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GJA1 rs2071165 A>G Variant Increased Gastric Cancer Risk in Females of Northwest China: A Case-control Study

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Abstract

Background: Gastric cancer (GC) is one of the most common malignancies and its incidence rates vary widely between men and women. Previous studies have suggested that Cx43 and SCAMP1 are key functional proteins in tumors. Herein, the association between *GJA1* and *SCAMP1* polymorphisms and GC susceptibility and prognosis was evaluated.

Methods: A total of three SNPs among 681 GC patients and 756 controls were tested using the Agena Mass ARRAY RS1000 system including *GJA1* rs2071165, *SCAMP*1 rs4530741, and rs6874309. The strength of the association with cancer risk was assessed by the odds ratios and 95% confidence intervals generated from the logistic regression model. Kaplan-Meier Curve, long-rank tests, and a multivariate Cox proportional hazard model were used for prognosis analysis. The expression of *GJA1* was assessed by immunohistochemistry.

Results: The *GJA1* rs2071165 AA/AG genotype significantly increased the risk of GC in the female Chinese population (odds ratio [OR] =1.55, 95% confidence interval, 95%CI] = 1.03–2.32, $p = 0.034$). Furthermore, the risk effect of rs2071165 was more evident in the subgroups of female patients with GC, stratified by age, clinical stage, tumor size, and recurrence/metastasis. However, no obvious differences in Cx43 expression in GC tissues were observed between males and females. Furthermore, no significant association between rs4530741 and rs6874309 polymorphisms in *SCAMP*1 and GC risk or prognosis was observed.

Conclusion: In conclusion, this study suggests that *GJA1* rs2071165 polymorphisms are associated with increased GC risk in females for the first time, which showed a potential new clinical marker for assessing GC risk in females.

Background

Gastric cancer ranks fifth in incidence rate and is the third leading cause of cancer-related deaths among all human cancers in both sexes worldwide (1, 2). Over 1,000,000 new cases and an estimated 783,000 deaths occurred globally in 2018 (3). The highest gastric cancer incidence and mortality rates were found in East Asia (4), ranking second (13.5%) for males and fifth (7.1%) for females among the most commonly diagnosed cancers in Chinese people in 2018 (5). GC is a multifactorial disease resulting from both environmental and genetic factors. Previous studies have shown that genetic factors, lifestyle conditions, and environmental factors play important roles in the development of gastric cancer (6).

GC incidence rates vary widely between men and women; females showed a lower overall incidence of gastric cancer compared to males (7). Female patients also showed a significantly poorer prognosis than male patients, especially among those with advanced GC aged ≤ 45 years (8).The reasons for such differences are not clear, however, physiological differences may contribute. For example, estrogens may protect females against the development of GC (9–11). Environmental or occupational exposures may also play a role, but the effect of smoking remains elusive (12). In addition, although hundreds of case-control studies examined candidate polymorphisms in relation to GC, there is still insufficient evidence for the genetic differences contributing to the different incidence rates of GC between men and women.

GJA1(gap junction protein alpha 1), encoding the connexin 43 (Cx43) protein, belongs to the connexin gene family, which encodes gap junction transmembrane channels, allowing the transfer of small molecules between the cytoplasm of two adjacent cells (13). There is compelling evidence supporting the correlation between aberrant Cx43 expression and tumor growth or metastasis (14). SCAMP1 (secretory carrier membrane protein 1) has been reported as a key functional protein in various tumors (15, 16), it also functions as an lncRNA in human tumors (17, 18). However, no studies have shown an association between the polymorphisms of these two genes and gastric cancer. Therefore, three SNPs were selected in this study rs2071165 in *GJA1*, and rs4530741 and rs6874309 in *SCAMP*1, to explore their relationship with gastric risk and prognosis.

