

RANTES Promoter Genotype and Gastric Cancer Risk in a Japanese Population

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Abstract. *Background:* A complex interaction of genetic and environmental factors is relevant in gastric carcinogenesis. Previous studies reported that the expression of RANTES is enhanced in *Helicobacter pylori*-infected gastric mucosa. Elevated serum level of RANTES in gastric cancer patients was also reported. We aimed to clarify the effect of RANTES promoter polymorphism on the risk of gastric cancer (GC) in a Japanese population. *Materials and Methods:* A total of 191 GC and 335 non-cancer patients including *H. pylori*-positive gastritis ($n=180$) and *H. pylori*-negative healthy stomach ($n=155$) were genotyped for polymorphisms at -28 C/G in the RANTES gene promoter region. *Results:* RANTES promoter genotype distributions were not significantly different among GC, overall non-cancer patients, healthy stomach and gastritis. In the comparison of genotype frequency between GC and healthy stomach, only a weak correlation was found between -28G/G genotype and GC in individuals more than 70 years of age (odds ratio (OR)=7.65, 95% confidence interval (CI)=0.78-75.0, $p=0.07$), with advanced stage ($OR=6.58$, 95% $CI=0.72$ -59.77, $p=0.07$), lymph node metastasis ($OR=7.20$, 95% $CI=0.79$ -65.46, $p=0.06$) and peritoneal dissemination ($OR=10.93$, 95% $CI=0.96$ -124.64, $p=0.07$). *Conclusion:* The effect of -28 C/G polymorphism in the RANTES gene promoter on GC development may not to be very strong. The role of RANTES promoter polymorphism in gastric carcinogenesis needs further evaluation.

Gastric cancer (GC) is one of the most common malignancies worldwide and remains a leading cause of death in Asia and some European countries (1). Many epidemiological and experimental data suggest the impact of *Helicobacter pylori* infection as a risk factor of GC (2-4) and some investigators studied the efficacy of *H. pylori* eradication in order to reduce its risk and mortality (5, 6). Other investigators also studied the efficacy of endoscopic examination in early detection (7). However, considering the fact that only a small percentage of *H. pylori*-infected patients develop GC, some genetic factors may play an important role in modifying the risk of developing GC in long-term *H. pylori* infection (8-13); implementation reflecting an individual's risk for developing GC would be ideal.

RANTES (short for 'regulated upon activation, normal T-cell expressed and secreted') is a member of the large and growing family of immunoregulatory cytokines called chemokines. RANTES belongs to the C-C chemokine subfamily. It is a potent chemotactic agent for T lymphocytes and monocytes (14) and is expressed after cellular activation in fibroblasts, T-cells, monocytes, endothelial cells, and certain epithelial cells. Therefore, RANTES has been shown to contribute to the infiltration of lymphocytes in *H. pylori*-infected gastric mucosa. Like that of interleukin (IL)-8, RANTES expression is increased *in vitro* and *in vivo* in gastric mucosa following *H. pylori* infection (15-17). Persistent expression and secretion of RANTES are closely related to residual infiltration of memory T lymphocytes for a prolonged period after *H. pylori* eradication (18).

Recently, it was also reported that RANTES production in peripheral blood mononuclear cells (PBMCs) stimulated by highly metastatic GC cell line-conditioned supernatants was higher than in those stimulated by a less metastatic GC cell line-conditioned supernatant (19). In addition, the plasma level of RANTES was significantly higher in GC patients than in healthy controls, especially in more advanced stages (20). These data suggest the potential role of RANTES in *H. pylori*-related inflammation and carcinogenesis in the stomach.

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Genetic studies on the *RANTES* gene have identified a number of polymorphisms, including one that causes a nucleotide substitution in promoter region -28 C/G. The -28G allele of the *RANTES* promoter was associated with higher protein level than those of the C allele (21). Recent studies showed that *RANTES* promoter genotype was associated with diabetic nephropathy in type 2 diabetics (22), late onset asthma (21), atopic dermatitis (23), and progression of AIDS (24, 25).

