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ORIGINAL ARTICLE

Association between *IRS-2* G1057D polymorphism and risk of gastric cancer

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Abstract

AIM: To investigate the relationship between insulin receptor substrate-2 (*IRS-2*) G1057D polymorphism and the risk of gastric cancer (GC) in a Chinese population.

METHODS: A case-control study with 197 GC patients and 156 age- and sex- matched control subjects was conducted. The genotypes of polymorphism were assessed by polymerase chain reaction-restriction fragment length polymorphism.

RESULTS: The genotype frequencies of *IRS-2* G1057D polymorphism in cases were obviously different from those in the control group (P = 0.031). Compared with GG genotype carriers, the risk for GC was significantly higher (adjusted odds ratio = 2.32, 95% CI: 1.03-5.23, P = 0.042) in the individuals with the *IRS-2* DD genotype. Furthermore, stratified analysis was performed based on age, sex, smoking status and residence, but no significant difference between the two groups was found. In addition, no significant association between genotypes and clinicopathological features was observed either.

CONCLUSION: This study demonstrates that *IRS-2* G1057D is involved in susceptibility to GC, although further large-sample studies are still needed.

Key words: Gastric cancer; *Insulin receptor substrate-2*; Polymorphism; Genotype; Case-Control study

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INTRODUCTION

Gastric cancer (GC) remains a major medical challenge and one of the prevalent malignant diseases. Extensive invasion and metastasis are the pivotal factors for its poor prognosis. As shown in epidemiological studies, GC is the fourth most common malignancy and the second most frequent cause of cancer-related death worldwide[1,2]. Moreover, nearly half of GC cases occur

in China alone[3]. Although the cause is largely unknown, GC is thought to result from a combination of multiple environmental factors and the accumulation of specific genetic alterations, including polymorphisms[4-8].

Insulin receptor substrates (IRS) are a family of six (IRS-1 to IRS-6) structurally related cytoplasmic adaptor proteins that integrate and coordinate numerous biologically key extracellular signals within the cell[9-13]. Among the six family members, humans express three members (IRS-1, IRS-2 and IRS-4), while IRS-1 and IRS-2 are widely expressed[10,11,12]. Despite a high level of sequence homology, IRS-1 and IRS-2 mediate distinct cellular functions. IRS-1 controls body growth and peripheral insulin action and IRS-2 regulates body weight control and glucose homeostasis[14,15].

Although IRS proteins do not have intrinsic kinase activity, they act as adaptors and organize signaling complexes to initiate intracellular signaling cascades[14] and function between multiple growth factor receptors possessing tyrosine kinase activity, such as the insulin receptor (IR), Type I insulin-like growth factor receptor (IGF-IR) and a complex network of intracellular signaling molecules containing Src homology 2 domains[16-18]. It is now clear that IRSs are the core signaling molecules of the actions of the IGF-IR signaling[19,20]. In recent years, numerous studies have shown that these signaling adaptors are themselves oncogenic and can induce malignant transformation. Dearth *et al*[14] reported that IRS-2 was able to transform NIH3T3 cells in a foci-formation assay. Also, many studies have shown that both IRS-1 and IRS-2 were overexpressed in hepatocellular carcinoma[21-23]. Yamashita *et al*[24] found that there was a possibility that the silencing of IRS-2 was causally related to development and progression of GC.

IRS-2 was first discovered as an alternative IRS, initially named 4PS, in insulin-stimulated cells derived from *Irs-1*$^{-/-}$ mice[25]. IRS-2 is widely expressed and is the primary mediator of insulin dependent mitogenesis and regulation of glucose metabolism in most cell types[16]. The *IRS-2* gene is located on chromosome 13q34. To date, a number of polymorphisms have been identified in the *IRS-2* gene. Among those, the amino acid substitution Gly1057Asp (GGC-GAC at codon 1057, G1057D rs1805097) was found to be associated with various human diseases. A study conducted by Almind *et al*[26] reported decreased serum insulin and C-peptide concentrations during an oral glucose tolerance test in middle-aged glucose tolerant Danish male subjects carrying the D1057 allele. There were reports about the association of G1057D with type 2 diabetes in Danish[27], Finnish, Chinese, Swedish[26,28] and German[29] populations, but the results were inconsistent. Recent observations also indicated that G1057D polymorphism was associated with endometrial cancer[30], colon cancer[31] and polycystic ovary syndrome[32].

