ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2018 February 7; 24(5): 549-656

Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

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Weekly Volume 24 Number 5 February 7, 2018

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AIMS AND SCOPE

World Journal of Gastroenterology (*World J Gastroenterol*, *WJG*, print ISSN 1007-9327, online ISSN 2219-2840, DOI: 10.3748) is a peer-reviewed open access journal. *WJG* was established on October 1, 1995. It is published weekly on the 7th, 14th, 21st, and 28th each month. The *WJG* Editorial Board consists of 642 experts in gastroenterology and hepatology from 59 countries.

The primary task of *WJG* is to rapidly publish high-quality original articles, reviews, and commentaries in the fields of gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, hepatobiliary surgery, gastrointestinal oncology, gastrointestinal radiation oncology, gastrointestinal imaging, gastrointestinal interventional therapy, gastrointestinal infectious diseases, gastrointestinal pharmacology, gastrointestinal pathophysiology, gastrointestinal pathology, evidence-based medicine in gastroenterology, pancreatology, gastrointestinal laboratory medicine, gastrointestinal molecular biology, gastrointestinal immunology, gastrointestinal microbiology, gastrointestinal genetics, gastrointestinal translational medicine, gastrointestinal diagnostics, and gastrointestinal therapeutics. *WJG* is dedicated to become an influential and prestigious journal in gastroenterology and hepatology, to promote the development of above disciplines, and to improve the diagnostic and therapeutic skill and expertise of clinicians.

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World Journal of Gastroenterology (*WJG*) is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central and Directory of Open Access Journals. The 2017 edition of Journal Citation Reports® cites the 2016 impact factor for *WJG* as 3.365 (5-year impact factor: 3.176), ranking *WJG* as 29th among 79 journals in gastroenterology and hepatology (quartile in category Q2).

NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

EDITORIAL OFFICE
Ze-Mao Gong, Director
World Journal of Gastroenterology
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLICATION DATE
February 7, 2018

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/bpg/gerinfo/204

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http://www.f6publishing.com

World Journal of Gastroenterology

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World J Gastroenterol 2018 February 7; 24(5): 602-612

DOI: 10.3748/wjg.v24.i5.602

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

Case Control Study

Impact of SNP-SNP interactions of DNA repair gene *ERCC5* and metabolic gene *GSTP1* on gastric cancer/atrophic gastritis risk in a Chinese population

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Author contributions: Yuan Y conceived and designed the experiments and revised the manuscript; Sang L, Sun LP, Xu Q and Lv Z performed the experiments; Sang L, Lv Z and Sun LP analyzed the data; Sang L wrote the paper.

Supported by the National Science and Technology Support Program, No. 2015BAI13B07.

Institutional review board statement: This study was approved by the Human Ethics Review Committee of China Medical University (Shenyang, China).

Informed consent statement: All participants provided written informed consent according to the Declaration of Helsinki and its later revision.

Conflict-of-interest statement: The authors declare no conflict of interest.

Data sharing statement: No additional data are available.

Manuscript source: Unsolicited manuscript

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Received: November 9, 2017
Peer-review started: November 9, 2017
First decision: November 21, 2017
Revised: December 5, 2017
Accepted: December 12, 2017
Article in press: December 12, 2017
Published online: February 7, 2018

Abstract

AIM

To investigate the interactions of the DNA repair gene excision repair cross complementing group 5 (*ERCC5*) and the metabolic gene glutathione S-transferase pi 1 (*GSTP1*) and their effects on atrophic gastritis (AG) and gastric cancer (GC) risk.

METHODS
Seven *ERCC5* single nucleotide polymorphisms (SNPs) (rs1047768, rs2094258, rs2228959, rs4150291, rs4150383, rs751402, and rs873601) and *GSTP1* SNP rs1695 were detected using the Sequenom MassARRAY platform in 450 GC patients, 634 AG cases, and 621 healthy control subjects in a Chinese population.

RESULTS
Two pairwise combinations (*ERCC5* rs2094258 and rs873601 with *GSTP1* rs1695) influenced AG risk ($P_{interaction}$ = 0.008 and 0.043, respectively), and the ERCC5 rs2094258-GSTP1 rs1695 SNP pair demonstrated an antagonistic effect, while *ERCC5* rs873601-*GSTP1* rs1695 showed a synergistic effect on AG risk OR = 0.51 and 1.79, respectively). No pairwise combinations were observed in relation to GC risk. There were no cumulative effects among the pairwise interactions (*ERCC5* rs2094258 and rs873601 with *GSTP1* rs1695) on AG susceptibility (P_{trend} > 0.05). When the modification effect of *Helicobacter pylori* (*H. pylori*) infection was evaluated, the cumulative effect of one of the aforementioned pairwise interactions (*ERCC5* rs873601-*GSTP1* rs1695) was associated with an increased AG risk in the case of negative *H. pylori* status (P_{trend} = 0.043).

CONCLUSION
There is a multifarious interaction between the DNA repair gene *ERCC5* SNPs (rs2094258 and rs873601) and the metabolic gene *GSTP1* rs1695, which may form the basis for various inter-individual susceptibilities to AG.

Key words: Excision repair cross complementing group 5; Glutathione S-transferase pi 1; Atrophic gastritis; Gastric cancer; Single nucleotide polymorphisms

Core tip: We detected seven excision repair cross complementing group 5 (*ERCC5*) single nucleotide polymorphisms (SNPs) and a glutathione S-transferase pi1 (*GSTP1*) SNP using the Sequenom MassARRAY platform in a Chinese population and used them to investigate their interactions and their effects on atrophic gastritis and gastric cancer risk. The results showed a multifarious interaction between the DNA repair gene *ERCC5* SNPs (rs2094258 and rs873601) and the metabolic gene *GSTP1* rs1695. In addition, the cumulative effect of one pairwise interaction (*ERCC5* rs873601-*GSTP1* rs1695) was associated with an increased atrophic gastritis risk in the case of negative *H. pylori* status when the modification effect of *H. pylori* infection was evaluated.