This study was performed to investigate relations between polymorphisms of the *RANTES* gene promoter and GC, including its clinical phenotypes in a Japanese population.

Materials and Methods

Study population. We studied 526 patients attending the Endoscopy Center of Fujita Health University Hospital from January 2005 to July 2007. The 526 patients comprised 191 patients with GC (mean age=64.8±12.1 years, female: male=135:56, *H. pylori* infection positive =88.5%) and 335 non-cancer patients. GC was diagnosed histologically and was classified according to Lauren (26). Detailed information was obtained about the stage, anatomical location, venous and lymphatic invasion, lymph node metastasis, distant metastasis, and peritoneal dissemination. Non-cancer patients underwent upper gastroscopy for their health check, secondary complete check up for stomach cancer following barium X ray examination, or for the complaint of abdominal discomfort. Individuals with peptic ulcer disease or reflux esophagitis were excluded from this study. The 335 non-cancer patients were also divided into two groups: gastritis (n=180; mean age=62.6±11.7 years, female: male=99:81) and healthy stomach (n=155; mean age=57.7±16.5 years, female: male=77:78). A diagnosis of gastritis was based on negative results for macroscopic lesions such as ulcer but positive for *H. pylori* gastritis by culture, the urea breath test (UBT), or antibodies to *H. pylori*. Patients who had severe systemic disease and had received non-steroidal anti-inflammatory drugs were excluded from this study. Patients who did not have macroscopic lesions and had a negative result for *H. pylori* gastritis were considered as healthy stomach. The Ethics Committee of Fujita Health University School of Medicine approved the protocol and written informed consent was obtained from all of the participants.

Genotyping for *RANTES* promoter. Genomic DNA was extracted from non-neoplastic gastric biopsies or peripheral blood using the standard phenol/chloroform method. Polymorphisms of -28 C/G in the *RANTES* gene promoter region was investigated by PCR-based RFLP assays as described elsewhere (24).

Detection of *H. pylori* infection. The *H. pylori* infection status was determined on the basis of histology, culture, the urea breath test (UBT), and antibodies to *H. pylori*. Infection was diagnosed when at least one of these 4 tests was positive.

Statistical analysis. Differences of *RANTES* promoter genotype frequencies among two groups were determined by the Fisher's exact test. The odds ratio (OR) and 95% confidence interval (CI) were also calculated. A probability value of less than 0.05 was considered statistically significant.

Results

***RANTES* promoter genotype.** Polymorphisms of -28 C/G in the *RANTES* gene promoter region was genotyped in all 526 subjects. *RANTES* promoter genotype distribution was 251 C/C (74.9%), 77C/G (23.0%) and 7 G/G (2.1) overall for non-cancer patients, with 121 C/C (78.1%), 33 C/G (21.3%) and 7 G/G (0.6%) for healthy stomach; 130 C/C (72.2%), 44 C/G (24.5%) and 6 G/G (3.3) for gastritis; and 140 C/C (73.3%), 45 C/G (23.6%) and 6 G/G(0.6) for GC. The frequency of *RANTES* promoter polymorphism in the healthy stomach, gastritis and GC patients did not deviate significantly from those expected under the Hardy-Weinberg equilibrium ($p=0.43, 0.35, 0.32$ respectively). There was no significant association between *RANTES* promoter genotype distribution and risk of GC when compared in non-cancer patients overall, healthy stomach, or gastritis (Table I).

To further investigate whether the *RANTES* promoter polymorphism influenced the clinicopathological features of GC, different generation, tumor location, stage, Lauren's classification, lymphatic and venous invasion, lymph node metastasis, peritoneal dissemination, and distant metastasis were included in a stratified analysis (Table II). In the comparison of genotype frequency between GC and healthy stomach, weak correlation was found between the -28G/G genotype and GC in individuals more than 70 years of age (OR=7.65, 95% CI=0.78-75.0, $p=0.07$). In addition, we found that the frequency of the same genotype also tended to be higher in patients with advanced stage (OR=6.58, 95% CI=0.72-59.77, $p=0.07$), with lymph node metastasis (OR=7.20, 95% CI=0.79-65.46, $p=0.06$) and with peritoneal dissemination (OR=10.93, 95% CI=0.96-124.64, $p=0.07$).