The mechanism by which the nonconservative G1057D variant affects risk of cancer or other diseases is not clear, but a charged amino acid (D) in place of a neutral one (G) in the domain of IRS-2 molecule located in between two putative tyrosine phosphorylation sites (at positions 1042 and 1072) of the protein could produce alterations in downstream signaling through IRS-2[33]. If this variant causes alterations of downstream signaling of IGF-IR signaling which promote GC progression and invasion, it may influence GC susceptibility. Also, to our knowledge, no study has examined the influence of the polymorphism on the risk of GC. Therefore, we conducted a hospital-based case-control study to investigate the potential link between this polymorphism and GC in a Chinese population.

MATERIALS AND METHODS

Study population

One hundred and ninety seven consecutive, unrelated GC patients were recruited at the Nanjing Medical University Affiliated Hospital. The diagnosis of GC was confirmed histologically. Patients with secondary or recurrent tumors were excluded. 156 genetically unrelated cancer-free individuals were selected from the inpatients admitted to the hospital during the same period with no history or diagnosis of any cancer and genetic disease. They were matched with the cases on age (within 5 years) and sex. All subjects were Han nationality and from Jiangsu Province or its surrounding regions. A structured questionnaire was administered by interviewers to collect information on demographic information and personal medical history. Individuals who formerly or currently smoked ≥ 10 cigarettes per day on average for at least 2 years were defined as smokers. Pathological variables were obtained from the medical records of the GC patients. All gastric carcinomas were classified according to the TNM classification criteria of International Union Against Cancer[34]. Differentiation-grade was classified according to World Health Organization classification. The study was approved by the Nanjing Medical University Affiliated Hospital Ethics Committee and informed consent was obtained from each participant.

Genotyping analysis

Genomic DNA was isolated from peripheral blood lymphocytes according to the protocol described in our previous study[35]. The polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay was used to identify the *IRS-2* G1057D genotypes. PCR was done in 20 μL reaction mixtures containing 10 μL 2 × PCR Master mix (Genetime biotechnology, NanJing, China), 0.25 μmol/L each primer (forward 5'-GTCCCC-GTCGTCGTCTCT-3', reverse 5'-CTCGACTCCC GA-CACCTG-3') and 200 ng genomic DNA. The amplification protocol is as follows: initial denaturation at 95℃ for 4 min, followed by 35 cycles of denaturation at 95℃ for 30 s, annealing at 57℃ for 30 s, extension at 72℃ for 30 s and then with a final elongation at 72℃ for 5 min. The 286 bp PCR products were digested by the restriction enzyme *Hae II* (New England BioLabs), 10 units for 1 h at 37℃, followed by electrophoresis on a 3% agarose gel containing ethidium bromide, and bands were then visual-