Sang L, Lv Z, Sun LP, Xu Q, Yuan Y. Impact of SNP-SNP interactions of DNA repair gene *ERCC5* and metabolic gene *GSTP1* on gastric cancer/atrophic gastritis risk in a Chinese population. *World J Gastroenterol* 2018; 24(5): 602-612 Available from: URL: http://www.wjgnet.com/1007-9327/full/v24/i5/602.htm DOI: http://dx.doi.org/10.3748/wjg.v24.i5.602

INTRODUCTION

In light of the study of gastric cancer (GC) pathogenesis, there is increasing evidence to suggest that the interactions between various inherited susceptibility genes may affect the risk of GC development in individuals[1]. Single nucleotide polymorphisms (SNPs), as one of the most general forms of genetic variation, play a key role in predicting cancer risk in individuals and are widely applied to study tumor incidence and prognostic evaluation. However, they are inadequately utilized for studies of various genes in intricate diseases such as cancer[2], and the presently investigated polymorphisms for each single gene may not entirely reveal a definite phenotype[1]. Some studies have shown that interactions among genes are more significant than solitary genes in determining cancer susceptibility[3,4].

Numerous epidemiological studies have shown that inherited polymorphisms involved in xenobiotic metabolism and DNA repair are related to GC[1,5]. These genes are acknowledged as risk-modifier indicators, especially those whose allelic polymorphisms are accountable for the repair of oxidative stress induced DNA damage and/or the impaired metabolism of exogenous carcinogens. Excision repair cross complementing group 5 (*ERCC5*) is a critical element of the nucleotide excision repair (NER) pathway, and the *ERCC5* gene is mapped to a region on chromosome 13q33 and comprises 15 exons[6]. It encodes a structure-specific endonuclease that has multiple functions during NER[7]. Its main role is to identify and shear damage to the DNA chain 3' terminus[8]. Its gene mutation may lead to abnormal cell proliferation and differentiation and increased cancer susceptibility. SNPs of *ERCC5* linked with GC susceptibility have been reported, including rs2094258, rs751402, rs2296147, rs1047768, rs873601, rs2227869, and rs17655[6,9-15]. We previously analyzed six SNPs of the *ERCC5* gene in 2686 subjects from northern China and found that the selected polymorphisms of the ERCC5 gene were not significantly associated with atrophic gastritis (AG)/GC risk[16]. Glutathione S-transferase (GST) is an important member of the phase Ⅱ metabolic enzymes, including GSTM1, GSTT1, and glutathione S-transferase pi1 (GSTP1)[17], which can affect detoxification processes and increase individual susceptibility to cancers[18]. The GSTP1 Ile105Val polymorphism produces the amino acid replacement of Ile (105) with Val *via* the change of A (Ile) to G (Val) in exon 5, which diminishes enzyme catalytic activity[6] and indirectly stimulates DNA repair and protection of the cell genome[7,8]. Our previous study also identified SNP rs1695 in *GSTP1*, which appears to drastically change the susceptibility of individuals to

GC[9]. This finding is consistent with previous studies[10,11].

Although some studies have found that *ERCC5* SNPs and *GSTP1* polymorphisms were related to GC risk, there are limited data on the effects of gene-gene interactions, and some results are equivocal[12,13]. Additionally, given the vital impact of environmental factors on the susceptibility to GC and our previous findings regarding gene interaction and environmental factors[4,14,16], we explored possible two-dimensional gene interactions among inherited polymorphisms in the DNA repair gene *ERCC5* (rs1047768, rs2094258, rs2228959, rs4150291, rs4150383, rs751402, and rs873601) and the metabolic gene *GSTP1* (rs1695), as well as the three-dimensional interactions between SNP-SNP and environmental factors in diverse stages of gastric carcinogenesis to assess the possibility of predicting GC risk and the identification of a combination of biomarkers for precancerosis and GC.

MATERIALS AND METHODS

Study population

In all, 1705 subjects were included in the present study, comprising 621 healthy controls, 634 cases of AG, and 450 cases of GC. All registered individuals originated from a Screening Program for Gastric Diseases or hospitals in Zhuanghe and Shenyang of Liaoning Province, China between 2002 and 2013, as previously described[16]. Metadata for every participant was collected using a standardized questionnaire survey and stored in a spreadsheet, including gender, age, history of illness, status of smoking, and alcohol consumption. Every participant signed a written informed consent from, according to the Declaration of Helsinki and its later revision. We collected peripheral venous blood from all participants, and experienced endoscopists simultaneously performed gastroscopic examination. All subjects received histopathological diagnosis according to the updated Sydney System[15] and the World Health Organization criteria, independently, by two gastrointestinal pathologists. This project was approved by the Human Ethics Review Committee of China Medical University (Shenyang, China).

SNP selection and genotyping assay

Briefly, as described in our previous study[16], we extracted *ERCC5* genotype data from the HapMap Chinese Han Beijing population (http://www.HapMap.org). Tag SNPs were derived from pairwise linkage disequilibrium information to maximally capture (r^2 > 0.8) common or rare variants [minor allele frequency (MAF) > 0.05] using Haploview 4.2 (http://www.broadinstitute.org/mpg/haploview). FastSNP Search was used to predict potential SNP function. Finally, a total of seven *ERCC5* SNPs (rs1047768, rs2094258, rs2228959, rs4150291, rs4150383, rs751402, and rs873601) were chosen in this study. In addition, *GSTP1* rs1695 was selected according to our previous study and literature references[9-11]. Genomic DNA was isolated from blood samples using a routine phenol-chloroform method and then diluted to working concentrations (50 ng/μL) for genotyping. Samples were placed randomly in 384-well plates and blinded for disease status. Selected SNP genotyping was performed using the Sequenom MassARRAY platform (Sequenom, San Diego, CA, United States) according to the manufacturer's instructions[16]. The average genotyping rate was 99.3% and the results of all duplicated samples were 100% consistent.

Assessment of Helicobacter pylori serology

Helicobacter pylori (*H. pylori*) immunoglobulin G levels was tested using an enzyme-linked immunosorbent assay (ELISA kit, Biohit, Helsinki, Finland) according to the manufacturer's instructions, as previously described[16]. *H. pylori* positivity was defined as a numerical reading exceeding 34 enzyme immune units.

