

# Contribution of Interleukin-4 Promoter Genotypes to Gastric Cancer Risk in Taiwan

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## Abstract

**Background/Aim:** Gastric adenocarcinoma (GACA) remains a major global health concern, particularly in Asia, due to its poor prognosis and complex etiology. The interaction between genetic factors and environmental exposures, such as smoking, alcohol consumption, and *Helicobacter pylori* (HP) infection, plays a crucial role in GACA risk.

**Materials and Methods:** Interleukin-4 (*IL-4*) gene promoter polymorphic rs2243248 (T-1099G), rs2243250 (C-589T), and rs2070874 (C-33T) genotypes were analyzed in 161 GACA patients and 483 non-cancer control subjects from a Taiwanese population by PCR-RFLP methodology. The gene-environment interactions were evaluated by stratified analysis.

**Results:** Genotypic analysis revealed no significant association between *IL-4* polymorphisms and GACA risk (all  $p > 0.05$ ). However, interactions between *IL-4* C-589T and C-33T genotypes with HP infection were observed ( $p = 0.0114$  and  $0.0009$ ). In addition, T-1099G and C-33T genotypes interacted with alcohol consumption ( $p = 0.0346$  and  $0.0295$ ).

*continued*

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T-1099G and C-589T variant genotypes were associated with an increased risk of metastasis ( $p=0.0313$  and  $0.0118$ ). Moreover, *IL-4* polymorphisms did not correlate with smoking behavior in influencing GACA susceptibility.

**Conclusion:** While *IL-4* polymorphisms alone are not predictors of GACA risk, their interactions with environmental factors may contribute to the progression of the disease. Our study emphasizes the need for further research to explore the clinical implications of *IL-4* genetic variants in diverse populations and their role in GACA progression.

**Keywords:** Cancer risk, gastric cancer, genotype, interleukin-4, single nucleotide polymorphism, Taiwan.

## Introduction

Gastric cancer (GACA) is the fifth most prevalent malignancy and the third leading cause of cancer-related deaths globally (1, 2). Despite significant advances in treatment, GACA remains a major global public health concern due to its complex pathogenesis, poor prognosis, and lack of reliable predictive biomarkers (3, 4). The incidence and mortality rates of GACA are particularly high in Asia, with Eastern Asia alone accounting for over 60% of the global cases (5). Identified risk factors include *Helicobacter pylori* (HP) infection (6), smoking (7, 8), alcohol consumption (9, 10), obesity (11, 12), and high salt intake (13, 14). Moreover, the interaction between environmental risk factors and genetic predisposition plays a critical, albeit not yet fully understood, role in the multifactorial etiology of GACA (15-18). Despite this, the identification of genetic markers for diagnosing and assessing GACA susceptibility remains largely underexplored.

Interleukine-4 (IL-4) is a four-helix bundle glycoprotein, which is primarily generated by activated T helper 2 (Th2) cells, eosinophils, and macrophages, and has essential roles as a mediator and modulator of immunological responses (19, 20). It is mainly produced along with other interleukins (ILs), such as IL-5, IL-10 and IL-13, which are mainly responsible for the promotion of humoral immunity (21, 22). IL-4, like other ILs, is a cytokine glycoprotein that mediates immune responses by binding to specific cell surface receptors (23). Through its interactions with a variety of receptors, including TLRs, IL-4 contributes to anti-

inflammatory responses (24). IL-4 inhibited proliferation of HTB-135 GACA cells by down-regulating G0-G1 cell cycle nuclear-regulating factors, including retinoblastoma gene product, c-myc, and cyclin D1 (25). IL-4 could cause G1 phase arrest in the CRL 1739 GACA cell line (26). IL-4 can also inhibit the growth of GACA cells and this effect is positively correlated with the level of IL-4R expression (27).

The *IL-4* gene is located on human chromosome 5q31 and encodes a protein consisting of 153 amino acids. Its structure includes a signal peptide (amino acids 1-24) and a mature peptide (amino acids 25-153) (28). Chronic inflammatory conditions are characterized by persistent cytokine expression and the recruitment of immune cells, often driven by genetic variations in humans. These genetic variations, particularly single-nucleotide polymorphisms (SNPs), are believed to contribute to phenotypic differences among individuals. In recent years, numerous studies have focused on investigating the associations between *IL-4* genotypes and GACA susceptibility worldwide; however, the results remain inconsistent (29-39).

