impact on gastric acid output. So, previous hypothesis that *H pylori* infection leads to IL-1B mRNA overexpression in IL-1B-511 T/T genotype, thereby directly inhibits gastric acid secretion is impossible, at least *in vivo*, in low gastric cancer prevalence region.

Hence, we inferred that the other pathways (such as chronic inflammatory process[21]), but not low acid secretion regulated by IL-1B (a pre-inflammatory factor), lead to mucosal atrophy. Our results, also taking into consideration the reports of several studies, suggested that IL-1B gene polymorphism was a susceptibility factor to gastric carcinoma in population-based studies. Furthermore, Lundell *et al*[21,22] have reported that acid-suppressive therapy maintained for 3 years facilitates neither the development of gastric glandular atrophy of the corpus mucosa nor the occurrence of intestinal metaplasia in *H pylori*-infected GERD patients. Fox *et al*[23] argued that coca leaf chewers (added with slaked lime or ash) did not have a higher prevalence of *H pylori* infection, or a higher rate of progression to gastric atrophy. So, we propose a new hypothesis that IL-1B gene polymorphism acts as a gastric cancer risk factor via upregulating IL-1B expression but downregulating acid secretion.

The individuals included in our study had a strong physiological captivity of acid output in the gastric mucosa as their age ranged from 19 to 24 years. This might be the reason that acid secretion levels were not seen significantly different between upregulated IL-1B mRNA and unchanged IL-1B mRNA groups. But using younger population in the present study is not unreasonable. As we know *H pylori* infection and genetic background play crucial roles in carcinogenesis beginning from early age. Further studies, however, should focus on larger age-range subjects or on other races to identify our results.

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