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RESEARCH PAPER

# Tumor Necrosis Factor-Related Apoptosis Inducing Ligand Gene Polymorphisms are Correlated with Gastric Cancer in Central China

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## ABSTRACT

***Purpose*** To investigate the association of tumor necrosis factor-related apoptosis inducing ligand (TRAIL) gene polymorphisms with gastric cancer in Chinese Han population in central China.

***Methods*** A total of 304 patients with gastric cancer confirmed by histopathology and 421 unrelated healthy controls were studied. Gene polymorphisms of TRAIL (G1525A and C1595T) were genotyped by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis.

***Results*** The frequency of the genotype carriers of TRAIL 1525A (GA + AA) and 1595T (CT + TT) was significantly lower in gastric cancer than in healthy controls (37.2% *vs.* 61.5%, $P<0.001$, OR = 0.581, 95% CI 0.442 ~ 0.764; 36.2% *vs.* 62.0%, $P<0.001$, OR = 0.570, 95% CI 0.433 ~ 0.750, respectively). Stratification analysis showed that both TRAIL 1525A (GA + AA) and 1595T (CT + TT) carriers were associated with poorly-differentiated gastric cancer compared to 1525GG genotype and 1595CC genotype (OR = 0.516, 95%CI 0.279 ~ 0.957, $P=0.026$; OR = 0.395, 95%CI 0.207 ~ 0.753, $P=0.004$, respectively).

***Conclusions*** TRAIL G1525A and C1595T gene polymorphisms were significantly correlated with the susceptibility to gastric cancer in Chinese Han population in central China.

**KEY WORDS** gastric cancer · genetic polymorphism · restriction fragment length polymorphism-polymerase chain reaction · risk factors · tumor necrosis factor-related apoptosis-inducing ligand

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## ABBREVIATIONS

| | |
|---|---|
| CI | Confidence interval |
| DR | Death receptor |
| EDTA | Ethylenediamine tetraacetic acid |
| Hp | Helicobacter pylori |
| OR | Odds ratio |
| RFLP | Restriction fragment length polymorphism-polymerase chain reaction |
| TIL | Tumor-infiltrating lymphocytes |
| TNF | Tumor necrosis factor |
| TRAIL | Tumor necrosis factor-related apoptosis-inducing ligand |

## INTRODUCTION

Apoptosis plays an important role in the maintenance of homeostasis. The imbalance of homeostasis may cause malignant tumors. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) was reported by Weliy in 1995 (1), which is a member of tumor necrosis factor (TNF) super family and plays an important role in the apoptosis. TRAIL triggers intracellulare caspase cascade reaction by binding to the death receptor (DR) located in the membranes of the cells (especially DR4 or DR5), and induces programmed cell death (2). Furthermore, TRAIL can induce the apoptosis of many tumor cell lines, whereas normal cells generally are resistant to this action (1). Hu *et al.* (3) found that the expression of TRAIL in gastric cancer was lower than in normal tissues nearby, indicating that low expression of TRAIL might be related to the development of gastric cancer. One of our previous studies showed that TNF gene polymorphisms was associated with H. *pylori* infection in patients with non-cardia gastric cancer, which indicated that there might exist a potential relationship between TRAIL and gastric cancer in Chinese patients (4).

The aim of this study is to investigate the association between G1525A and C1595T gene polymorphisms in fifth exon of TRAIL gene 3′UTR with gastric cancer.

## MATERIALS AND METHODS

### Patients and Healthy Controls

Three hundred and four patients with gastric cancer were identified from the department of gastroenterology and oncology of Zhongnan Hospital, Wuhan University School of Medicine from 2007 to 2010. The diagnosis of gastric cancer was made based on histological examinations. A total of 204 males and 100 females were included in this study, with a mean age at diagnosis of gastric cancer of $57.5 \pm 0.6$ years old. The blood samples were collected before the patients were treated with chemotherapy and radiotherapy.

At the same time, 421 healthy volunteers, including 256 males and 165 females, matched in age and sex were enrolled from Zhongnan Hospital Medical Center, Wuhan University School of Medicine as normal controls. The mean age at time of enrollment was $56.9 \pm 0.54$ years. All subjects were from Hubei province and had no family history of malignant tumors. The ethic committee of Zhongnan Hospital of Wuhan University approved the study. Consents were signed by all subjects participated in this study.