This study aimed at achieving two primary objectives. The first was to characterize the genotypic distribution of *IL-4* promoter rs2243248 (T-1099G), rs2243250 (C-589T), and rs2070874 (C-33T) (Figure 1) in a well-defined Taiwanese cohort consisting of 161 GACA patients and 483 cancer-free controls. The second objective was to investigate how *IL-4* genotypes interact with age, sex, body mass index (BMI), smoking, alcohol consumption, HP infection, and metastasis status in influencing GACA susceptibility.

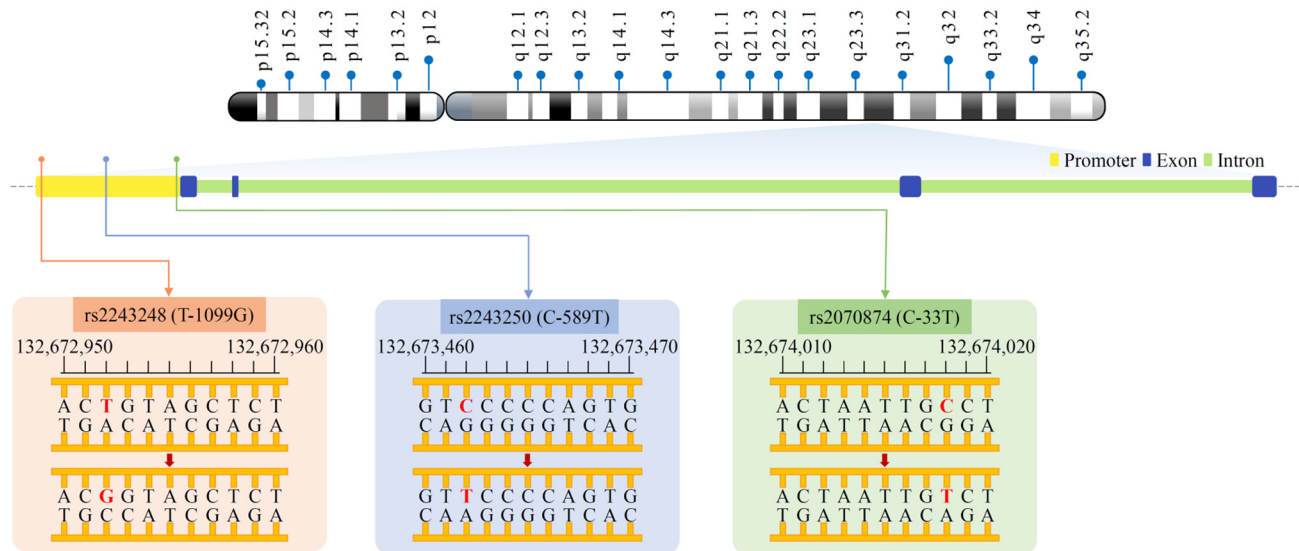


Figure 1. Physical map of *IL-4* T-1099G (rs2243248), C-589T (rs2243250), and C-33T (rs2070874) polymorphic sites.

## Materials and Methods

**Recruitment of GACA cases and non-cancer controls.** A hospital-based cohort comprising 161 GACA patients was recruited from the general surgery outpatient clinics at China Medical University Hospital (CMUH), as previously documented (40, 41). Each participant voluntarily provided a 5 ml peripheral blood sample for genetic analysis. For comparison, a control group of 483 age- and sex-matched healthy, cancer-free individuals was selected from the CMUH Health Examination Cohort database. The study design and protocols were reviewed and approved by the Institutional Review Board (IRB) of CMUH (IRB number: DMR100-IRB-107). Written informed consent was obtained from all participants with the assistance from the colleagues of Tissue Bank of China Medical University Hospital. Table I summarizes the demographic characteristics of the study population, including age, sex, body mass index (BMI), smoking and alcohol consumption habits, *HP* infection status, and histological classifications.

