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A new familial gastric cancer-related gene polymorphism: T1151A in the mismatch repair gene hMLH1

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Abstract We designed to understand the effects of the T1151A gene polymorphism in the hMLH1 gene on the pathogenesis of familial gastric cancer. Peripheral blood DNA from 113 patients with familial gastric cancer or suspected familial gastric cancer that were newly identified in the same year, along with 180 healthy subjects, was subjected to polymerase chain reaction-denaturing high-performance liquid chromatography (PCR-DHPLC) and DNA sequencing of exon 12 in the hMLH1 gene. Our results as following, the T1151A detection rate was remarkably higher in patients with familial gastric cancer or suspected familial gastric cancer compared to normal control patients ($P < 0.05$). Stratified analysis showed that there was a significant difference in the detection rate between the control group and elderly patients whose age of onset was greater than 50 years old ($P < 0.05$). The detection rate of patients from high-risk families were relatively high ($P < 0.05$). An especially significant distribution was observed in patients who had suffered precancerous diseases related to gastric cancer ($P < 0.01$). In conclusion, familial gastric carcinoma families in China carrying the T1151A polymorphism may have a higher risk of suffering from gastric cancer. This gene polymorphism can be used as a candidate screening index for high-risk populations.

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Introduction

Gastric cancer is a common disease in humans, ranking fourth in incidence among all malignant tumors and second in respect to lethality rate [1]. Most gastric cancers are sporadic. However, about 10% of gastric cancer presents with a pattern of familial clustering [2]. The pathological types of familial gastric cancer include the intestinal type and the diffuse type. The risk of developing intestinal or diffuse gastric cancer in patients with familiar gastric cancers can be increased by 1.4–7 times, respectively [3]. At present, gastric cancer incidence in China is still rising, and the increasing risk mentioned above cannot be neglected. However, genetic indexes of familial gastric cancer which can be adopted for screening in high-risk populations are very limited [4]. DNA mismatch repair (MMR) is an important DNA-repair mechanism that plays a key role in maintaining genome stability [5]. Correlation between MMR gene abnormality and the development of tumors has been widely confirmed. The relationship between MMR gene abnormality and familial gastric cancer is still controversial [6, 7]. Presently, MMR gene abnormality in familial gastric cancer is considered to mainly present as hypermethylation of the promoter sequence, but little is known about the roles that MMR gene abnormalities play in that process [8]. The correlation between MMR gene variants and familial gastric cancer is valuable because in Chinese hereditary non-polyposis colorectal cancer (HNPCC) MMR gene variant is the main causes, the gastric cancer incidence outclasses that in the Western population. Gastric cancer is the most common extracolonic cancer in Chinese

patients with HNPCC [9, 10]. In a study based on familial gastric cancer patients in China, several MMR gene variants with great value have been identified [11]. T1151A (Val384Asp) in the MMR gene, hMLH1, is a polymorphic site with specificity to East Asians and has not been reported in Western populations [12–15]. T1151A has been detected in several kinds of tumor tissues types and is closely related to the onset of some these tumors [16–18]. Early research in our own laboratory has demonstrated that T1151A has not only genetic susceptibility elements for sporadic gastric cancer but also has conspicuous distributions within gastric cancer patients with a family history of cancer in their relatives [16, 19]. Thus, we systematically carried out a study on the probable effects on etiology of T1151A by extensively collecting cases of patients with familial or suspected familial gastric cancer suffering from newly diagnosed disease in the same year.

Materials and methods

General materials

Sample source

Epidemiological investigations and sample acquisition were performed at Huaian, Taizhou and Jintan, which are located in north, central and south Jiangsu, respectively. Cancer samples included peripheral blood DNA collected from patients, in the same year, that were all newly diagnosed with gastric cancer and had not received treatment with radiotherapy or chemotherapy.

Native, unrelated, healthy subjects were taken as normal controls. While collecting blood samples (5 ml of peripheral venous blood), detailed demographic data, living habits and styles and tumor and precancerous disease history of the patients was collected by investigation personnel that were trained before the investigation and a uniform questionnaire.

Familial gastric cancer or suspected familial gastric cancer patients

Obvious regional differences in the pathological types of familial gastric cancer were present with the intestinal type being the most common type present in high-risk gastric cancer areas, such as China.

The clinical diagnosis of familial gastric cancer was based on the Amsterdam Standard as follows [7]:

(1) The number of gastric cancer patients greater than or equal to three cases and the number of first-order relatives included greater than one case, (2) At least two successive generations suffered from gastric cancer and (3) The number of patients whose age of onset was younger than 50 years old was greater than or equal to one case.