### Extraction of DNA

Five milliliters (ml) venous blood anticoagulated with ethylenediamine tetraacetic acid (EDTA) was drawn from all subjects, genomic DNA was extracted by proteinase K and phenol/chloroform method.

### TRAIL G1525A and C1595T Genotyping

Restriction fragment length polymorphism-polymerase chain reaction (RFLP –PCR) was performed to analyze the polymorphisms of TRAIL G1525A and C1595T. Primers were designed as the literature (5), upstream 5′-AACATCTTCTG TCTTTATAATC-3′, downstream 5′-AAATAACACGT ACTTACTGAAG- 3′. PCR conditions: 94°C for 3 min; 94°Cfor 30s, 48°C for 90s, 72°C for 45 s, for a total of 30 cycles; followed by 72°C for 10 min. Then utilized restriction enzyme TasI and RsaI to cleavage, water-bath in 65°C and 37°C for 10 h respectively. The electrophoresis of the PCR products was detected by 2.5% agarose gel. The gene sequencing conducted on an ABI 3730XL DNA Analyzer for the PCR products was done to confirm the DNA fragment (Figs 1, 2 and 3).

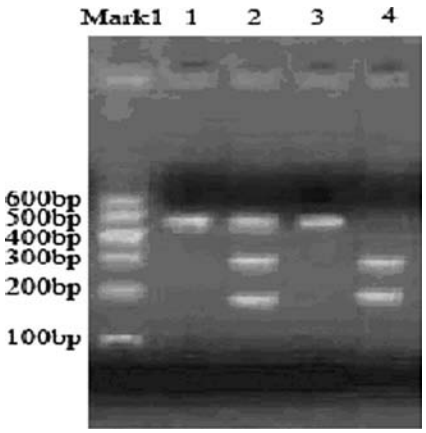


**Fig. 1** TasI enzyme cleavage products of TRAIL gene 1525, number 1 and 3 lanes are GG, number 2 lane is GA, and number 4 lane is AA.

For TRAIL G1525A, the definition of genotype was as follows: GG, 473 bp and 10 bp; GA, 473 bp, 278 bp, 186 bp, and 10 bp; AA, 278 bp, 186 bp, and 10 bp. For C1595T, CC, 292 bp, and 191 bp; CT, 292 bp, 191 bp, 129 bp, and 62 bp; TT, 292 bp, 129 bp, and 62 bp.

### Statistical Analysis

SPSS 13.0 software (SPSS for Windows version 13.0, Chicago, IL, USA) was used to conduct the statistical analysis. Chi-square ($\chi^2$) test was used for Hardy-Weinberg equilibrium and comparison of genotype frequency between healthy controls and gastric cancer. A two-tailed P-value of less than 0.05 was considered statistically significant.

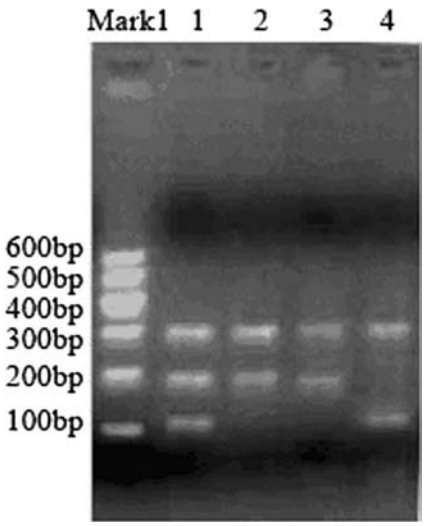


**Fig. 2** RsaI enzyme cleavage products of TRAIL gene 1595, number 1 lane is CT, number 2 and 3 lane are CC, and number 4 is TT.