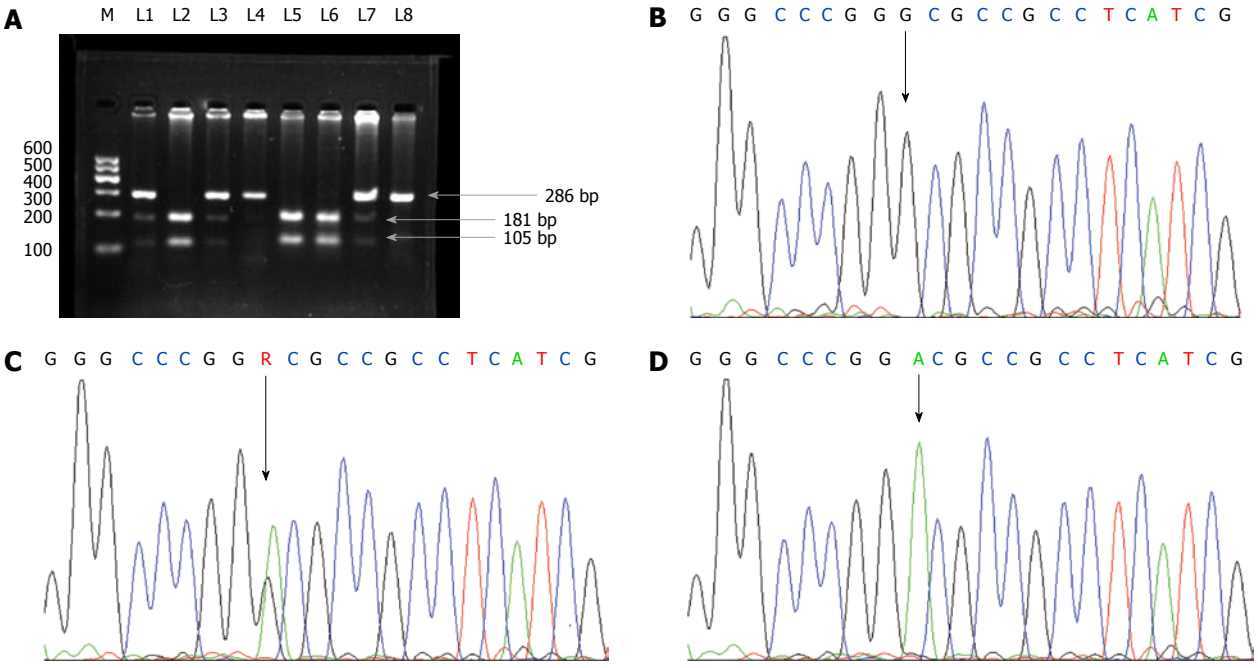

Figure 1 Genotypes of *insulin receptor substrate-2* G1057D confirmed by polymerase chain reaction-restriction fragment length polymorphism assay and direct sequencing. A: Representatives of genotypes by polymerase chain reaction-restriction fragment length polymorphism assay. L4, L8 were identified as DD; L1, L3 and L7 were identified as GD; L2, L5 and L6 were identified as GG; B, C and D: Representatives of GG, GD, DD genotypes by direct DNA sequencing respectively.

ized by ultraviolet transillumination. The genotypes were assessed as follows: The wild-type homozygotes (GG) produced two bands at 105 and 181 bp, while the variant homozygotes (DD) produced one band at 286 bp and the heterozygous (GD) produced three bands at 286, 181 and 105 bp (Figure 1). About 10% of the samples were randomly selected to do the repeated assays and the results were 100% concordant. Genotyping was performed without knowledge of the subject's case and control status. In addition, PCR products of the polymorphism with different genotypes were selected and verified by direct sequencing using ABI 3730 DNA analyzer (Applied Biosystems, Foster City, CA, USA) (Figure 1).

Statistical analysis

All statistical analyses were performed using SPSS 16.0 software (SPSS Inc., Chicago, IL, USA). All of the tests were two-tailed and statistical significance was defined as $P < 0.05$. Quantitative variables departing from the normal distribution, including age and weight, were summarized as median and analyzed by Mann-Whitney rank sum test. Pearson's χ^2 test was used to compare the difference in the distribution of categorical variables and genotype frequencies between cases and controls. The Hardy-Weinberg equilibrium of the *IRS-2* genotypes was analyzed by the goodness-of-fit χ^2 test. Odds ratio (OR) and 95% CI were calculated to evaluate the association between the polymorphism and the risk of GC. Carriers of the wild genotype GG were used as the reference. The crude OR was assessed by the Woolf approximation method and the adjusted OR was computed using the unconditional logistic regression method, with adjustment for age, sex, smoking status, residence, hypertension and diabetes.

Table 1 Demographic information *n* (%)

Characteristics	Cases (*n* = 197)	Controls (*n* = 156)	*P* value
Gender (male)	152 (77.16)	118 (75.64)	0.739
Age[1] (yr)	60 (50-67.5)	58 (47.25-65)	0.197
Weight[1] (kg)	62 (55-70)	67 (60-73.25)	0.001
Hypertension	43 (21.83)	29 (18.83)	0.490
Diabetes	10 (5.08)	14 (9.03)	0.144
Smoking	44 (22.34)	26 (16.67)	0.205
Residence			
Rural	84 (42.64)	70 (45.45)	0.598
Urban	113 (57.36)	84 (54.55)	

[1]Median (25th-75th percentiles).

RESULTS

Demographic information

The demographic characteristics of the participants are listed in Table 1. As expected, there was no significant difference in age and sex distribution between the case and control groups. Moreover, the two groups were similar with respect to smoking status, residence, history of hypertension and diabetes. Nevertheless, compared with controls, GC patients had a lower body weight ($P = 0.001$).