The patients with suspected cases of familial gastric cancer met at least one item mentioned above. We collected seven cases of familial gastric cancer and 106 cases of suspected familial gastric cancer from newly suffering gastric cancer patients. These patients all came from different families. Gastric cancer families were classified as follows based on the onset risk prediction standard of colorectal cancer and HNPCC families [20]:

(1) Forty-five cases of high-risk families, which were defined based on any one of the following items: the number of gastric cancer patients or patients suffered tumor related with gastric cancer in one family was greater than or equal to three cases, one linear relative or second relative suffered greater than or equal to two types of tumors related to gastric cancer or the age of onset of one linear relative was less than 50 years old.
(2) Fifty-five cases of medium-risk families, which met any one of the following items: one linear relative suffered from gastric cancer and the age of disease onset was greater than or equal to 50 years old and another second relative was diagnosed with gastric cancer without an age limit or two-first-order relatives were diagnosed with gastric cancer and both had an age of onset greater than or equal to 50 years old.

There is no reference standard regarding young patients without a family history of gastric cancer. Therefore, these cases were listed alone.

Gastric ulcer, atrophic gastritis, partial gastritis and gastric polyps are common precancerous diseases related to gastric cancer [21, 22], and there were 45 cases of patients with precancerous disease histories in our research.

Normal control

The control group included normal healthy subjects without precancerous diseases related to gastric cancer and with no obvious cancer within their first-order relatives. The normal control group included 126 men and 54 women and the ages of the individuals ranged from 16 to 70 years old.

Methods

PCR reaction primer sequence

5′-ACAGACTTTGCTACCAGGACTTG-3′ (upstream) and 5′-TGTCTTATCCTCTGTGACAATGG-3′ (downstream).

The amplified product spanned from the 24th base in exon 12 upstream of the hMLH1 gene to the 1251st base in

the protein coding region of the gene. The length of the PCR product was 216 base-pairs. The PCR reaction contained 25 μl of 50–100 ng of genomic DNA, 0.2 mM dNTP, 0.5 μM of both the upstream and downstream primers, and 2 U of Taq DNA polymerase. The PT2200 gradient amplification cycle was as follows: 35 cycles of pre-denaturation at 94°C for 5 min, denaturation at 94°C for 20 s, annealing at 59°C for 20 s, extension at 72°C for 30 min followed by an extension at 72°C for 5 min, denaturation at 94°C for 4 min, the temperature was decreased to 25°C by a gradient of 0.1°C/s. Amplified products were stored at 4°C and detected by 1.2% agarose gel electrophoresis.

DHPLC analysis

PCR products were analyzed using a high-performance liquid chromatography (HPLC) machine (WAVEsystem, Transgenomic). A single sample input was 5–8 μl, the column temperature was 62°C, the mobile phase was 0.1 M N2TEAA (analytically pure) and acetonitrile with different concentration gradients, the flow rate was 0. 9 ml/min, and ultraviolet detection was performed at 260 nm.

DNA sequence analysis

PCR products with abnormal elution-peaks in DHPLC maps were sequenced. For genotyping results, 10% of the samples were randomly selected for repeat experiments.

Statistical methods

Epi Info 6.0 software was adopted. Methods included the Mantel–Haenszel χ^2 test and a risk-degree analysis. Statistical significance was defined as $P < 0.05$.

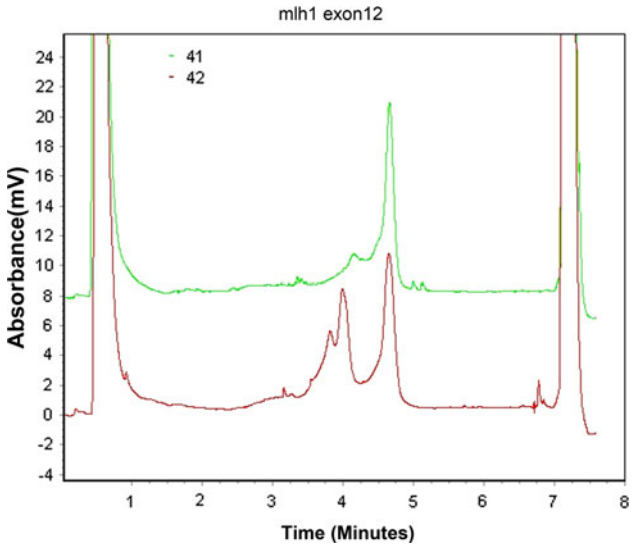

Fig. 1 The DHPLC map of exon 12 of the hMLH1 gene. The three-peaks on the map correspond to a heterozygote (mutation) and the single-peak corresponds to a homozygote (normal)