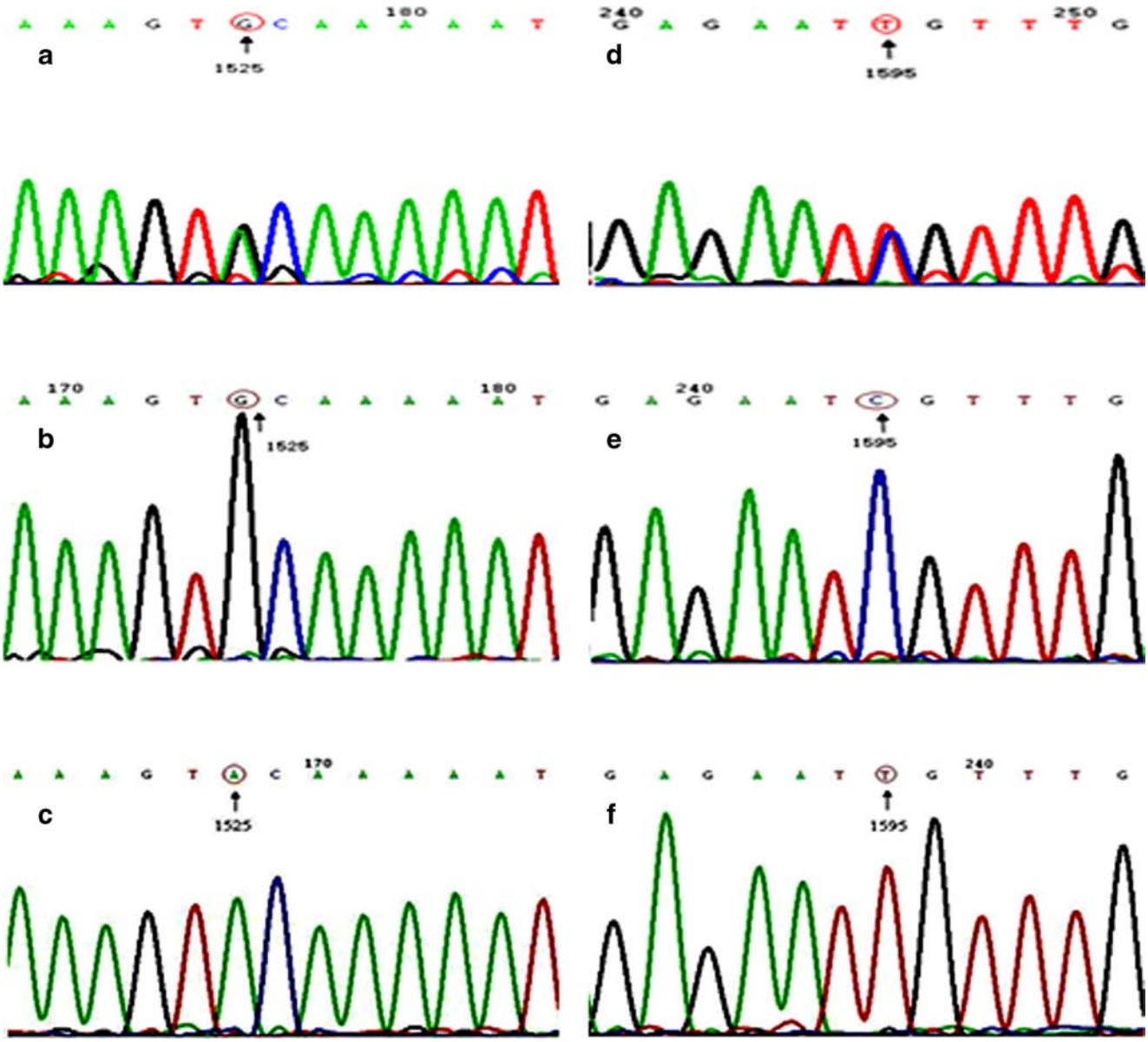


**Fig. 3** Chromatogram of direct sequencing of amplified PCR product of TRAIL gene: (**a**, **b**, **c**) 1525GA, 1525GG and 1525AA, and (**d**, **e**, **f**) 1595CT, 1595CC and 1595TT, respectively.

## RESULTS

### TRAIL Gene G1525A and C1595T Polymorphisms in Patients with Gastric Cancer and Healthy Controls

In healthy controls, the distribution of TRAIL G1525A and C1595T genotype was in consistent with Hardy-Weinberg equilibrium ($P>0.05$). For TRAIL gene 1525, the frequency of both carrier A and allele A in gastric cancer was significantly lower than that in healthy controls (37.2% *vs.* 61.5%, OR=0.581, 95% CI 0.442~0.764, P<0.001; 25.5% *vs.* 39.3%, OR=0.528, 95% CI 0.420~0.664, P<0.001, respectively). For TRAIL gene 1595, the frequency of both carrier T and the allele T in gastric cancer was significantly lower than that in healthy controls (36.2% *vs.* 62.0%, OR=0.570, 95% CI 0.433~0.750,$P<0.001$; 25.5% *vs.* 39.4%, OR=0.526, 95% CI 0.418~0.661, $P<0.001$, respectively). The distributions of TRAIL gene 1525 and 1595 genotype, carrier and allele frequencies in gastric cancer and healthy controls were shown in Table I.