**Methodology of *IL-4* genotype identification.** Genomic DNA was extracted from peripheral blood leukocytes and

processed according to previously established protocols (42, 43). Polymerase chain reaction (PCR) amplification was carried out under standard cycling conditions: an initial denaturation at 94°C for 5 min, followed by 35 cycles of 94°C for 30 s, 55°C for 30 s, and 72°C for 30 s, with a final extension at 72°C for 10 min. The primer sequences used for *IL-4* genotyping were as follows: forward 5'-GGTCCTTACGTTCACTGCTG-3' and reverse 5'-GGC TCAAGTGCTCCTCTAC-3' for *IL-4* T-1099G. Forward 5'-TAAACTTGGGAGAACATGGT-3' and reverse 5'-TGG GGAAAGATAGAGTAATA-3' for *IL-4* C-589T. Forward 5'-CTGGAAGAGAGGTGCTGATT-3' and reverse 5'-ACTC ACCTTCTGCTCTGTGA-3' for *IL-4* C-33T. Genotyping was performed using PCR-restriction fragment length polymorphism (PCR-RFLP) analysis. The PCR products for *IL-4* rs2243248, rs2243250, and rs2070874 were digested with *SfcI*, *Avall*, and *BsmAI*, respectively. Digested products were resolved via 3% agarose gel electrophoresis at 100V for 30 min and subsequently visualized for genotype determination. The PCR-RFLP procedure achieved a 100% success rate. All genotypic analyses were conducted independently and in a blinded manner by two researchers.

Table I. Selected characteristics of the control and gastric cancer groups.

Character	GACA Cases (n=161)	Controls (n=483)	p-Value <sup>a</sup>
Age (SD)	53.7 (12.4)	52.0 (8.6)	0.3519
Gender (female/male)	72/89	215/267	1.0000
BMI average (SD)	25.4 (2.7)	25.3 (1.9)	0.5015
Cigarette consume			
Non-smokers	102 (63.4)	400 (82.8)	
Smokers (%)	59 (36.6)	83 (17.2)	0.0001*
Heavy smokers (%) <sup>c</sup>	18 (11.2)	14 (2.9)	0.0001*
Alcohol consume			
Non-drinkers (%)	106 (65.8)	382 (79.1)	
Drinkers (%)	55 (34.2)	101 (20.9)	0.0010*
Heavy drinkers (%) <sup>b</sup>	20 (12.4)	19 (3.9)	0.0001*
H. pylori infection			
Non-infectors (%)	49 (30.5)	256 (53.0)	
Infectors (%)	112 (69.5)	227 (47.0)	0.0001*
Tumor location			
Upper (%)	23 (14.2)		
Middle (%)	69 (42.9)		
Lower (%)	69 (42.9)		
Distant metastasis			
No (%)	70 (43.5)		
Yes (%)	91 (56.5)		

GACA: Gastric cancer; BMI: Body mass index. <sup>a</sup>p-value based on chi-square test; <sup>b</sup>Drunk alcohol more than twice weekly or consumed more than 100 ml per day for at least half year; <sup>c</sup>More than one pack per day for at least half year. \*Statistically significant.

**Statistical analyses.** To ensure that the control subjects were representative of the Taiwanese population and to minimize potential genotyping errors, the genotypic frequencies of *IL-4* polymorphisms in the healthy control group were assessed for compliance with Hardy-Weinberg equilibrium (HWE) using a goodness-of-fit test. Additionally, Pearson's chi-square test was employed to analyze the distribution of *IL-4* polymorphic genotypes across different subgroups. The associations between *IL-4* genotypes and GACA risk were evaluated by calculating odds ratios (ORs) with corresponding 95% confidence intervals (CIs). A p-value of <0.05 was considered statistically significant.

## Results

Table I summarizes the demographic characteristics of 161 GACA patients and 483 non-cancer control subjects.

Since the case and control groups were matched for age and sex, no significant differences were observed in age ( $p=0.3519$ ) or sex distribution ( $p=1.0000$ ). However, significant disparities were noted in smoking habits, alcohol consumption, and *HP* infection status between GACA patients and controls (all  $p<0.0001$ ), suggesting these factors as potential risk indicators for GACA in the Taiwanese population. Regarding tumor localization, GACA cases exhibited tumors in the upper (14.2%), middle (42.9%), and lower (42.9%) regions of the stomach. Additionally, distant metastasis was identified in 91 (56.5%) of the GACA patients (Table I).