Statistical analysis

Statistical analyses in the study were completed by applying SPSS 17.0 software (SPSS Inc., Chicago, IL, United States). We used the χ^2 test to calculate the differences in demographic characteristics and genotypes between cases and controls. The two- or three-dimensional interaction effects among SNP-SNP with or without environmental factors were estimated using multivariate logistic regression models. General linear regression modeling was used to assess the trends with an increasing number of mutation genotypes in the cumulative effect. Associations were evaluated by odds ratios (ORs) and 95% confidence intervals (CIs) adjusted by sex, age, and *H. pylori* infection status except for being stratified by *H. pylori* infection status. Two-sided *P*-values < 0.05 were considered statistically significant.

RESULTS

Demographic and geographic characteristics

The distribution characteristics of gender, age, and *H. pylori* infection status of all participants are shown in Table 1. No significant differences were found in the gender or age distribution among the case and control groups. The study subjects consisted of 634 AG patients, 450 GC patients, and two control groups, including 620 and 535 for AG and GC cases, matched by gender and age, respectively. Additionally, there were significantly higher *H. pylori* infection rates (59.5% and 49.6%, respectively) in the AG and GC groups compared to the two matched control groups (27.1% and 26.7%, respectively, *P* < 0.001).

Pairwise interactions between the ERCC5 SNPs and GSTP1 rs1695 polymorphism

We primarily examined SNP-SNP two-dimensional interaction effects in the main effect analysis using a full-factor model. Two pairwise SNP combinations

Table 1 Baseline characteristics of the subjects *n* (%)

Variable	AG *vs* CON		GC *vs* CON	
	CON	AG	CON	GC
	n = 620	*n* = 634	*n* = 535	*n* = 450
Gender	*P* = 0.492		*P* = 0.588	
Male	362 (58.4)	358 (56.5)	363 (67.9)	298 (66.2)
Female	258 (41.6)	276 (43.5)	172 (32.1)	152 (33.8)
Age	*P* = 0.845		*P* = 0.235	
mean ± SD	54.7 ± 9.1	54.8 ± 9.0	55.6 ± 9.2	56.3 ± 10.1
Median	54	55	56	57
Range	17-85	16-82	17-85	26-84
H. pylori infection status	*P* < 0.001		*P* < 0.001	
Positive	168 (27.1)	377 (59.5)	143 (26.7)	223 (49.6)
Negative	452 (72.9)	257 (40.5)	392 (73.3)	227 (50.4)

AG: Atrophic gastritis; GC: Gastric cancer; CON: Controls.

were found that could affect AG risk, but no pairwise combination was found in relation to GC risk. The results indicated that the *ERCC5* rs2094258 and rs873601 polymorphisms with *GSTP1* rs1695 polymorphism could engender interaction effects for AG risk ($P_{interaction}$ = 0.008 and 0.043 respectively, Table 2). The *ERCC5* rs2094258-*GSTP1* rs1695 SNP pair demonstrated an antagonistic effect, while ERCC5 rs873601-GSTP1 rs1695 showed a synergistic effect on AG risk (OR = 0.51 and1.79, respectively, Table 2). No significant differences were observed among other SNP-SNP interactions (P > 0.05).

Epistatic effect of two-way interactions

We further investigated epistatic effects between pairs of *ERCC5* rs2094258 and rs873601 polymorphisms with *GSTP1* rs1695. For *ERCC5* rs2094258 and *GSTP1* rs1695, the AG/AA genotypes of rs2094258 and AA genotype of rs1695 were related to an increased risk of AG, but GA/GG genotypes of rs1695 were associated with a reduced risk of AG (OR = 1.523 and 0.678, respectively). For *ERCC5* rs873601 and *GSTP1* rs1695, AA genotype of rs873601 resulted in a reduced risk of AG, only in the presence of AA genotype of rs1695 (OR = 0.678) (Table 3). These findings illustrated that *ERCC5* rs2094258 and rs873601, individually, had no main effect but did display epistatic interactions with *GSTP1* rs1695.

Cumulative effect of the interacting factors of ERCC5 SNPs-GSTP1 rs1695

We also investigated the cumulative effect among the interacting SNPs of *ERCC5* rs2094258 and rs873601 with *GSTP1* rs1695, but neither had a statistically significant relationship to AG risk (P > 0.05, Table 4). We further analyzed the cumulative effect of interacting SNPs modified by *H. pylori*. The *ERCC5* rs873601-*GSTP1* rs1695 SNP pair had significant differences in AG risk among the subgroups with negative *H. pylori* infection status (P_{trend} = 0.043). Moreover, AG risk was significantly reduced while one or two mutation genotypes were present (OR = 0.66, 95%CI: 0.37-1.16, and OR = 0.73, 95%CI: 0.53-1.02, respectively).

Three-dimensional analysis of the effect of interactions of ERCC5 SNPs-GSTP1 rs1695-environmental factors on AG risk

To explore the influence of environmental factors on the interaction, we further explored probable three-dimensional interactions among *ERCC5* SNPs (rs2094258 and rs873601), *GSTP1* rs1695, and environmental factors (smoking, alcohol consumption, and *H. pylori* infection status). We found no significant three-dimensional interactions with regard to AG risk (P > 0.05, Supplementary Table 1).