**Table I** Distribution of Genotype, Gene Carrier and Allele in Patients with Gastric Cancer and Healthy Controls

| | Gastric cancer $n=304$ | Healthy controls $n=421$ | $P$ value | OR | 95% CI |
|---|---|---|---|---|---|
| 1525 | | | | | |
| Genotype | n(%) | n(%) | | | |
| G/G | 191(62.8) | 162(38.5) | | | |
| G/A | 71(23.4) | 187(44.4) | | | |
| A/A | 42(13.8) | 72(17.1) | <0.001[a] | | |
| Gene carrier | n(%) | n(%) | | | |
| G | 262(86.2) | 349(82.9) | | | |
| A | 113(37.2) | 259(61.5) | <0.001[a] | 0.581 | 0.442～0.764 |
| Allele | 2n(%) | 2n(%) | | | |
| G | 453(74.5) | 511(60.7) | | | |
| A | 155(25.5) | 331(39.3) | <0.001[a] | 0.528 | 0.420～0.664 |
| 1595 | | | | | |
| Genotype | n(%) | n(%) | | | |
| C/C | 194(63.8) | 160(38.0) | | | |
| C/T | 65(21.4) | 190(45.1) | | | |
| T/T | 45(14.8) | 71(16.9) | <0.001[a] | | |
| Gene carrier | n(%) | n(%) | | | |
| C | 259(85.2) | 350(83.1) | | | |
| T | 110(36.2) | 261(62.0) | <0.001[a] | 0.570 | 0.433～0.750 |
| Allele | 2n(%) | 2n(%) | | | |
| C | 453(74.5) | 510(60.6) | | | |
| T | 155(25.5) | 332(39.4) | <0.001[a] | 0.526 | 0.418～0.661 |

[a] indicate significant difference

### Association Between TRAIL Gene G1525A and C1595T Polymorphisms and Risk Factors of Gastric Cancer

As shown in Table II, the frequency of TRAIL 1525A and 1595T carriers were both significantly lower in patients with poorly differentiated adenocarcinoma(OR=0.516, 95%CI 0.279～0.957, $P=0.026$; OR=0.395, 95%CI 0.207～0.753, $P=0.004$, respectively). The other factors had no significant associations between TRAIL gene G1525A and C1595T polymorphisms and gastric cancer.

## DISCUSSION

A study from Japan showed that the genotype GG of the TRAIL 1595 was susceptible to multiple sclerosis (6). A Chinese study has shown that A1525A and T1595T of this gene had a lower risk for fatty liver in Shandong, northern China (7). There were also many studies about the relation between TRAIL-related death receptor DR4 or DR5 gene polymorphisms and the susceptibility of cancer (8-12) Some studies reported that TRAIL gene polymorphisms were correlated with breast cancer and lymphoma (13,14). However, it is still unclear whether TRAIL functional gene G1525A and C1595T was associated with gastric cancer in China.

Our study showed that the frequency of TRAIL gene 1525A carriers and 1595T carriers is lower than in patients with gastric cancer compared with healthy controls (37.2% *vs.* 61.5%, $P<0.001$, OR=0.581; 36.2% *vs.* 62.0%, $P<0.001$, OR=0.570), which indicated that 1525A and 1595 T gene carriers might decrease the risk of gastric cancer. Furthermore, we found that both of the frequency of TRAIL 1525A and 1595T carriers were significantly lower in patients with poorly differentiated adenocarcinoma. Our study showed that TRAIL 1525 and 1595 gene polymorphisms played a protective role in gastric cancer in Chinese patients.