Methods

Study population

In all, 1437 Han Chinese subjects were enrolled in the study, 681 of which were patients with gastric cancer that underwent radical surgery at the Tangdu and Xijing Hospitals. In all, 756 healthy individuals were randomly selected through health screening at Tangdu Hospital. There were no age, sex, or disease stage restrictions for recruitment. All GC patients were unrelated, of Han Chinese descent, and newly diagnosed and histologically confirmed to have GC. Follow-up of all patients was carried out according to our standard protocol (every 6 months during the first 2 years, then once in 12 months through telephone, outpatient review, or medical records). The latest follow-up data in this analysis were obtained in October 2014. Recurrence and mortality events were recorded and recurrence-free survival (RFS) was calculated for prognosis assessment. Written permission was obtained from all participants and the study was approved by the Institutional Review Board of the Air Force Military Medical University (Xi' an, China). The procedures were performed according to the approved guidelines and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Genotyping

The association between the three SNPs and gastric cancer was evaluated. Peripheral venous blood samples (5 mL) were collected from all subjects in EDTA vacutainers. Genomic DNA was obtained from the peripheral blood lymphocytes of study subjects using the Genomic DNA Extraction Kit (Omega Bio-Tek, Norcross, GA, USA or GoldMag Ltd, Xian, China) according to the manufacturer's protocol. All samples were collected before curative resection and stored at -80 °C for subsequent analysis. The *GJA1* gene rs2071165 G > A, *SCAMP1* gene rs4530741 A > C, and rs6874309 T > A polymorphisms were genotyped on the Agena Mass ARRAY RS1000 platform according to the standard protocol (Applied Biosystems, Foster City, CA, USA). Primers were designed using the Agena Mass ARRAY Assay Design 4.0 software.

Statistical analysis

Analyses were performed using SPSS version 20.0. Student's t-test was used to compare differences in age between the two groups. The chi-square or Fisher's exact test was used for sex and genotype frequency estimation. The odds ratio (OR) and confidence interval (CI) values of associations of genotype frequencies were calculated using binary logistic regression with the SNPstats web tool (http://bioinfo.iconcologia.net/snpstats/start.htm), adjusting for age and gender. Kaplan-Meier curves and log-rank tests were also used to estimate the associations between SNP and OS and RFS. The Cox proportional hazard regression model was applied to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for predicting the effects of SNPs on GC prognosis. All statistical analyses were two-sided, and $p < 0.05$ was considered statistically significant.

Immunohistochemistry

Gastric cancer tissue specimens were collected from 45 patients (33 male, 12 female); 33 non-tumor adjacent normal tissue samples were obtained from a segment of the resected specimens that were farthest from the tumor (> 5 cm (23 male, 10 female). All patients were pathologically diagnosed postoperatively. Written informed consent was obtained from all participants.

Immunohistochemical analysis was performed on paraffin-embedded specimens. The slides were incubated in 0.3% H_2O_2 in methanol for 20 min. For antigen retrieval, the slides were boiled in 10-mM sodium citrate buffer solution (pH 6.0) in a microwave oven for 15 min. After blocking nonspecific binding with 5% BSA for 1 h, the slides were incubated with an anti-connexin 43 antibody (1:100, Abcam) overnight at 4 °C. Then, the slides were incubated with a biotinylated sheep anti-rabbit antibody and DAB. The specific immunoreactivity showed clear brown staining.

Semi-quantitative count of the staining was scored according to Barne's method. Assessment of score standard was based on staining intensity and percentage of positive cells. Immunostaining results were scored as the sum of the extent and intensity of immunoreactivity.

All data were analyzed using the GraphPad Prism 8.0 software. A t-test was used for comparison between groups. A p-value < 0.05 was considered statistically significant.

Results

The genotype frequencies and their associations with the risk of gastric cancer in the Han Chinese population are shown in Table 1. Three genotypes were detected at each single-nucleotide polymorphism (SNP) locus with similar frequencies of each genotype in the case and control groups, respectively. The p-value of each SNP from the Hardy–Weinberg equilibrium (HWE) test was more than 0.05. Moreover, no significant association was observed between each SNP and GC susceptibility without regard to gender differences.