The genotypic distributions of the *IL-4* promoter polymorphisms T-1099G (rs2243248), C-589T (rs2243250), and C-33T (rs2070874) among the GACA cases and controls are shown in Table II. First, the genotypic distributions of 1099G, C-589T and C-33T among non-cancer control subjects fitted well with HWE (all  $p_{HWE}>0.05$ , Table II). Second, there was no association between the genotypes of T-1099G, C-589T or C-33T and GACA susceptibility in the Taiwanese cohort (all  $p$  for trend and  $p$ -values were larger than 0.05) (Table II). The combined heterozygous and homozygous variant genotypes of T-1099G, C-589T or C-33T were not associated with any altered GACA risk (all  $p$ -values were larger than 0.05, Table II).

To further confirm these findings based on the genotypic frequency distribution in Table II, the allelic frequency distribution analysis for *IL-4* T-1099G, C-589T and C-33T was also conducted and the results are presented in Table III. In support, none of the variant alleles at *IL-4* T-1099G, C-589T or C-33T was significantly associated with GACA risk (all  $p$ -values were larger than 0.05).

Overall, the findings presented in Table II and Table III support the preliminary conclusion that none of the *IL-4* T-1099G, C-589T or C-33T genotypes can serve as reliable predictors of GACA diagnostic risk.

We have further examined the interactions between *IL-4* T-1099G, C-589T and C-33T genotypes and various demographic, lifestyle, and clinical factors to assess their

Table II. Associations between interleukin-4 genotypes and gastric cancer risk.

Polymorphic cite	Genotype	Cases	Controls	<i>p</i> -Value	OR (95%CI)
rs2243248 (T-1099G)	TT	139 (86.3%)	412 (85.3%)		1.00 (Ref)
	GT	20 (12.4%)	67 (13.9%)	0.7526	0.88 (0.52-1.51)
	GG	2 (1.3%)	4 (0.8%)	0.6460	1.48 (0.27-8.18)
	GT+GG	22 (13.7%)	71 (14.7%)	0.8460	0.91 (0.55-1.54)
<i>P</i> <sub>trend</sub>				0.8085	
<i>P</i> <sub>HWE</sub>				0.4892	
rs2243250 (C-589T)	TT	104 (64.6)	324 (67.1)		1.00 (Ref)
	CT	51 (31.7)	145 (30.0)	0.7173	1.10 (0.74-1.62)
	CC	6 (3.7)	14 (2.9)	0.7541	1.34 (0.50-3.56)
	CT+CC	57 (35.4%)	159 (33.0%)	0.6299	1.12 (0.77-1.62)
<i>P</i> <sub>trend</sub>				0.7836	
<i>P</i> <sub>HWE</sub>				0.6444	
rs2070874 (C-33T)	CC	100 (62.1)	317 (65.6)		1.00 (Ref)
	CT	54 (33.5)	151 (31.3)	0.5876	1.13 (0.77-1.66)
	TT	7 (4.4)	15 (3.1)	0.5621	1.48 (0.59-3.73)
	CT+TT	61 (37.9%)	166 (34.4%)	0.4750	1.16 (0.80-1.69)
<i>P</i> <sub>trend</sub>				0.6147	
<i>P</i> <sub>HWE</sub>				0.5587	

OR: Odds ratio; CI: confidence interval; Ref: reference; *p*-Values were calculated via Chi-square with Yates' correction; ( $n \geq 5$ ) or Fisher's exact tests ( $n < 5$ ); *P*<sub>HWE</sub>: *p*-Value for Hardy-Weinberg Equilibrium; *P*<sub>trend</sub>: *p*-Value for trend analysis.

Table III. Distributions of interleukin-4 allelic frequencies among the investigated gastric cancer patients and non-cancer control subjects.