DISCUSSION

GC is an outcome of the interaction between multiple genes and environmental factors and is considered a multistep and multifactor process involving different carcinogen metabolic and DNA repair pathways[19,20]. Currently, researchers are concentrating more on the gene-gene interaction effect rather than a single-gene effect. In this study, we examined the possible interaction effect of DNA repair gene *ERCC5* SNPs and the metabolic detoxification gene *GSTP1* polymorphism. We first found new two-pair SNP interactions among *ERCC5* SNPs and the *GSTP1* polymorphism (*ERCC5* rs2094258-*GSTP1* rs1695 and *ERCC5* rs873601-GSTP1 rs1695), which could alter the susceptibility to AG compared to host genetic effects alone. Moreover, the cumulative effect resulting from two-way interaction of *ERCC5* rs873601-*GSTP1* rs1695 was shown to differ in a stratified analysis of *H. pylori* infection status. The change from no cumulative effect to significant difference in AG risk in the case of negative *H. pylori* status indicated that *H. pylori* infection status could modify the cumulative effect mentioned above for the interacting SNPs. Genetic polymorphisms may explain partial individual deviations in disease risk, but a more multifarious condition involving numerous gene-gene interactions and gene-environment characteristics must

Table 2 Impact of two-way interactions between *ERCC5* polymorphisms and *GSTP1* rs1695 on risk of atrophic gastritis and gastric cancer[1]

Gene	Genotype	Number of participants	GSTP1 rs1695			
			AA	GA + GG	AA + GA	GG
AG *vs* CON						
(*n* = 634 *vs* 620)						
ERCC5 rs1047768	TT	No. of cases/controls	231/200	124/116	338/307	17/9
		OR (95%CI)	1 (Ref.)	0.93 (0.68-1.27)	1 (Ref.)	1.72 (0.75-3.91)
	TC + CC	No. of cases/controls	177/188	102/116	270/289	9/15
		OR (95%CI)	0.82 (0.62-1.08)	0.76 (0.55-1.06)	0.85 (0.68-1.07)	0.55 (0.24-1.26)
			$P_{interaction}$ = 0.317		$P_{interaction}$ = 0.683	
			Interaction index = 0.88		Interaction index = 1.13	
	TT + TC	No. of cases/controls	376/345	207/214	559/538	24/21
		OR (95%CI)	1 (Ref.)	0.89 (0.70-1.13)	1 (Ref.)	1.10 (0.61-2.00)
	CC	No. of cases/controls	32/43	19/18	49/58	2/3
		OR (95%CI)	0.68 (0.42-1.10)	0.97 (0.50-1.87)	0.81 (0.55-1.21)	0.64 (0.11-3.86)
			$P_{interaction}$ = 0.296		$P_{interaction}$ = 0.531	
			Interaction index = 0.88		Interaction index = 0.88	
ERCC5 rs2094258	GG	No. of cases/controls	132/162	93/84	214/234	11/12
		OR (95%CI)	1 (Ref.)	1.36 (0.94-1.98)	1 (Ref.)	1.00 (0.43-2.32)
	GA + AA	No. of cases/controls	276/226	133/148	394/362	15/12
		OR (95%CI)	1.50 (1.12-2.00)	1.10 (0.79-1.53)	1.19 (0.94-1.50)	1.37 (0.63-2.99)
			$P_{interaction}$ = 0.008		$P_{interaction}$ = 0.842	
			Interaction index = 0.51		Interaction index = 1.13	
	GG + GA	No. of cases/controls	337/328	195/204	508/510	24/22
		OR (95%CI)	1 (Ref.)	0.93 (0.73-1.19)	1 (Ref.)	1.10 (0.61-1.98)
	AA	No. of cases/controls	71/60	31/28	100/86	2/2
		OR (95%CI)	1.15 (0.79-1.68)	1.08 (0.63-1.84)	1.17 (0.85-1.60)	1.00 (0.14-7.15)
			$P_{interaction}$ = 0.594		$P_{interaction}$ = 0.620	
			Interaction index = 0.83		Interaction index = 0.58	
ERCC5 rs2228959	CC	No. of cases/controls	371/346	198/215	548/539	21/22
		OR (95%CI)	1 (Ref.)	0.86 (0.67-1.09)	1 (Ref.)	0.94 (0.51-1.73)
	CA + AA	No. of cases/controls	37/42	28/17	60/57	5/2
		OR (95%CI)	0.82 (0.52-1.31)	1.54 (0.83-2.86)	1.04 (0.71-1.52)	2.46 (0.48-12.73)
			$P_{interaction}$ = 0.103		$P_{interaction}$ = 0.435	
			Interaction index = 2.00		Interaction index = 2.11	
	CC + CA	No. of cases/controls	408/383	224/231	606/590	26/24
		OR (95%CI)	1 (Ref.)	0.91 (0.72-1.15)	1 (Ref.)	1.06 (0.60-1.86)
	AA	No. of cases/controls	0/5	2/1	2/6	0/0
		OR (95%CI)	NA	1.88 (0.17-20.79)	0.32 (0.07-1.61)	NA
			$P_{interaction}$ = NA		$P_{interaction}$ = 0.720	
			Interaction index = NA		Interaction index = 1.12	
ERCC5 rs4150291	AA	No. of cases/controls	347/332	193/205	517/516	23/21
		OR (95%CI)	1 (Ref.)	0.90 (0.70-1.15)	1 (Ref.)	1.09 (0.60-2.00)
	AT + TT	No. of cases/controls	61/56	33/27	91/80	3/3
		OR (95%CI)	1.04 (0.70-1.54)	1.17 (0.69-1.99)	1.14 (0.82-1.57)	1.00 (0.20-4.97)
			$P_{interaction}$ = 0.667		$P_{interaction}$ = 0.679	
			Interaction index = 1.17		Interaction index = 0.68	
	AA + AT	No. of cases/controls	406/382	225/232	605/590	26/24
		OR (95%CI)	1 (Ref.)	0.91 (0.73-1.15)	1 (Ref.)	1.06 (0.60-1.86)
	TT	No. of cases/controls	2/6	1/0	3/6	0/0
		OR (95%CI)	0.31 (0.06-1.56)	NA	0.49 (0.12-1.96)	NA
			$P_{interaction}$ = NA		$P_{interaction}$ = 0.703	
			Interaction index = NA		Interaction index = 1.12	
ERCC5 rs4150383	GG	No. of cases/controls	365/344	197/202	539/526	23/20
		OR (95%CI)	1 (Ref.)	0.92 (0.72-1.18)	1 (Ref.)	1.12 (0.61-2.07)
	GA + AA	No. of cases/controls	43/44	29/30	69/70	3/4
		OR (95%CI)	0.92 (0.59-1.44)	0.91 (0.54-1.55)	0.96 (0.68-1.37)	0.73 (0.16-3.29)
			$P_{interaction}$ = 0.720		$P_{interaction}$ = 0.894	
			Interaction index = 1.15		Interaction index = 1.12	
	GG + GA	No. of cases/controls	406/387	226/231	606/594	26/24
		OR (95%CI)	1 (Ref.)	0.93 (0.74-1.17)	1 (Ref.)	1.06 (0.60-1.87)
	AA	No. of cases/controls	2/1	0/1	2/2	0/0
		OR (95%CI)	1.91 (0.17-21.11)	NA	0.98 (0.14-6.98)	NA
			$P_{interaction}$ = NA		$P_{interaction}$ = 0.695	
			interaction index = NA		interaction index = 1.13	
ERCC5 rs751402	CC	No. of cases/controls	191/173	97/104	281/266	7/11
		OR (95%CI)	1 (Ref.)	0.85 (0.60-1.19)	1 (Ref.)	0.60 (0.23-1.58)