Table 1
Genetic variants associated with the susceptibility of GC

Model	Genotype	Control	Case	OR (95% CI)	*p*	OR (95% CI)	*p*[1]
rs2071165	HWE *p* = 0.699						
Co-dominant	GG	423	382	1.00	0.99	1.00	0.96
	AG	288	257	0.98 (0.79–1.22)		1.03 (0.82–1.30)	
	AA	45	41	1.01 (0.64–1.57)		1.03 (0.65–1.64)	
Dominant	GG	423	382	1.00	0.89	1.00	0.77
	AG-AA	333	298	0.99 (0.80–1.21)		1.03 (0.83–1.29)	
rs4530741	HWE *p* = 0.121						
Codominant	CC	250	228	1.00	0.43	1.00	0.33
	AC	351	330	1.03 (0.82–1.30)		1.04 (0.81–1.32)	
	AA	156	122	0.86 (0.64–1.15)		0.83 (0.61–1.14)	
Dominant	CC	250	228	1.00	0.84	1.00	0.81
	AC-AA	507	452	0.98 (0.78–1.22)		0.97 (0.77–1.22)	
rs6874309	HWE *p* = 0.246						
Codominant	AA	635	571	1.00	0.6	1.00	0.78
	AT	114	106	1.03 (0.78–1.38)		0.96 (0.71–1.30)	
	TT	8	4	0.56 (0.17–1.86)		0.65 (0.18–2.37)	
Dominant	AA	635	571	1.00	0.98	1.00	0.7
	AT-TT	122	110	1.00 (0.76–1.33)		0.94 (0.70–1.27)	
1: adjust by age and gender.							

Furthermore, stratification analysis was performed to evaluate the association between the polymorphisms and gastric cancer risk (Table 2). A significant association between *GJA1* polymorphisms and GC risk in females was observed other than the *SCAMP1* rs4530741 and rs6874309 polymorphisms. Compared to the rs2071165 GG genotype, the dominant model demonstrated that the combined genotype AG/AA was significantly associated with an increased risk of GC in women, after adjusting for age (odds ratio, OR = 1.55, 95% confidence interval, 95%CI = 1.03–2.32, *p* = 0.034). The frequencies of AA and AG genotypes in female patients were higher compared with those in female controls, while the frequencies of GG genotypes in female cases were lower compared with those in female controls (Supplementary Table 2). No significant associations were observed in men. In addition, no significant association between the AG/AA genotypes and other subgroups were observed, stratifying by age, clinical stages, tumor size, tumor position, and recurrence/metastasis. Moreover, there were no significant differences in specific genotypes or allelic frequencies associated with the prognosis of gastric cancer (Table 4 and Supplementary Table 5).

Table 2
Stratification analyses for the association between genetic polymorphism and GC susceptibility

	Genotype	Control	Case	OR (95% CI)	*p*	OR (95% CI)	p^2
Age[1]							
< 55	rs2071165						
	GG	235	133	1.00	0.36	1.00	0.32
	AG	173	98	1.00 (0.72–1.38)		1.02 (0.73–1.42)	
	AA	21	19	1.60 (0.83–3.08)		1.66 (0.86–3.22)	
	AG/AA	194	117	1.06 (0.78–1.45)	0.71	1.09 (0.80–1.49)	0.59
	rs4530741						
	CC	127	84	1.00	0.37	1.00	0.46
	AC	213	122	0.87 (0.61–1.23)		0.89 (0.62–1.27)	
	AA	90	43	0.72 (0.46–1.14)		0.75 (0.47–1.18)	
	AC/AA	303	165	0.82 (0.59–1.15)	0.26	0.84 (0.60–1.18)	0.33
	rs6874309						
	AA	358	215	1.00	0.63	1.00	0.68
	AT	68	33	0.81 (0.52–1.27)		0.83 (0.53–1.30)	
	TT	4	2	0.83 (0.15–4.58)		0.76 (0.14–4.27)	
	AT/TT	72	35	0.81 (0.52–1.25)	0.34	0.82 (0.53–1.28)	0.39
≥ 55	rs2071165						
	GG	188	249	1.00	0.44	1.00	0.36
	AG	115	158	1.04 (0.76–1.41)		1.15 (0.81–1.63)	
	AA	24	22	0.69 (0.38–1.27)		0.70 (0.35–1.39)	
	AG/AA	139	180	0.98 (0.73–1.31)	0.88	1.07 (0.77–1.49)	0.69
	rs4530741						
	CC	123	142	1.00	0.22	1.00	0.7
	AC	138	208	1.31 (0.94–1.80)		1.15 (0.80–1.66)	
	AA	66	79	1.04 (0.69–1.56)		1.00 (0.63–1.59)	
	AC/AA	204	287	1.22 (0.90–1.65)	0.2	1.11 (0.79–1.55)	0.56
	rs6874309						
	AA	277	354	1.00	0.29	1.00	0.48
	AT	46	73	1.24 (0.83–1.85)		1.18 (0.75–1.85)	
	TT	4	2	0.39 (0.07–2.15)		0.38 (0.05–3.02)	
	AT/TT	50	75	1.17 (0.79–1.74)	0.42	1.13 (0.72–1.75)	0.6
Gender[3]							
Male	rs2071165						
	GG	262	305	1.00	0.35	1.00	0.74