Allelic pattern	Cases	Controls	<i>p</i> -Value	OR (95%CI)
rs2243248				
T-1099G				
T	298 (92.5%)	891 (92.2%)		1.00 (Ref)
G	24 (7.5%)	75 (7.8%)	0.9518	0.96 (0.59-1.54)
rs2243250				
C-589T				
T	259 (80.4%)	793 (82.1%)		1.00 (Ref)
C	63 (19.6%)	173 (17.9%)	0.5604	1.12 (0.81-1.54)
rs2070874				
C-33T				
C	254 (78.9%)	785 (81.3%)		1.00 (Ref)
T	68 (21.1%)	181 (18.7%)	0.3923	1.16 (0.85-1.59)

OR: Odds ratio; CI: confidence interval; Ref: reference; *p*-Value was calculated by Chi-square with Yates' correction.

combined impact on GACA risk (Table IV, Table V, Table VI). The results showed that *IL-4* T-1099G genotypes interact with BMI ( $p=0.0091$ ) and alcohol consumption ( $p=0.0346$ ) to influence the risk of GACA (Table IV). Particularly, the genotypic frequencies of *IL-4* T-1099G GT and GG genotypes were significantly higher among ever drinkers than never drinkers (18.2% and 3.6% versus 9.4% and 0%, Table IV). In addition, *IL-4* T-1099G GT and

GG genotypes were significantly more frequent among GACA patients with metastasis compared to those without (17.6% and 2.2% versus 5.6% and 0%,  $p=0.0313$ , Table IV).

Regarding *IL-4* C-589T, the results showed that its genotypes interact with *HP* infection ( $p=0.0114$ ) to increase the risk of GACA (Table V). Particularly, the genotypic frequencies of *IL-4* C-589T CT and CC genotypes

Table IV. Combinative effects of interleukin-4 rs2243248 (T-1099G) genotype with demographic and clinical features on gastric cancer risk.

Characteristic	Subgroup	Cases, n	Interleukin-4 T-1099G genotype, n (%)			p-Value <sup>a</sup>
			TT	GT	GG	
Age	≤50 Years	73	64 (87.7)	8 (11.0)	1 (1.3)	0.8714
	>50 Years	88	75 (85.2)	12 (13.6)	1 (1.2)	
Sex	Male	72	60 (83.3)	11 (15.3)	1 (1.4)	0.6025
	Female	89	79 (88.8)	9 (10.1)	1 (1.1)	
BMI	≤25 kg/m <sup>2</sup>	62	60 (38.7)	2 (41.9)	0 (0.0)	0.0091*
	>25 kg/m <sup>2</sup>	99	79 (79.8)	18 (18.2)	2 (2.0)	
Cigarette smoker	Never	102	92 (90.2)	10 (9.8)	0 (0.0)	0.0648
	Ever	59	47 (79.7)	10 (16.9)	2 (3.4)	
Alcohol drinker	Never	106	96 (90.6)	10 (9.4)	0 (0.0)	0.0346*
	Ever	55	43 (78.2)	10 (18.2)	2 (3.6)	
<i>H. pylori</i> infection	Negative	49	45 (91.8)	4 (8.2)	0 (0.0)	0.3412
	Positive	112	94 (83.9)	16 (14.3)	2 (1.8)	
Metastasis	Negative	70	66 (94.3)	4 (5.6)	0 (0.0)	0.0313*
	Positive	91	73 (80.2)	16 (17.6)	2 (2.2)	

BMI: Body mass index. <sup>a</sup>Based on Chi-square with Fisher's exact test (any n<5); \*significant p-values (p<0.05).

Table V. Combinative effects of interleukin-4 rs2243250 (C-589T) genotype with demographic and clinical features on gastric cancer risk.

Characteristic	Subgroup	Patients, n	Interleukin-4 C-589T genotype, n (%)			p-Value <sup>a</sup>
			TT	CT	CC	
Age	≤50 Years	73	50 (68.5)	22 (30.1)	1 (1.4)	0.3005
	>50 Years	88	54 (61.4)	29 (33.0)	5 (5.7)	
Sex	Male	72	49 (68.0)	21 (29.2)	2 (2.8)	0.6653
	Female	89	55 (61.8)	30 (33.7)	4 (4.5)	
BMI	≤25 kg/m <sup>2</sup>	62	45 (72.6)	15 (24.2)	2 (3.2)	0.2410
	>25 kg/m <sup>2</sup>	99	59 (59.6)	36 (36.4)	4 (4.0)	
Cigarette smoker	Never	102	69 (67.6)	31 (30.4)	2 (2.0)	0.2375
	Ever	59	35 (59.3)	20 (33.9)	4 (6.8)	
Alcohol drinker	Never	106	71 (67.0)	32 (30.2)	3 (2.8)	0.5601
	Ever	55	33 (60.0)	19 (34.5)	3 (5.5)	
<i>H. pylori</i> infection	Negative	49	40 (81.6)	8 (16.3)	1 (2.1)	0.0114*
	Positive	112	64 (57.1)	43 (38.4)	5 (4.5)	
Metastasis	Negative	70	54 (77.2)	15 (21.4)	1 (1.4)	0.0118*
	Positive	91	50 (54.9)	36 (39.6)	5 (5.5)	