Distributions of the IRS-2 genotype in cases and controls and risk estimates

Data for genotype frequencies and the associations between *IRS-2* G1057D polymorphism and the risk of GC are shown in Table 2. The genotype distributions

Table 2 Distribution of the *IRS-2* genotype in cases and controls and risk estimates *n* (%)

IRS-2 genotype	Cases[1]	Controls[1]	Crude OR (95% CI)	*P* value	Adjusted OR[2] (95% CI)	*P* value
Overall	197	156				
GG	69 (35.02)	64 (41.03)	1.00		1.00	
GD	98 (49.75)	82 (52.56)	1.11 (0.71-1.74)	0.653	0.96 (0.60-1.53)	0.864
DD	30 (15.23)	10 (6.41)	2.78 (1.26-6.15)	0.011	2.32 (1.03-5.23)	0.042
GD + DD	128 (64.98)	92 (58.97)	1.29 (0.84-1.99)	0.248	1.11 (0.71-1.75)	0.637
G allele	236 (59.90)	210 (67.31)	1.00			
D allele	158 (40.10)	102 (32.69)	1.38 (1.01-1.88)	0.043		

[1]Distribution of the insulin receptor substrate-2 (*IRS-2*) genotype in cases and controls were in Hardy-Weinberg equilibrium ($P = 0.204$, $P = 0.425$, respectively); [2]Adjusted for age, sex, smoking status, residence, hypertension and diabetes. OR: Odds ratio.

Table 3 Stratified analyses for variant *IRS-2* genotypes in cases and controls *n* (%)

Variable	(GD + DD)/GG		Crude OR (95% CI)	*P* value	Adjusted OR[1] (95% CI)	*P* value
	Cases	Controls				
Age (median) (yr)						
≤ 58	53 (26.9)/40 (20.3)	46 (29.5)/39 (25.0)	1.29 (0.71-2.33)	0.412	1.10 (0.59-2.05)	0.762
> 58	69 (35.0)/35 (17.8)	46 (29.5)/25 (16.0)	1.22 (0.64-2.32)	0.538	1.15 (0.60-2.23)	0.674
Sex						
Females	28 (14.2)/17 (8.6)	21 (13.5)/17 (10.9)	1.33 (0.55-3.21)	0.521	1.13 (0.44-2.87)	0.800
Males	94 (47.7)/58 (29.4)	71 (45.5)/47 (30.1)	1.27 (0.77-2.10)	0.342	1.12 (0.67-1.87)	0.668
Smoking status						
Smokers	32 (16.2)/12 (6.1)	16 (10.4)/10 (6.5)	1.88 (0.66-5.33)	0.238	1.52 (0.49-4.70)	0.467
Non-smokers	90 (45.7)/63 (32.0)	75 (48.7)/53 (34.4)	1.16 (0.72-1.87)	0.550	1.00 (0.61-1.65)	0.990
Residence						
Urban	73 (37.1)/40 (20.3)	51 (33.1)/33 (21.4)	1.44 (0.80-2.61)	0.226	1.30 (0.70-2.42)	0.406
Rural	49 (24.9)/35 (17.8)	41 (26.6)/29 (18.8)	1.04 (0.55-1.98)	0.905	0.89 (0.46-1.75)	0.743

[1]Adjusted for age, sex, smoking status, residence, hypertension and diabetes. OR: Odds ratio.

complied well with Hardy-Weinberg equilibrium in cases and controls ($P = 0.204$, $P = 0.425$, respectively). The distribution of the *IRS-2* genotype was significantly different between GC cases and controls ($P = 0.031$). Moreover, the frequency of D allele was significantly higher in GC patients than in control subjects (40.10% *vs* 32.69%, $P = 0.043$). With the wild genotype GG as reference, we found that the DD genotype was associated with an increased risk of GC (adjusted OR = 2.32; 95% CI: 1.03-5.23, $P = 0.042$). The *IRS-2* D allele elevated GC risk compared with G allele, the relative risk for the *IRS-2* D allele was 1.38 (adjusted OR = 1.38; 95% CI: 1.01-1.88, $P = 0.043$) for the GC patients compared with population controls.