Discussion

Members of the chemokine supergene family, particularly the CXC and CC chemokine subfamilies, are thought to be responsible for recruitment of these inflammatory cells into the gastric mucosa (15-18, 27-30). RANTES is a CC chemokine produced by epithelial cells, CD8⁺ T-cells, fibroblasts and platelets that mediates the trafficking and homing of classical lymphoid cells such as T-cells and monocytes. RANTES also acts on a range of other cells, including basophils, eosinophils, natural killer cells, dendritic cells and mast cells (14, 31). Increased RANTES production is a feature of *H. pylori*-induced gastric inflammation (15-18, 28). RANTES mRNA expression is also thought to play an important role in maintaining residual memory T lymphocytes and eosinophils in gastric mucosa following *H. pylori* eradication (18).

Concerning the effect of RANTES in carcinogenesis in the stomach, it was reported that RANTES production in PBMCs stimulated by highly metastatic GC cell line-

Table I. Association between RANTES promoter polymorphism and risk of GC Variable (n).

Variable (n)	Genotype, n (%)		
	G/G	G/C	C/C
Overall non-cancer (335)	251 (74.9)	77 (23.0)	7 (2.1)
Healthy stomach (155)	121 (78.1)	33 (21.3)	1 (0.6)
Gastritis (180)	130 (72.2)	44 (24.5)	6 (3.3)
GC (191)	140 (73.3)	45 (23.6)	6 (3.1)
G/G vs. Others	OR	95% CI	p-Value
Overall non-cancer vs. GC	3.34	0.83-13.52	1
Healthy stomach vs. GC	4.96	0.59-41.66	0.14
Gastritis vs. GC	2.53	0.50-12.71	1
G carrier vs. G/G	OR	95% CI	p-Value
Overall non-cancer vs. GC	1.3	0.87-1.96	0.67
Healthy stomach vs. GC	1.16	0.71-1.88	0.62
Gastritis vs. GC	1.44	0.90-2.31	0.15

carrer: G/G+G/C. Statical analysis was performed by two-sided Fisher's exact test.

conditioned supernatants was also higher than in those stimulated by a less metastatic GC cell line-conditioned supernatant and the serum RANTES level was also elevated in GC patients especially for more advanced stages.

Changes in gene expression in human monocytes after stimulation of RANTES have been examined by the oligonucleotide array method, showing that RANTES activates the transcription of cytokine genes (*MCP-1*, pro interleukin-1 β , IL-8), membrane receptors (oxidized LDL receptor), regulators of extracellular matrix proteins (MMP-9 e), and enzymes regulating intracellular signal transduction (MAPK) (32). Four binding sites for nuclear factor- κ B in the *RANTES* promoter are critical for induction by the proinflammatory cytokines tumor necrosis factor- α and interleukin-1 β and induction through the CD28 co-stimulatory pathway (33). The *RANTES* promoter -28C/G polymorphism is located immediately downstream of the first of these nuclear factor- κ B sites (-40 to -31). Recent reports show quantitative differences in *RANTES* protein expression between different *RANTES* promoter genotypes. Hizawa et al. showed that the -28G allele of the *RANTES* promoter had a higher level of mRNA protein expression than that of the C allele (21). Although we did not investigate the RANTES expression in serum or gastric tissue in GC patients, if the *RANTES* promoter polymorphism may influence the quantitative differences of RANTES expression in normal mucosa or tumor tissue in the stomach, it is possible that the *RANTES* promoter genotypes would modify the risk of GC development and progression.