BMI: Body mass index. <sup>a</sup>Based on Chi-square with Yates' correction (all n≥5) or Fisher's exact test (any n<5); \*significant p-values (p<0.05).

were significantly higher among individuals with a history of HP infection compared to those without (38.4% and 4.5% versus 16.3% and 2.1%, Table V). Similar to those of *IL-4* T-1099G, *IL-4* C-589T CT and CC genotypes were significantly higher among those GACA patients with metastasis than those without (39.6% and 5.5% versus 21.4% and 1.4%, p=0.0118, Table V).

As for *IL-4* C-33T, the results showed that its genotypes interact with alcohol consumption (p=0.0295) and HP infection (p=0.0009) to increase the risk of GACA (Table VI). For the former factor, the genotypic frequencies of *IL-4* C-33T CT and TT genotypes were notably higher among ever drinkers than never drinkers (40.0% and 9.1% versus 30.2% and 1.9%, Table VI). For the later factor, the

Table VI. Combinative effects of interleukin-4 rs2070874 (C-33T) genotype with demographic and clinical features on gastric cancer risk.

Characteristic	Subgroup	Patients, n	Interleukin-4 C-33T genotype, n (%)			p-Value <sup>a</sup>
			CC	CT	TT	
Age	≤50 Years	73	51 (69.9)	20 (27.4)	2 (2.7)	0.1662
	>50 Years	88	49 (55.7)	34 (38.6)	5 (5.7)	
Sex	Male	72	48 (66.7)	22 (30.5)	2 (2.8)	0.4678
	Female	89	52 (58.4)	32 (36.0)	5 (5.6)	
BMI	≤25 kg/m <sup>2</sup>	62	45 (72.6)	14 (22.6)	3 (4.8)	0.0657
	>25 kg/m <sup>2</sup>	99	55 (55.6)	40 (40.4)	4 (4.1)	
Cigarette smoker	Never	102	67 (65.7)	32 (31.4)	3 (2.9)	0.3280
	Ever	59	33 (55.9)	22 (37.3)	4 (6.8)	
Alcohol drinker	Never	106	72 (67.9)	32 (30.2)	2 (1.9)	0.0295*
	Ever	55	28 (50.9)	22 (40.0)	5 (9.1)	
<i>H. pylori</i> infection	Negative	49	41 (83.7)	7 (14.3)	1 (2.0)	0.0009*
	Positive	112	59 (52.7)	47 (42.0)	6 (5.3)	
Metastasis	Negative	70	50 (71.4)	18 (25.7)	2 (2.9)	0.0990
	Positive	91	50 (54.9)	36 (39.6)	5 (5.5)	

BMI: Body mass index. <sup>a</sup>Based on Chi-square with Yates' correction (all n≥5) or Fisher's exact test (any n<5); \*significant p-values (p<0.05).

genotypic frequencies of *IL-4* C-33T CT and TT genotypes were higher among HP ever infectors than never infectors (42.0% and 5.3% versus 14.3% and 2.0%, Table VI).

## Discussion

Clinically, *IL-4* expression is up-regulated in GACA patients. Gabitass and his colleagues reported significantly higher plasma *IL-4* levels in 25 GACA patients compared to 54 healthy controls (44). Similarly, Cárdenas and his colleagues observed elevated serum *IL-4* levels in 17 GACA patients relative to 30 healthy individuals (45). Furthermore, Diaz Orea *et al.* analyzed 30 GACA biopsy samples *via* immunohistochemistry and found significantly higher *IL-4* expression in early-stage (I and II) compared to late-stage (III and IV) tumors, suggesting a potential growth-inhibitory role of *IL-4* in GACA progression (46).