TRAIL as a type of immune surveillance protein plays an important role in anti-tumor. Soluble TRAIL could inhibit the growth of mouse tumor cells (15), if TRAIL was inhibited (blocked), the growth and metastasis of tumor would accelerated (16,17). TRAIL could express on the membrane of tumor cell, which was regulated by IFN-γ, it could inhibit the growth of tumor cells (16). Except NK cells, B cells, monocytes and dendrite cells can all express membrane-associated TRAIL induced by IL-1 and IL-2. Membrane-associated TRAIL can kill tumor cells (18). Membrane-associated TRAIL and its receptors are highly expressed on the membrane of primary gastric cancer and malignant peritoneal tumor secondary to gastric cancer. These molecules were also found in tumor-infiltrating lymphocytes (TIL)

**Table II** Association Between TRAIL 1525 and 1595 Gene Carrier and Risk Factors of Gastric Cancer

| Factors | Number | 1525 gene carrier (A/not A) | *P* value | OR(95%CI) | 1595 gene carrier (T/not T) | *P* value | OR(95%CI) |
|---|---|---|---|---|---|---|---|
| Age | | | | | | | |
| ≥50 | 124 | 49/75 | 0.468 | 1.073(0.594～1.940) | 37/94 | 0.384 | 0.862(0.454～1.637) |
| <50 | 74 | 28/46 | | | 21/46 | | |
| Sex | | | | | | | |
| Male | 118 | 46/72 | 0.547 | 1.010(0.564～1.808) | 38/80 | 0.175 | 1.425(0.754～2.693) |
| Female | 80 | 31/49 | | | 20/60 | | |
| Smoking | | | | | | | |
| Yes | 77 | 35/42 | 0.087 | 1.567 (0.874～2.811 | 26/51 | 0.173 | 1.418(0.454～1.637) |
| No | 121 | 42/79 | | | 32/89 | | |
| Drinking | | | | | | | |
| Yes | 61 | 19/42 | 0.091 | 0.616(0.325～1.168) | 14/47 | 0.127 | 0.630(0.314～1.263) |
| No | 137 | 58/79 | | | 44/93 | | |
| Hp infecion | | | | | | | |
| Hp+ | 167 | 61/106 | 0.263 | 0.575(0.217～1.527) | 44/123 | 0.545 | 0.930(0.314～2.759) |
| Hp- | 18 | 9/9 | | | 5/13 | | |
| Family history of tumor | | | | | | | |
| Yes | 45 | 16/29 | 0.366 | 0.832(0.417～1.660) | 11/34 | 0.269 | 0.730(0.341～1.563) |
| No | 153 | 61/92 | | | 47/106 | | |
| Site | | | | | | | |
| Cardia | 41 | 15/26 | 0.440 | 0.884(0.434–1.801) | 15/26 | 0.168 | 1.530(0.740～3.161) |
| Not cardia | 157 | 62/95 | | | 43/114 | | |
| Differention | | | | | | | |
| Poorly | 138 | 47/91 | 0.0.026[a] | 0.516(0.279–0.957) | 32/106 | 0.004[a] | 0.395(0.207～0.753) |
| Moderately-well | 60 | 30/30 | | | 26/34 | | |
| Lauren | | | | | | | |
| Intestine | 146 | 61/85 | 0.108 | 1.615(0.823–3.170) | 43/103 | 0.542 | 1.030(0.513–2.069) |
| Diffused/mixed | 52 | 16/36 | | | 15/37 | | |
| TNM | | | | | | | |
| I/II | 36 | 16/20 | 0.284 | 1.325(0.638–2.749) | 12/24 | 0.344 | 1.261(0.582–2.730) |
| III/IV | 162 | 61/101 | | | 46/116 | | |

[a] indicate significant difference

metastasis by these primary tumor cells. Compared with primary gastric cancer, TIL (include $CD8^+CD11b^-$, $CD8^+CD11b^+$, $CD4^+CD62L^-$ and $CD4^+CD62L^+$) from malignant ascites highly expressed TRAIL and its receptors, which indicated that the immune system was up-regulated when metastasis of gastric cancer. However, for primary gastric cancer and malignant peritoneal tumor, even if TRAIL and DR4/DR5 expressed on these cells, nearly no apoptosis of tumor cells was observed, which may indicate TRAIL-induced apoptosis is not effective enough *in vivo*. TIL apoptosis is significantly higher in primary gastric cancer compared with malignant ascites. The reason may be that TRAIL expressed on the malignant peritoneal tumor combined with DR4/DR5 of CD3+ T cells, which cause the death of CD3 + T cells before the immune effect, and finally it causes that gastric cancer cells could escape immune surveillance when metastasis. TRAIL receptor might be not effective enough to attack TIL of primary gastric cancer, so no TIL apoptosis observed (19).