Results

DHPLC and DNA sequence analysis

In the normal control group, there were nine cases with a uniform abnormal peak-type. The same peak-type was found in 14 cases of familial or suspected familial gastric cancer patients (Fig. 1). DNA sequence analysis demonstrated that the base transversion of T → A at the 1151st base in the hMLH1 gene was the reason for the appearance of the abnormal peak-type, defining a heterozygote (Fig. 2). This base-pair transversion results in the conversion of Val to Asp corresponding to the 384th site within the protein.

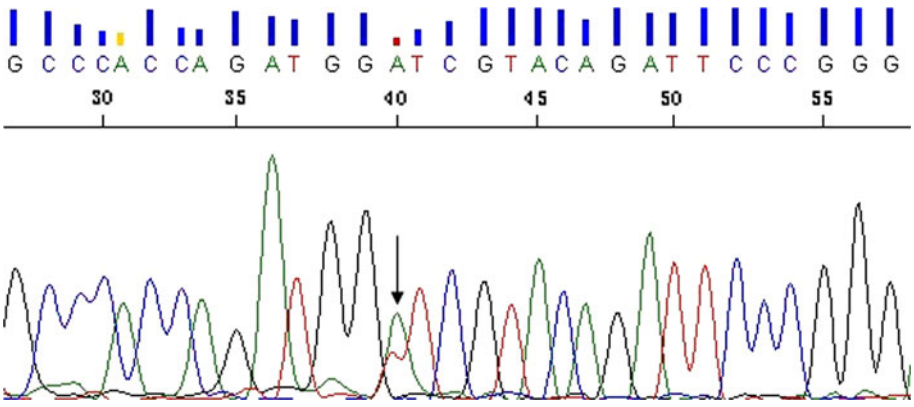

Fig. 2 The sequence analysis of exon 12 of the hMLH1 gene. Sequence results demonstrate the transversion of T → A at the base 1151

Table 1 Comparison of the basic properties between the familial gastric cancer cases and the controls

Basic properties	Cases ($n = 113$)		Controls ($n = 180$)		χ^2	P value
	Number	%	Number	%		
Age (years old)						
<50	35	31.9	66	36.7	0.993	0.319
≥50	78	68.1	114	63.3		
Gender						
Male	85	75.2	126	70	0.936	0.333
Female	28	24.8	54	30		
Smoking status						
Never	57	50.4	113	62.8	4.953	0.026
Ever	56	49.6	67	37.2		
Alcohol status						
Never	70	61.9	128	71.1	2.652	0.104
Ever	43	38.1	52	28.9		

Basic properties comparison between the familial gastric cancer case group and the control group

The age range of the gastric cancer case group was between 26 and 80 years old, while the age range of the control group was between 16 and 70 years old. The age and gender differences between both groups were not significant ($P > 0.05$). The ratio of smokers in the gastric cancer case group was much higher than the control group ($P < 0.05$), and there was no significant difference in the ratio of alcohol drinkers between the two groups ($P > 0.05$). Statistical results can be seen in Table 1.

Genotype frequency distributions of the T1151A polymorphism and their relationship to familial gastric cancer

The genotype frequency distributions of the T1151A polymorphism within the normal control group were not significantly different from the results calculated by the Handy-Weinberg formula. These data indicate that the control group was a representative population. Each genotype frequency distribution of the T1151A polymorphism and the relationships between them and familial gastric cancer can be seen in Table 2. The genotype frequency of the three kinds of genotypes were 87.6% (TT), 10.6% (TA) and 1.8% (AA), respectively, in the 113 patients with familial gastric cancer. In the control group, the corresponding genotype frequency values were 94.7% (TT), 5.3% (TA) and 0% (AA), respectively. In familial or suspected familial gastric cancer patients, the frequency of the TA+AA gene polymorphism in T1151A was significantly higher than the control group ($P < 0.05$). Risk degree analysis demonstrated that risk of suffering gastric cancer in individuals carrying the mutated TA+AA genotype was increased remarkably, with an increased value of 169% (OR = 2.69, 95% CI: 1.04–7.29), compared to the TT wild-type gene.