Given the significant differences observed in *IL-4* protein expression between GACA patients and healthy individuals, considerable scientific interest has been directed toward investigating *IL-4* SNPs as potential genetic biomarkers for GACA. Among the three *IL-4* polymorphic loci examined in this study (T-1099G, C-589T, and C-33T), the C-589T polymorphism has garnered the

most research attention, as it has been reported to influence *IL-4* secretion capacity (47). Specifically, the TT genotype has been associated with reduced *IL-4* expression (48). The earliest investigation of *IL-4* C-589T in relation to GACA risk was conducted by El-Omary's team in 2003, analyzing 314 GACA cases and 210 cancer-free controls in the United States (29). Their findings indicated no significant association between *IL-4* C-589T genotypes and GACA risk. In the same year, Wu and his colleagues conducted a study in China with 220 GACA patients and 210 healthy controls, yielding similar negative results (30). However, both studies lacked rigorous adherence to HWE in their control cohorts, potentially affecting the reliability of their findings. Subsequently, in 2005, Lai and his colleagues performed a study in Taiwan with a smaller cohort (123 GACA cases and 162 controls), ensuring compliance with HWE. Despite this methodological improvement, their results also failed to reveal a significant association (31). In 2007, Garcia-Gonzalez *et al.* expanded the investigation to a Spanish cohort, analyzing 404 GACA cases and 404 controls, and similarly reported no significant correlation (32). In 2008, Crusius and his colleagues conducted a study on a mixed European cohort comprising 242 GACA

cases and 1,154 controls from 10 countries, reinforcing the absence of association (33). Both Garcia-Gonzalez and Crusius' studies were notable for their large sample sizes and well-balanced control groups that adhered to HWE. In 2009, Ando's team examined a Japanese cohort (330 GACA cases and 190 controls), yet again finding no significant association (34). That same year, Ko *et al.* in South Korea undertook a rare attempt to include *IL-4* C-589T in a GACA genotyping study; however, their sample set was relatively small (84 GACA cases vs. 336 controls), and the control group did not meet HWE standards (35). Their findings remained consistent with prior studies, showing no significant association. A contrasting result emerged in 2017 when Yun and his colleagues reported a significant association between the *IL-4* C-589T polymorphism and GACA risk in a Chinese cohort (340 GACA cases and 364 controls). Their study indicated that individuals carrying the CC and CT genotypes had an increased risk of developing GACA compared to those with the TT genotype (36). However, another study reported by Wang and his colleagues in China that same year (362 GACA cases and 384 controls) failed to replicate these findings (37). In 2018, Pavithra's team conducted a study in India, again reporting no significant association (38). Interestingly, in 2020, a study in Chile involving 310 GACA cases and 311 controls reported a significant association, with the T allele being identified as a risk factor (39). However, this study lacked detailed genotype-specific data. According to the NCBI database (49), the T allele of *IL-4* C-589T exhibits a high frequency in East Asian (0.7795) and African (0.7300) populations, an intermediate frequency in Admixed Americans (0.3660), and a low frequency among Caucasians (0.1635). Despite early attention to *IL-4* C-589T as a candidate locus, most studies—both in East Asian and non-East Asian populations—have found no significant association between this polymorphism and GACA risk. This aligns with our current findings (Table II and Table III) and is further supported by the most recent meta-analysis on this topic (50). A notable discrepancy remains regarding Yun's findings in Inner Mongolia. Given China's vast

geographic expanse and ethnically diverse populations, a plausible explanation for their unique results could be the genetic homogeneity and conservation of Inner Mongolia due to its relative geographic and cultural isolation. In summary, regardless of whether the study population is from Inner Mongolia, Chile, or any other region, larger, multi-center genotypic studies are essential to elucidate the potential ethnic- or region-specific impact of the *IL-4* C-589T polymorphism on GACA susceptibility.