Stratified analyses of the polymorphism and GC risk

To further clarify the relationship between *IRS-2* variant and the GC risk, we performed stratified analysis. Table 3 presents the results of stratified analyses by the median age of controls (58 years), sex, smoking status and residence with the *IRS-2* variant genotypes. No statistically significant difference was observed in younger subjects (age ≤ 58) and older subjects (age > 58) in the association between the polymorphism and susceptibility to GC (adjusted OR = 1.10, 95% CI: 0.59-2.05 and adjusted OR = 1.15, 95% CI: 0.60-2.23, respectively). Analogously, we did not note statistically significant associations in the stratified analyses of sex, smoking status and residence.

Variant genotypes and clinicopathological characteristics of GC

Finally, we also estimated the correlations of the *IRS-2* variant genotypes with clinicopathological features of GC, including tumor differentiation, depth of tumor infiltration, lymph node status and tumor location. As shown in Table 4, no statistically significant association was found.

DISCUSSION

The genetics and heredity of complex human traits have been studied for over a century. Over the last decade, genetic studies have identified numerous associations between single nucleotide polymorphism alleles in the human genome and important human diseases. Studies about genetic polymorphism have proven to be powerful and efficient in identifying genetic variants associated with various diseases. In the present study, for the first time we investigated the role of *IRS-2* gene G1057D polymorphism in GC susceptibility in a Chinese population and we found that the DD genotype conferred an increased risk of GC.

Involving the two important cancer-related pathways (MAPK/ERK, PI3K/Akt), IGF-IR was documented

Table 4 Associations between variant *IRS-2* genotypes and clinicopathological characteristics of gastric cancer

Variable	GD + DD	GG	Crude OR (95% CI)	*P* value	Adjusted OR[1] (95% CI)	*P* value
Tumor differentiation						
Well	15	6	1		1	
Moderate	80	35	0.91 (0.33-2.55)	0.864	0.95 (0.33-2.76)	0.921
Poor	29	25	0.46 (0.16-1.38)	0.166	0.38 (0.11-1.35)	0.135
Depth of tumor infiltration						
T1	21	14	1		1	
T2	20	5	2.67 (0.81-8.77)	0.106	2.70 (0.70-10.47)	0.150
T3	60	26	1.54 (0.68-3.49)	0.302	1.46 (0.60-3.52)	0.401
T4	24	22	0.73 (0.30-1.77)	0.483	0.73 (0.29-1.86)	0.507
Lymph node metastasis						
Negative	47	23	1		1	
Positive	78	43	0.89 (0.48-1.65)	0.708	0.94 (0.49-1.77)	0.837
Localization						
Cardia	27	15	1		1	
Non-cardia	101	54	1.04 (0.51-2.12)	0.916	1.08 (0.51-2.29)	0.838

[1]Adjusted for age, sex, smoking status, residence, hypertension and diabetes. OR: Odds ratio.

to promote tumor growth, progression and invasion. Increased expression levels of both IGF and IGF-IR are found in gastrointestinal carcinomas[36,37]. Exogenous IGFs promote the proliferation of GC cells and the blocking of IGF-IR inhibits tumor development[36,38-40]. As the major downstream effector of the IGFs, IRS-2 plays a critical role in determining the cellular response to IGF stimulation and is proven to be one of the key factors accelerating tumor progression and metastasis in various types of cancers. For example, IRS-2 dependent signaling promotes cell motility and invasion in neuroblastoma and mesothelioma cells[41-43]. The up-regulation of IRS-2 expression in pancreatic and hepatocellular carcinoma suggests a positive contribution of this IRS family member to tumor progression[23,44]. Another study conducted by Yamashita *et al*[24] found that there was a possibility that the silencing of IRS-2 was causally related to the development and progression of GCs.

An amino acid substitution of Gly to Asp change at codon 1057 has been associated with insulin sensitivity and may subtly mediate interaction with downstream signaling molecules[45]. The variant lies between two putative sites of tyrosine phosphorylation (at position 1042 and 1072) and a non-conservative amino acid substitution in this domain may result in a subtle alteration of the affinity between IRS-2 and downstream signaling elements, which may change the interaction with downstream signaling molecule[33]. However, there is the possibility that this polymorphism is not functional but may be in linkage disequilibrium with a currently unrecognized functional polymorphism. Based on these previous observations, it would therefore be plausible to expect that the *IRS-2* G1057D polymorphism may be associated with GC.