	CT + TT	No. of cases/ controls	203/198	124/118	308/303	19/13
		OR (95%CI)	0.93 (0.70-1.23)	0.95 (0.69-1.32)	0.96 (0.76-1.21)	1.38 (0.67-2.86)
			$P_{interaction}$ = 0.196		$P_{interaction}$ = 0.109	
			Interaction index = 1.39		Interaction index = 2.84	
	CC + CT	No. of cases/ controls	355/324	193/196	526/500	22/20
		OR (95%CI)	1 (Ref.)	0.90 (0.70-1.15)	1 (Ref.)	1.05 (0.56-1.94)
	TT	No. of cases/ controls	39/47	28/26	63/69	4/4
		OR (95%CI)	0.76 (0.48-1.19)	0.98 (0.56-1.71)	0.87 (0.60-1.25)	0.95 (0.24-3.81)
			$P_{interaction}$ = 0.488		$P_{interaction}$ = 0.886	
			Interaction index = 1.31		Interaction index = 1.13	
ERCC5 rs873601	GG	No. of cases/ controls	126/109	57/59	178/165	5/3
		OR (95%CI)	1 (Ref.)	0.84 (0.54-1.30)	1 (Ref.)	1.55 (0.36-6.57)
	GA + AA	No. of cases/ controls	282/279	169/173	430/431	21/21
		OR (95%CI)	0.87 (0.64-1.19)	0.85 (0.61-1.18)	0.93 (0.72-1.19)	0.93 (0.49-1.76)
			$P_{interaction}$ = 0.197		$P_{interaction}$ = 0.770	
			Interaction index = 1.44		Interaction index = 0.78	
	GG + GA	No. of cases/ controls	321/279	167/177	473/441	15/15
		OR (95%CI)	1 (Ref.)	0.82 (0.63-1.07)	1 (Ref.)	0.93 (0.45-1.93)
	AA	No. of cases/ controls	87/109	59/55	135/155	11/9
		OR (95%CI)	0.69 (0.50-0.96)	0.93 (0.62-1.39)	0.81 (0.62-1.06)	1.14 (0.47-2.78)
			$P_{interaction}$ = 0.043		$P_{interaction}$ = 0.488	
			Interaction index = 1.79		Interaction index = 1.55	
GC *vs* CON (n = 450 *vs* 535)						
ERCC5 rs1047768	TT	No. of cases/ controls	142/162	78/105	204/259	16/8
		OR (95%CI)	1 (Ref.)	0.85 (0.59-1.23)	1 (Ref.)	2.54 (1.07-6.05)
	TC + CC	No. of cases/ controls	128/164	102/104	211/255	19/13
		OR (95%CI)	0.89 (0.65-1.23)	1.12 (0.79-1.59)	1.05 (0.81-1.36)	1.86 (0.89-3.85)
			$P_{interaction}$ = 0.101		$P_{interaction}$ = 0.594	
			interaction index = 1.56		interaction index = 0.73	
	TT + TC	No. of cases/ controls	247/292	158/193	374/467	31/18
		OR (95%CI)	1 (Ref.)	0.97 (0.74-1.27)	1 (Ref.)	2.15 (1.18-3.91)
	CC	No. of cases/ controls	23/24	22/16	41/47	4/3
		OR (95%CI)	0.80 (0.46-1.39)	1.63 (0.84-3.16)	1.09 (0.70-1.69)	1.67 (0.37-7.49)
			$P_{interaction}$ = 0.115		$P_{interaction}$ = 0.640	
			Interaction index = 2.07		Interaction index = 0.66	
ERCC5 rs2094258	GG	No. of cases/ controls	110/131	66/77	165/197	11/11
		OR (95%CI)	1 (Ref.)	1.02 (0.67-1.55)	1 (Ref.)	1.19 (0.51-2.82)
	GA + AA	No. of cases/ controls	160/195	114/132	250/317	24/10
		OR (95%CI)	0.98 (0.70-1.36)	1.03 (0.72-1.47)	0.94 (0.72-1.23)	2.87 (1.33-6.17)
			$P_{interaction}$ = 0.923		$P_{interaction}$ = 0.134	
			Interaction index = 0.97		Interaction index = 2.47	
	GG + GA	No. of cases/ controls	226/275	158/185	352/441	32/19
		OR (95%CI)	1 (Ref.)	1.04 (0.79-1.37)	1 (Ref.)	2.11 (1.18-3.79)
	AA	No. of cases/ controls	44/51	22/24	63/73	3/2
		OR (95%CI)	1.05 (0.68-1.63)	1.12 (0.61-2.04)	1.08 (0.75-1.56)	1.88 (0.31-11.31)
			$P_{interaction}$ = 0.801		$P_{interaction}$ = 0.834	
			Interaction index = 0.90		Interaction index = 0.81	
ERCC5 rs2228959	CC	No. of cases/ controls	247/295	164/194	380/470	31/19
		OR (95%CI)	1 (Ref.)	1.01 (0.77-1.32)	1 (Ref.)	2.02 (1.12-3.63)
	CA + AA	No. of cases/ controls	23/31	16/15	35/44	4/2
		OR (95%CI)	0.89 (0.50-1.56)	1.27 (0.62-2.63)	0.98 (0.62-1.57)	2.47 (0.45-13.58)
			$P_{interaction}$ = 0.491		$P_{interaction}$ = 0.813	
			Interaction index = 1.40		Interaction index = 1.26	
	CC + CA	No. of cases/ controls	268/322	180/208	413/509	35/21
		OR (95%CI)	1 (Ref.)	1.04 (0.80-1.35)	1 (Ref.)	2.05 (1.18-3.58)
	AA	No. of cases/ controls	2/4	0/1	2/5	0/0
		OR (95%CI)	0.60 (0.11-3.31)	NA	0.49 (0.10-2.55)	NA
			$P_{interaction}$ = NA		$P_{interaction}$ = NA	
			Interaction index = NA		Interaction index = NA	
ERCC5 rs4150291	AA	No. of cases/ controls	222/276	143/182	338/440	27/18
		OR (95%CI)	1 (Ref.)	0.98 (0.74-1.29)	1 (Ref.)	1.95 (1.06-3.61)
	AT + TT	No. of cases/ controls	48/50	37/27	77/74	8/3
		OR (95%CI)	1.19 (0.77-1.84)	1.70 (1.01-2.89)	1.36 (0.96-1.92)	3.47 (0.91-13.18)
			$P_{interaction}$ = 0.385		$P_{interaction}$ = 0.818	
			Interaction index = 1.37		Interaction index = 1.20	
	AA + AT	No. of cases/ controls	267/321	177/209	410/509	34/21
		OR (95%CI)	1 (Ref.)	1.02 (0.79-1.32)	1 (Ref.)	2.01 (1.15-3.52)
	TT	No. of cases/ controls	3/5	3/0	5/5	1/0
		OR (95%CI)	0.72 (0.17-3.05)	NA	1.24 (0.36-4.32)	NA