Stratified analysis of T1151A gene polymorphism in the case group and the control group

In Table 3, to further stratify the confounding factors, we performed an analysis on the relationship between the polymorphism and the onset of familial gastric cancer. A significant difference in the detection of the polymorphism between the control group and patients with familial or suspected familial gastric cancer patients who were older than 50 years old was found ($P < 0.05$). After stratification based on age, risk degree analysis showed that the risk

Table 2 The frequency distribution of the T1151A genotype in the familial gastric cancer case group and the control group

T1151A genotype	Case group ($n = 113$)		Control group ($n = 180$)		P value	OR (95% CI)
	Number	%	Number	%		
TT	99	87.6	171	95.0		1.00
TA	12	10.6	9	5.0	0.063	2.30 (0.85–6.41)
AA	2	1.8	0	0	0.270	
TA+AA	14	12.4	9	5.0	0.022	2.69 (1.04–7.29)

Table 3 Stratified analysis of the T1151A genotype and the confounding factors

Groups	Cases [number (%)]		Controls [number (%)]		*P* value	OR (95% CI)	
	TT	TA+AA	TT	TA+AA		TT	TA+AA
Age (years old)							
<50	32 (91.4)	3 (8.6)	63 (95.5)	3 (4.5)	0.686	1.00	1.96 (0.32 ~ 11.95)
≥50	67 (87.5)	11 (12.5)	108 (94.7)	6 (5.3)	0.035	1.00	2.96 (0.94 ~ 10.15)
Gender							
Male	75 (87.1)	10 (12.9)	119 (94.4)	7 (5.6)	0.105	1.00	2.26 (0.81 ~ 6.53)
Female	24 (89.6)	4 (10.4)	52 (96.3)	2 (3.7)	0.200	1.00	4.25 (0.71 ~ 35.11)
Smoking							
Never	50 (89.3)	6 (10.7)	63 (94.0)	4 (6.0)	0.529	1.00	1.88 (0.49 ~ 7.93)
Ever	49 (85.9)	8 (14.1)	108 (95.6)	5 (4.4)	0.061	1.00	3.50 (1.08 ~ 12.3)
Drinking							
Never	37 (86.0)	6 (14.0)	49 (94.2)	3 (5.8)	0.316	1.00	2.62 (0.61 ~ 13.58)
Ever	62 (88.6)	8 (11.4)	122 (95.3)	6 (4.7)	0.144	1.00	2.61 (0.85 ~ 8.38)

value was increased to 196% (OR = 2.96, 95% CI: 0.94–10.15), while there was no significant difference in patients younger than 50 years old.

After stratification based on gender, smoking and/or alcohol drinking, no statistically significance between the polymorphism and familial gastric cancer risk degree was found.

Stratification based on onset risk prediction showed that the distribution of this polymorphism in patients from high-risk families was higher than that in the control group and the difference had statistical significance ($P < 0.05$). The risk value increased 279% (OR = 3.79, 95% CI: 1.37–10.37). There was also an increased risk both in patients from medium-risk families and mutation carriers in young patients without a family history of cancer. The calculated risk values were OR = 2.25, 95% CI: 0.73–6.53 and OR = 3.23, 95% CI: 0.45–14.53, respectively, but neither were statistically significant due to sample quantity ($P > 0.05$).

Based on the classification of patients with and without precancerous diseases related to gastric cancer, it was detected that the risks of mutation carriers in patients affected by precancerous diseases was greatly increased compared to the control group ($P < 0.01$) with an increased risk value of 279% (OR = 3.79, 95% CI: 1.37–10.37) (Table 4).

Discussion

The genetic mechanism, a germ-line mutation, associated with the pathogenesis of familial gastric cancer was detected in three Maori diffuse gastric cancer families by Guilford et al. in 1998 [23]. This germline mutation in the E-cadherin gene (*CDH1*) leads to a truncated protein. Thereafter, several studies in different populations found over 30 types of *CDH1* gene mutations in hereditary diffuse gastric cancer (HDGC) [24–29]. However, *CDH1* gene mutations only accounted for 30% of the disease causes of HDGC, and no relatively specific gene mutations were found in the other 70% of HDGC patients and in patients with all other kinds of familial intestinal gastric cancer (FIGC) [7, 30]. *CDH1* gene mutations are mainly detected in European populations, while very few gene mutations were found in most of East Asian people. In studies of familial gastric cancer in Japan and Korea, germ-line mutations were detected in MET, TP-53 and other genes, but not in the CDH1 gene [31–33]. In a Chinese population, in addition to the genes mentioned above, germ-line mutation or polymorphism sites were found in the MMR gene [11]. A disparity in the genetic basis of the pathogenesis of familial gastric cancer was demonstrated to be due to region and race diversity. T1151A is located in exon 12 of the MMR gene, hMLH1. This gene polymorphism is correlated with race and with distributions in China, Japan and Korea. The frequency of mutant adenine in the East Asian population was between 3 and 6%, while no corresponding frequencies were found in a German and American population [12–15]. A correlation between T1151A and tumors has been confirmed extensively. Wang et al. first detected this polymorphism in gastric and colorectal cancer and verified that the polymorphism was a genetic susceptible factor of these two cancer types [12, 19]. In addition, T1151A has been associated with non-small cell lung cancer in subsequent investigations. However, T1151A may be a protective factor in prostate cancer. Furthermore, T1151A is not correlated with esophageal carcinoma and breast cancer [16–18]. However, these studies were all limited to sporadic tumor patients and did not report on whether T1151A plays similar roles in