To date, no study has examined the correlation between *IL-4* T-1099G and the risk of GACA. Our investigation is the first to demonstrate a lack of significant association (Table II and Table III). Concerning *IL-4* C-33T, four relevant studies have been documented. The first, conducted by Crusius and his colleagues in 2008, analyzed a multiethnic European cohort consisting of 242 GACA patients and 1,154 controls across 10 countries (33). The second study, led by Ko, involved a South Korean population comprising 81 GACA cases and 324 controls (35). Notably, both research teams had also investigated *IL-4* C-589T but reported no significant findings. The third study, conducted by Wu and his colleagues in 2009, focused on a South Chinese cohort with 1,045 GACA cases and 1,100 controls. Unlike the previous studies, this research examined only the *IL-4* C-33T variant and similarly found no substantial association with GACA (51). The last one and most recent study was conducted by He and his colleagues in 2019. They analyzed 479 GACA cases and 483 controls in Nanjing, China, and found no significant differences (52). All these findings align with our present results (Table II and Table III).

As mentioned in the introduction part, many risk factors are identified to be associated with GACA across the world. The most well-established risk factor is *HP* infection (6), and long-term *HP* infection has been reported to account for up to approximately 75% of GACA cases (53). In 2017, Yun and his colleagues reported that the *IL-4* C-589T genotype has combinative impacts with *HP* infection on determining personal GACA risk (36). However, a negative interaction was presorted by He's team in 2019 (52).

GACA has been established as a smoking-related malignancy (54, 55). Our study further confirmed that cigarette smoking is a significant risk factor for GACA in the Taiwanese population (Table I). However, we were unable to demonstrate any significant interaction between *IL-4* genotypes and smoking behavior in influencing individual susceptibility to GACA (Table IV, Table V, Table VI). In 2017, Yun and his colleagues reported that the *IL-4* C-589T genotype has a combined effect with smoking behavior in determining individual GACA risk (36).

An elevated risk was observed among subgroups of GACA patients who consumed alcohol and carried variant *IL-4* genotypes at T-1099G (Table IV) and C-33T (Table VI), but not at C-589T (Table V). The detailed mechanisms remain unclear. On the contrary, literature suggests that alcohol consumption can significantly elevate the effects of *IL-4* C-589T on the risk of GACA (36). Further studies are greatly warranted to confirm our results.

Notably, GACA patients harboring the *IL-4* T-1099G and C-589T variant genotypes exhibited a higher risk of distant metastasis compared to those with the corresponding wild-type genotypes (Table IV and Table V). Although the precise mechanisms by which *IL-4* influences the metastatic behavior of GACA remain unclear, our findings have significant clinical implications. Specifically, *IL-4*-based early, precise, and personalized genotypic screening could be beneficial for individuals with a history of alcohol consumption and/or long-term *HP* infection, encouraging proactive modifications to mitigate their risk. Moreover, GACA patients carrying *IL-4* T-1099G and/or C-589T variant genotypes may benefit from more intensive whole-body follow-up examinations to reduce the likelihood of distant metastasis.

In conclusion, our study provides compelling evidence that *IL-4* T-1099G, C-589T, and C-33T genotypes are not significantly associated with GACA susceptibility. Notably, *IL-4* T-1099G exhibited interactions with BMI and alcohol consumption, while *IL-4* C-589T and C-33T interacted with *HP* infection and alcohol consumption. Furthermore, the variant genotypes of *IL-4* T-1099G and C-589T were associated with an increased risk of distant metastasis.

These findings underscore the potential influence of gene-environment interactions in GACA pathogenesis, despite the absence of direct genotypic associations. Further validation across diverse ethnic populations is warranted to confirm the clinical relevance of *IL-4* genetic variants.

### Conflicts of Interest

All the Authors declare no conflicts of interest regarding this study.

### Authors' Contributions

Conceptualization: CKF, DTB, and HTL; Data curation: CKF, YCY, JCC, and MDY; Formal analysis: JCC, YCY, and HTL; Funding acquisition: CKF, DTB, and HTL; Investigation: HYS, CWT, CKF, and WSC; Methodology: CWT, WSC, and DTB; Project administration: CKF, HTL, WSC, and DTB; Resources: CKF and HTL; Supervision: WSC and DTB; Validation: CWT and WSC, and DTB; Writing-original draft: CKF, HTL, and DTB; Writing-review & editing: WSC and DTB.

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