			$P_{interaction}$ = NA		$P_{interaction}$ = NA	
			Interaction index = NA		Interaction index = NA	
ERCC5 rs4150383	GG	No. of cases/ controls	237/288	168/180	373/451	32/17
		OR (95%CI)	1 (Ref.)	1.13 (0.86-1.49)	1 (Ref.)	2.28 (1.24-4.16)
	GA + AA	No. of cases/ controls	33/38	12/29	42/63	3/4
		OR (95%CI)	1.06 (0.64-1.74)	0.50 (0.25-1.01)	0.81 (0.53-1.22)	0.91 (0.20-4.08)
			$P_{interaction}$ = 0.060		$P_{interaction}$ = 0.497	
			Interaction index = 0.43		Interaction index = 0.55	
	GG + GA	No. of cases/ controls	270/325	180/208	415/512	35/21
		OR (95%CI)	1 (Ref.)	1.04 (0.81-1.35)	1 (Ref.)	2.06 (1.18-3.59)
	AA	No. of cases/ controls	0/1	0/1	0/2	0/0
		OR (95%CI)	NA	NA	NA	NA
			$P_{interaction}$ = NA		$P_{interaction}$ = NA	
			Interaction index = 0.90		Interaction index = NA	
ERCC5 rs751402	CC	No. of cases/ controls	114/149	82/90	180/229	16/10
		OR (95%CI)	1 (Ref.)	1.19 (0.81-1.75)	1 (Ref.)	2.04 (0.90-4.59)
	CT + TT	No. of cases/ controls	142/161	89/109	212/259	19/11
		OR (95%CI)	1.15 (0.83-1.61)	1.07 (0.74-1.55)	1.04 (0.80-1.36)	2.20(1.02-4.74)
			$P_{interaction}$ = 0.453		$P_{interaction}$ = 0.945	
			Interaction index = 0.81		Interaction index = 0.96	
	CC + CT	No. of cases/ controls	225/275	156/174	348/432	33/17
		OR (95%CI)	1 (Ref.)	1.10 (0.83-1.45)	1 (Ref.)	2.41 (1.32-4.40)
	TT	No. of cases/ controls	31/35	15/25	44/56	2/4
		OR (95%CI)	1.08 (0.65-1.81)	0.73 (0.38-1.42)	0.98 (0.64-1.48)	0.62 (0.11-3.41)
			$P_{interaction}$ = 0.409		$P_{interaction}$ = 0.241	
			Interaction index = 0.69		Interaction index = 0.32	
		No. of cases/ controls	79/91	55/53	122/141	12/3
ERCC5 rs873601	GG	OR (95%CI)	1 (Ref.)	1.20 (0.74-1.94)	1 (Ref.)	4.62 (1.28-16.76)
		No. of cases/ controls	191/235	125/156	293/373	23/18
	GA + AA	OR (95%CI)	0.94 (0.66-1.34)	0.92 (0.63-1.35)	0.91 (0.68-1.21)	1.48 (0.76-2.87)
			$P_{interaction}$ = 0.901		$P_{interaction}$ = 0.217	
			Interaction index = 0.96		Interaction index = 0.40	
		No. of cases/ controls	205/232	139/156	317/375	27/13
	GG + GA	OR (95%CI)	1 (Ref.)	1.01 (0.75-1.36)	1 (Ref.)	2.46 (1.25-4.84)
		No. of cases/ controls	65/94	41/35	98/139	8/8
	AA	OR (95%CI)	0.78 (0.54-1.13)	0.88 (0.56-1.37)	0.83(0.62-1.12)	1.18 (0.44-3.18)
			$P_{interaction}$ = 0.477		$P_{interaction}$ = 0.384	
			Interaction index = 1.25		Interaction index = 0.57	

[1]*P* for interaction, logistic regression adjusted for gender, age, and *H. pylori* infection status; Statistically significant associations were highlighted in bold ($P < 0.05$). CON: Controls; AG: Atrophic gastritis; GC: Gastric cancer; NA: Not available; GSTP1: Glutathione S-transferase pi 1; ERCC5: Excision repair cross complementing group 5.

be mentioned.