TRAIL and its receptors are expressed on the normal gastric membranes, gastric epitheliums and gastric cancer cells (3,20). Whether the polymorphisms of TRAIL gene would influence the express of TRAIL mRNA or protein is unclear. One study about the relationship between TRAIL polymorphisms and disseminated sclerosis found that upstream nucleotide between 707 and 597 in onset of transcription, there were 4 SNPs (C707T, T665C, C621T and A597G) in TRAIL promoter region, which demonstrated no association with TRAIL protein and RNA express (21). In TRAIL promoter 716, allele C showed higher expression of mRNA compared

with allele T, and TRAIL gene was regulated by stimulatory protein 1(Sp1) and SP3 as well (13). For systemic lupus erythematosus (SLE) and nonalcoholic adiposis hepatica patients, TRAIL mRNA was up-regulated (7,22). However, Hu (3) *et al.* found that the express of TRAIL was lower than that of normal tissue around it, which suggested that TRAIL is highly expressed in autoimmune disease and inhibited in tumor.

H. *pylori* infection is a risk factor for gastric cancer, which could increase the apoptosis of gastric cells in chronic gastritis. In addition,, it could cause intestinal metaplasia, dysplasia and even gastric cancer. There was no significant difference between the number of TRAIL +, DR4 +/DR5+ and DcR2+ cells in H. *pylori*+ and H. *pylori*- gastric epitheliums. However, TRAIL +, DR4 +/DR5+and DcR2+infiltrating lymphocytes in the H. *pylori*+ mucosa is more than in H. *pylori*-. The apoptosis of H. *pylori*+ gastric epithelial and mucosal infiltration lymphocytes was significantly higher than that of H. *pylori*- mucosa, suggesting that TRAIL and DR4/DR5 may be involved in apoptosis of H. *pylori*- related gastric mucosal epithelial cells and the lymphoid infiltration cells (23). TRAIL and H. *pylori* could induce destruction of gastric cancer cells DNA, this synergistic effect was time- and concentration-dependent. H. *pylori* selectively increased TRAIL and DR4 mRNA and protein expression of gastric cancer cells. In H. *pylori*-associated gastritis, sinuses ventriculi and corpora ventriculi TRAIL expression was significantly up-regulated (20). The occurrence and development of TRAIL in H. *pylori*- associated gastritis and gastric cancer play an important role in immune regulation. However, our study did not find a significant correlation between TRAIL genotype and H. *pylori* infection in gastric cancer patients, Tbut we observed that more than 90% of gastric cancer patients were H. *pylori* positive, which still indicated H. *pylori* infection plays an important role in gastric cancer. The TRAIL gene 1525 and 1595 polymorphisms probably may not relate to H. *pylori* infection in patients with gastric cancer. Our study showed that the 1525G allele of control group was 60.7%, which was similar to 52.87% in population of Shandong Province, northern China (7), but was significantly different from that of African-Americans (82.58%) (5) and Caucasians (79.23%) (5). The frequency of 1595 C allele of control group in our study was 60.6%, which was similar to that of Japanese (59.18%) (6), but was significantly higher than that of African-Americans (15.83%) (5) and Caucasians (28.85%) (5). These differences in frequency may be related to ethnic difference, and sample size.

The limitation of our study is the small number of patients with gastric cancer, which might cause selected bias. Multicenter trials with large sample size need to be studied to confirm our conclusion. In addition, only the relationship between TRAIL gene genotype polymorphisms and gastric cancer was studied. Further studies about the genetic and molecule expression of TRAIL and its role on the development of gastric cancer should be investigated.

In conclusion, our study showed that in TRAIL gene 3′ UTR the fifth exon 1525A and 1595T gene carriers significantly reduced the risk of gastric cancer, which correlated with the degree of differentiation. TRAIL gene (G1525A and C1595T) polymorphisms were significantly associated with gastric cancer in Hubei Province, central China.

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