Table II. RANTES promoter polymorphism and clinicopathologic feature of gastric cancer.

Variables (n)	Genotype		
	G/G	G/C	C/C
Overall non-cancer (335)	251	77	7
Healthy stomach (155)	121	33	1
Gastritis (180)	130	44	6
Age			
≤70 years (128)	91	34	3
>70 years (63) [#]	49	11	3
Tumor location			
Cardia (6)	4	2	0
Non-cardia (185)	136	43	6
Upper third (9)	9	5	4
Middle third (97)	71	23	3
Lower third (78)	59	16	3
Staging			
Early (90)	66	22	2
Advanced (97) [†]	72	21	4
Unknown (4)	2	2	0
Lauren's classification			
Intestinal type (111)	82	25	4
Diffuse type (80)	58	20	2
Lymphatic invasion			
Positive (83)	60	21	2
Negative (65)	47	16	2
Unknown (43)	33	8	2
Venous invasion			
Positive (42)	32	9	1
Negative (106)	75	28	3
Unknown (43)	33	8	2
Lymph node metastasis			
Positive (89)*	70	15	4
Negative (100)	69	29	2
Unknown (2)	1	1	0
Peritoneal dissemination			
Positive (30) [‡]	23	5	2
Negative (161)	117	40	4
Liver metastasis			
Positive (6)	4	2	0
Negative (185)	136	43	6
Distant metastasis			
Positive (19)	8	4	0
Negative (179)	132	41	6

Note: G carrier, GG+CG. Statical analysis was performed by two-sided Fisher's exact test. Compared to healthy stomach, GG vs. others, [#]p=0.07, [†]p=0.06, *p=0.06 and [‡]p=0.07.

We investigated the *RANTES* promoter polymorphism in GC patients because RANTES may play an important role in the pathogenesis of *H. pylori*-related gastric inflammation and carcinogenesis. However, we did not find direct association between *RANTES* promoter genotypes and GC except for the weak correlation between -28G/G genotype and several subtypes of GC such as patients more than 70 years of age, those with advanced tumor stage, lymph node metastasis or peritoneal

dissemination. Our result of only a weak correlation may be due to the limited samples of GC and low frequency of the -28G/G genotype in this Japanese population. In addition, we did not observe any correlation between -28G/G genotype and these subtypes when compared to non-cancer patients overall as well as those with gastritis, suggesting that the group of patients with *H. pylori*-positive gastritis may include a considerable number of patients with a pre-malignant condition such as atrophic gastritis.

Elevated serum level of RANTES has been shown to be associated with more advanced stage and poor prognosis in several types of cancer including GC (20, 34, 35). Because the -28G allele of the *RANTES* promoter has also been shown to have a higher level of mRNA protein expression than that of the C allele, it seems reasonable for the G/G genotype to be a risk factor for more advanced stage, lymph node metastasis and peritoneal dissemination in GC. Thus, our hypothesis needs to be confirmed by a larger study in the future. Interestingly, we also found a weak correlation between the same genotype and GC in individuals more than 70 years of age. GC developing in the younger generation has been shown to have more advanced pathological phenotypes than that developing in the older generation. It remains to be explained why the -28G/G genotype also modifies the risk of GC developing in the older generation.

In conclusion, we have shown that polymorphism of *RANTES* promoter is not directly associated with the susceptibility to GC.

Only weak correlation was found between -28 G/G genotype and GC in patients more than 70 years of age, with advanced tumor stage, lymph node metastasis and peritoneal dissemination in this Japanese population. We investigated *RANTES* promoter polymorphism in a limited region of central Japan. Previous reports suggest that *RANTES* promoter polymorphism shows variations in different ethnic groups (24, 25, 36). In addition, other polymorphism have been described in the human *RANTES* promoter that remain to be studied in GC (24, 25). Further studies will be needed to confirm the influence of this molecule on carcinogenesis in the stomach. This study is the first investigating the potential association between *RANTES* promoter genotypes and GC.

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