A combination of SNPs would produce synergistic or antagonistic effects compared to an SNP, which could change the susceptibility to disease[21,22]. Individually, two *ERCC5* SNPs (rs2094258 and rs873601; unpublished data) showed no effect on either AG or GC risk ($P > 0.05$). However, our findings revealed a main effect on AG risk while these polymorphisms interacted with *GSTP1* rs1695 ($P_{interaction}$ = 0.008 and 0.043, respectively). The pairwise ERCC5 rs2094258-*GSTP1* rs1695 and *ERCC5* rs873601-GSTP1 rs1695 combinations had an OR of 0.51 and 1.79, respectively, for AG risk in the above two-way interaction analysis. In all, this evidence suggests that polymorphisms harbored in *ERCC5* (rs2094258 and rs873601) had a synergistic or antagonistic effect with *GSTP1* rs1695, which could alter the risk of an individual towards AG. According to the potential mechanism of SNP-SNP interactions, the *ERCC5* gene, as an NER pathway gene, may be responsible for repairing DNA damage from biological and environmental mutagens or regular cellular metabolism. In addition, *GSTP1* as an important phase Ⅱ metabolizing xenobiotic enzyme might promote DNA damage repair through an exogenous metabolic detoxification pathway. When exogenous or endogenous carcinogens cause damage to DNA, the metabolic gene *GSTP1* removes some harmful substances through the detoxification effect and then promotes DNA damage repair to protect against carcinogenic progression. The DNA repair gene *ERCC5* can identify and incise a DNA wound on the 3′ terminus to ensure reliable repair of DNA damage[23]. The interaction polymorphisms can produce a superposition or counteracting effect. This may partly explain the epigenetic heritability loss of precancerosis risk and suggests novel insight into the multifactorial etiology of AG risk with regard to DNA repair gene *ERCC5* and xenobiotic metabolic gene *GSTP1* pathways. However, further independent studies of the molecular mechanism of SNP-SNP interactions must be performed in the future.

The SNP-SNP interaction effect of the two genes was observed as epistasis in the absence of a significant main effect[24]. The epistasis was more pronounced than one sole susceptibility gene in terms of main effects,

Table 3 Epistatic effect of pair-wise interacting factors on the risk of atrophic gastritis and gastric cancer

Interacted pair-wise SNPs	Comparison	Subset	AG *vs* CON		GC *vs* CON	
			P value	OR (95%CI)	*P* value	OR (95%CI)
ERCC5 rs2094258 interacted with *GSTP1* rs1695	*ERCC5* rs2094258 GG *vs* AG + AA	GSTP1 rs1695 AA	**0.006**	**1.523 (1.125-2.062)**	0.948	0.989 (0.704-1.388)
		GSTP1 rs1695 GA + GG	0.205	0.766 (0.508-1.157)	0.820	0.951 (0.619-1.462)
	GSTP1 rs1695 AA *vs* GA + GG	ERCC5 rs2094258 GG	0.148	1.343 (0.901-2.002)	0.808	1.055 (0.685-1.625)
		ERCC5 rs2094258 AG + AA	**0.014**	**0.678 (0.497-0.926)**	0.799	1.045 (0.745-1.465)
ERCC5 rs873601 interacted with *GSTP1* rs1695	*ERCC5* rs873601 GA + GG *vs* AA	GSTP1 rs1695 AA	**0.025**	**0.678 (0.483-0.952)**	0.148	0.756 (0.517-1.105)
		GSTP1 rs1695 GA + GG	0.380	1.230 (0.775-1.951)	0.872	0.961 (0.592-1.560)
	GSTP1 rs1695 AA *vs* GA + GG	ERCC5 rs873601 GA + GG	0.054	0.758 (0.571-1.005)	0.955	0.991 (0.730-1.346)
		ERCC5 rs873601 AA	0.226	1.356 (0.828-2.222)	0.542	1.183 (0.690-2.027)

All tests were adjusted by age, sex, and *H. pylori* infection. Statistically significant associations were highlighted in bold ($P < 0.05$). GC: Gastric cancer; AG: Atrophic gastritis; CON: Controls; ERCC5: Excision repair cross complementing group 5; GSTP1: Glutathione S-transferase pi 1.

which embody the effect of multipart interaction[4]. Multiple studies have revealed a relationship between epistasis and cancer risk[25,26]. Our previous findings also indicated epistasis by combining individual SNPs, which had no effect on disease risk at a single locus[4,14]. In the present study, for *ERCC5* rs2094258 and *GSTP1* rs1695, the AG/AA genotype of rs2094258 and AA genotype of rs1695 were related to an increased risk of AG, but GA/GG genotypes of rs1695a were associated with a reduced risk of AG. For *ERCC5* rs873601 and *GSTP1* rs1695, AA genotype of rs873601 resulted in a reduced risk of AG, only in the presence of AA genotype of rs1695. Thus, there is still little direct evidence to reveal a specific functional association among the polymorphisms of *ERCC5* and *GSTP1*. In light of previous research findings, we hypothesized an interaction effect between the DNA repair gene and xenobiotic metabolism gene by various signal pathways, and our discoveries regarding the interactions of the DNA repair *ERCC5* gene and xenobiotic metabolism *GSTP1* gene pathways may reveal the above assumption. Further synthetic and functional research on these two gene pathways will be performed to assess the interaction effect of susceptibility genes that directly affect gastric carcinogenesis.

Gastric carcinogenesis is also affected by environmental factors, in addition to genetic factors. *H. pylori* is considered a class Ⅰ carcinogen by the World Health Organization and displays carcinogenic effects mediated by poisonous components[27,28]. Our previous studies have shown that the GSTP1 Val/Val genotype with smoking, alcohol consumption, or *H. pylori* IgG (+) could considerably increase AG and GC risk, and the NER SNPs (XPA rs2808668, DDB2 rs326222, rs3781619, rs830083, and XPC rs2607775) had interactive effects with alcohol consumption and smoking on AG or GC risk. In the present study, the cumulative effect was observed to be changed in subgroups with negative *H. pylori* infection status, which could imply an effect modification by *H. pylori* infection. Moreover, AG risk was significantly reduced, while one or two mutation genotypes were present (OR = 0.66 and 0.73, respectively). This suggested that *H. pylori* should be eliminated first for positive patients, which may be beneficial for reducing susceptibility to AG. However, we further analyzed the effect of three-dimensional interactions of the *ERCC5* SNPs (rs2094258 and rs873601)-*GSTP1* rs1695-environmental factors on the risk of AG, but no interaction effect was observed among them in terms of AG risk. This may be because our present sample size was relatively small, and some genotypes were scarce. In addition, there was a significant difference in *H. pylori* infection rates between the case groups and two matched control groups ($P < 0.001$). Although we performed all tests with an adjustment for *H. pylori* infection status except for those stratified by *H. pylori*, it still may be a limitation of the study. Nevertheless, it suggested that environmental factors were indispensable, although they cannot cause cancer or precancerosis alone. Genetic susceptibility may play a vital role in gastric carcinogenesis. Further large-sample and comprehensive study of the function of environmental factors in SNP-SNP interactions of *ERCC5* and *GSTP1* is necessary and may partially remedy probable false-negative results in the study.