Table 4 Comparison of the frequency of the alleles between the classified groups and the control group

Groups	Bases			*P* value	OR (95% CI)
	A	T	Total		
Normal controls	9 (2.5)	351 (97.5)	360		1.00
High-risk families	8 (8.93)	82 (91.07)	90	0.019	3.79 (1.37 ~ 10.37)
Medium-risk families	6 (3.91)	104 (96.09)	110	0.223	2.25 (0.73 ~ 6.53)
Young	2 (7.69)	24 (92.31)	26	0.33	3.23 (0.45 ~ 14.53)
With precancerous diseases	12 (10.9)	98 (89.1)	110	0.001	4.76 (1.93 ~ 12.05)
Without precancerous diseases	4 (3.4)	112 (96.6)	116	0.789	1.39 (0.37 ~ 4.54)

patients affected by genetic factors. T1151A has been shown to have a significant distribution ($P < 0.05$) in familial and suspected familial gastric cancer patients. The pathogenic risk of this polymorphism increased in these patients with familial gastric cancer compared to normal control in our research.

After stratified analysis based on age, we found that the polymorphism resulted in a significant difference compared to the normal control patients only in elderly patients with (suspected) familial gastric cancer. This is in contrast to the phenomenon that the polymorphism mainly distributed in young patients. The reason for this disparity is still not known.

By stratified analysis, we also found that T1151A was not significantly correlated with living habits, such as smoking and alcohol drinking, and might be an independent risk factor of familial gastric cancer. The T1151A polymorphism distributed remarkably in patients from high-risk families ($P < 0.05$) and had a tendency of increasing sickness risk in younger patients and those from medium-risk families. Thus, we believe that T1151A can be used as a disease risk reference for the classification for members in familial gastric cancer families.

In addition, T1151A was especially prevalent in patients suffering from precancerous diseases related to gastric cancer ($P < 0.01$). These data suggest that precancerous diseases were associated with carcinogenesis. Gene polymorphism may be able to affect an individual's response to the environment [34]. T1151A might make patients with precancerous diseases more sensitive to carcinogenic factors, such as *Helicobacter pylori*.

The pathogenic mechanism of T1151A has not been well understood. Transversion of T → A results in a neutral Val being mutated into an acidic Asp, which may have some effects on protein structure or stability. An amino acid change was shown to be able to affect protein function by Sort intolerant from tolerant (SIFT) software analysis, which was further verified by PolyPhen (Polymorphism Phenotyp). T1151A was defined as unclassified variants (UVs) in the UniProt protein database and the main pathogenic mechanism of UVs was related to splicing regulation. Therefore, we further investigated the impact of the T → A transversion on splicing regulation through ESEfinder3.0 software. We discovered that the mutation to adenine was able to weaken the activity of exonic splicing enhancers (ESEs), a splicing regulation element. However, this needs to be confirmed in vitro by functional splicing experiments.

Conclusion

In the present study, we found that there is a gene polymorphism site at T1151A in the *MMR* gene in Chinese patients with familial gastric cancer. The polymorphism has a significant relationship with the onset of familial gastric cancer and was associated with the age of onset. Also, T1151A can serve as an index of disease risk classification of family members. We detected a relationship between gene polymorphism and precancerous diseases, and this may provide a valuable reference for carcinogenic prediction. Taken together, in East Asians specifically, T1151A, coupled with other gene screening indexes, can be used as a screening index for high-risk familial gastric cancer patients and can be optimized as a screening strategy. However, single pathogenic gene site polymorphism only increased susceptibility and an additive effect of several pathogenic genes sites will likely play the decisive role. Research on genomic relationships that are currently underway will broaden this area for us.

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