Several epidemiological studies have investigated the association between the G1057D polymorphism and various diseases. There were reports about the association of the G1057D with type 2 diabetes in Danish[27], German[29] Finnish, Chinese and Swedish[26,28] populations, but the results were inconsistent. In a large case-control study in Asian Indians, Bodhini *et al*[46] found that DD genotype increased susceptibility to type 2 diabetes by interacting with obesity (P = 0.002). Another study conducted by Slattery *et al*[31] found that *IRS-2* G1057D heterozygote GD genotype significantly reduced the risk of colon cancer (OR = 0.8, 95% CI: 0.6-0.9). Recently, Cayan *et al*[30] reported the risk for endometrial cancer was 4.87 times higher in the individuals with the *IRS-2* DD genotype compared to the GG genotype (OR = 4.87, 95% CI: 1.74-13.63).

To further investigate the association between *IRS-2* G1057D polymorphism and the risk of GC, we conducted this hospital-based case-control study in a Chinese population. The frequency of the variant D allele was higher in GC patients than in control subjects. We also found that the DD genotypes conferred a 132% increased risk of developing GC in this Chinese population. The allele frequencies in controls was in the range of those in previous reports[31,46]. It is probable that the discrepancies in sample size, ethnic background, selection of cases and controls, and study design may partly explain the differences observed in this study and others.

We then performed stratification analyses by age, sex, smoking status and residence, but no statistically significant difference was observed. Although several studies have suggested that IRS-2 indicate a major role in cell motility and invasion[41-43], the current study found no significant correlation between the *IRS-2* G1057D polymorphism and tumor differentiation, depth of tumor infiltration, lymph node status and tumor location. However, since only a few studies have addressed the impact of the *IRS-2* gene G1057D polymorphism on the clinical features of solid tumors, and the sample size of our study might not be large enough for subgroup analyses, further studies are warranted to clarify the association between the *IRS-2* G1057D polymorphism and the clinicopathological features or the prognosis of GC.

Several limitations in our study need to be addressed. First of all, although this was a population based case–

control study, selection bias could not be avoided. Nevertheless, the *IRS-2* G1057D polymorphism variant allele frequency in control subjects was in the range of those in previous reports[31,46] and the genotype distribution of controls was in Hardy-Weinberg equilibrium. Secondly, the sample size of our study might not be large enough, especially for subgroup analyses. However, our preliminary data provides valuable guidance to future larger sample size studies in this area. Thirdly, *Helicobacter pylori* (*H. pylori*) infection is now established as a critical event in the development of GC but in our study, not enough information on *H. pylori* status was provided because it was unethical to do *H. pylori* tests in every subject.

In conclusion, our data suggests that the *IRS-2* G1057D polymorphism is associated with an increased risk of GC in the Chinese population. Further studies with a larger sample size are warranted to confirm these initial observations and extend the results.

COMMENTS

Background

Insulin receptor substrate-2 (IRS-2), an important member of IRS proteins, has been demonstrated play a crucial role in tumor growth, progression and invasion. *IRS-2* G1057D polymorphism has been implicated in a range of human diseases and recent studies have indicated that the polymorphism is associated with cancer risk.

Research frontiers

Using a polymerase chain reaction-restriction fragment length polymorphism method, this study explored the relationship between *IRS-2* G1057D polymorphism and gastric cancer (GC) risk.

Innovations and breakthroughs

IRS-2 G1057D polymorphism is associated with the elevated risk of GC in the Chinese population.

Applications

It is seen from this study that *IRS-2* G1057D polymorphism contributes to susceptibility to GC, which is meaningful for early diagnosis, prevention and individual-based treatment of GC.

Terminology

IRS-2 is an important member of IRS proteins that function as adaptors and organize signaling complexes to initiate intracellular signaling cascades. Single nucleotide polymorphisms are the most common type of sequence differences between alleles, which can be used as simple genetic markers.

Peer review

This is an interesting paper on the association between the *IRS-2* G1057D polymorphism and GC risk in a small cohort of patients with GC and controls. A borderline statistically significant relationship was reported.

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