The present study has several limitations. First, even if our study included a relatively large sample, prospective studies consisting of larger-scale sample and multicenter surveys are necessary to validate the results of SNP-SNP interaction effects shown here. Second, since we only included one metabolic gene polymorphism (*GSTP1* rs1695) of the GSTs in this study, further studies should involve other functional tagSNPs, such as GSTM1 and/or GSTT1, which should participate in SNP-SNP interactions between the DNA repair gene and xenobiotic metabolism gene pathways. In addition, the functions and mechanisms of the mentioned SNPs of the *ERCC5* gene and *GSTP1* gene pathways were not investigated and will require additional functional and molecular experiments to clarify.

In conclusion, we found for the first time that two pairwise interacting DNA repair gene *ERCC5* SNPs (rs2094258 and rs873601) and metabolic gene GSTP1 rs1695 polymorphism combinations were related to increased or reduced AG risk. Moreover, the results

Table 4 Cumulative effect of the interacting factors of ERCC5 SNPs-GSTP1 rs1696 on atrophic gastritis risk

No. of interacting genotypes	Total population			*H. pylori*-negative subpopulation			*H. pylori*-positive subpopulation		
	Cases/controls	P^1 value	OR (95%CI)	Cases/controls	P^2 value	OR (95%CI)	Cases/controls	P^2 value	OR (95%CI)
ERCC5 rs2094258-GSTP1 rs1695 on AG risk									
0	132/162		1 (Ref.)	57/115		1 (Ref.)	75/47		1 (Ref.)
1	369/310	0.008	1.48 (1.11-1.98)	216/79	0.125	1.35 (0.92-1.97)	216/79	0.017	1.72 (1.10-2.69)
2	133/148	0.782	1.05 (0.74-1.49)	47/106	0.655	0.90 (0.56-1.44)	86/42	0.363	1.270.76-2.14)
		P_{trend} = 0.528			P_{trend} = 0.720			P_{trend} = 0.349	
ERCC5 rs873601-GSTP1 rs1695on AG risk									
0	321/279		1 (Ref.)	138/206		1 (Ref.)	183/73		1 (Ref.)
1	254/286	0.013	0.73 (0.57-0.94)	99/201	0.061	0.73 (0.53-1.02)	155/85	0.090	0.72 (0.49-1.05)
2	59/55	0.670	0.911 (0.60-1.40)	20/45	0.150	0.66 (0.37-1.16)	39/10	0.241	1.57 (0.74-3.31)
		P_{trend} = 0.156			**P_{trend} = 0.043**			P_{trend} = 0.907	

[1]Adjusted by sex, age, and *H. pylori* infection; [2]Adjusted by sex and age. Statistically significant associations were highlighted in bold ($P < 0.05$). CON: Controls; AG: Atrophic gastritis; ERCC5: Excision repair cross complementing group 5; GSTP1: Glutathione S-transferase pi 1.

also demonstrated a significant difference in the cumulative effect in the *H. pylori*-negative subgroup on AG risk. The conclusions inferred from the present study about the effect of interactions between genetic polymorphisms may be conductive to proposing further studies to discover gene-gene interactions between DNA repair genes with xenobiotic metabolic gene pathways in gastric carcinogenesis.

ARTICLE HIGHLIGHTS

Research background

Previous studies suggested that the interactions between various inherited susceptibility genes may affect carcinogenesis in individuals. Single nucleotide polymorphisms (SNPs) are widely applied to the research of tumor incidence and prognostic evaluation.

Research motivation

We aimed to assess gene interactions amongst inherited polymorphisms between DNA repair gene excision repair cross complementing group 5 (*ERCC5*) SNPs and glutathione S-transferase pi1 (*GSTP1*) rs1695 to explore their possibility of predicting gastric cancer (GC) risk and identify combination biomarkers for precancerosis and GC.

Research objectives

The objective was to investigate the impact of interactions of the DNA repair gene *ERCC5* with metabolic gene *GSTP1* on atrophic gastritis (AG) and GC risk.

Research methods

Seven *ERCC5* SNPs (rs1047768, rs2094258, rs2228959, rs4150291, rs4150383, rs751402, and rs873601) and *GSTP1* rs1695 SNP were detected using the Sequenom MassARRAY platform in 450 GC patients, 634 AG cases, and 621 healthy control subjects in a Chinese population.

Research results

Two pairwise combinations (*ERCC5* rs2094258 and rs873601 with *GSTP1* rs1695) influenced AG risk, and the *ERCC5* rs2094258-GSTP1 rs1695 SNP pair demonstrated an antagonistic effect while ERCC5 rs873601-GSTP1 rs1695 shown a synergistic effect on AG risk. When the effect modification of *Helicobacter pylori* (*H. pylori*) infection was evaluated, the cumulative effect of one aforementioned pairs-way interaction (ERCC5 rs873601-GSTP1 rs1695) showed a risk in the case

of negative status of *H. pylori* infection.

Research conclusions

DNA repair gene ERCC5 SNPs (rs2094258 and rs873601) and metabolic gene GSTP1 rs1695 polymorphism combinations were related to an increased or reduced AG risk. Moreover, the results also demonstrated a significant difference in the cumulative effect on AG risk in the *H. pylori*-negative subgroup.

Research perspectives

The interaction effects between genetic polymorphisms may be conductive to proposing further studies to discover gene-gene interactions between DNA repair genes and xenobiotic metabolic genes in gastric carcinogenesis.

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ISSN 1007-9327