[1]:adjusted by gender;[2]:adjusted by age and gender; [3]:adjusted by age

[a]: Patient numbers may not add up to 100% of available subjects because of missing clinical data.

	Genotype	Control	Case	OR (95% CI)	*p*	OR (95% CI)	p^2
	AG	194	191	0.85 (0.65–1.10)		0.92 (0.69–1.22)	
	AA	33	30	0.78 (0.46–1.32)		0.84 (0.47–1.48)	
	AG/AA	227	221	0.84 (0.65–1.07)	0.16	0.91 (0.69–1.19)	0.48
	rs4530741						
	CC	150	167	1.00	0.77	1.00	0.65
	AC	242	263	0.98 (0.74–1.29)		1.04 (0.76–1.41)	
	AA	97	95	0.88 (0.61–1.26)		0.87 (0.59–1.29)	
	AC/AA	339	358	0.95 (0.73–1.24)	0.70	0.99 (0.74–1.32)	0.93
	rs6874309						
	AA	406	441	1.00	0.45	1.00	0.43
	AT	78	83	0.98 (0.70–1.37)		0.89 (0.62–1.29)	
	TT	5	2	0.37 (0.07–1.91)		0.33 (0.05–2.24)	
	AT/TT	83	85	0.94 (0.68–1.31)	0.73	0.86 (0.60–1.24)	0.43
Female	rs2071165						
	GG	161	77	1.00	0.1	1.00	0.084
	AG	94	66	1.47 (0.97–2.22)		1.49 (0.98–2.26)	
	AA	12	11	1.92 (0.81–4.54)		2.04 (0.85–4.87)	
	AG/AA	106	77	**1.52 (1.02–2.27)**	**0.04**	**1.55 (1.03–2.32)**	**0.034**
	rs4530741						
	CC	100	60	1.00	0.52	1.00	0.65
	AC	108	67	1.03 (0.66–1.61)		1.00 (0.64–1.57)	
	AA	59	27	0.76 (0.44–1.33)		0.79 (0.45–1.38)	
	AC/AA	167	94	0.94 (0.62–1.41)	0.76	0.93 (0.61–1.40)	0.72
	rs6874309						
	AA	228	129	1.00	0.9	1.00	0.84
	AT	36	23	1.13 (0.64–1.99)		1.19 (0.67–2.11)	
	TT	3	2	1.18 (0.19–7.14)		1.08 (0.17–6.69)	
	AT/TT	39	25	1.13 (0.66–1.96)	0.66	1.18 (0.68–2.05)	0.56
Recurrence and metasis [a]							
Negative	rs2071165						
	GG	423	208	1.00	0.86	1.00	0.76
	AG	288	148	1.05 (0.81–1.35)		1.08 (0.83–1.42)	
	AA	45	20	0.90 (0.52–1.57)		0.90 (0.50–1.61)	
	AG/AA	333	168	1.03 (0.80–1.32)	0.84	1.06 (0.81–1.38)	0.67
	rs4530741						
	CC	124	250	1.00	0.63	1.00	0.61

[1]:adjusted by gender;[2]:adjusted by age and gender; [3]:adjusted by age

[a]: Patient numbers may not add up to 100% of available subjects because of missing clinical data.

	Genotype	Control	Case	OR (95% CI)	*p*	OR (95% CI)	p^2
	AC	181	250	1.04(0.79–1.38)		1.00(0.75–1.35)	
	AA	71	156	0.92(0.64–1.31)		0.9075(0.62–1.32)	
	AC/AA	252	506	1.00(0.77–1.31)	0.98	0.9745(0.74–1.29)	0.86
	rs6874309						
	AA	310	634	1.00	0.42	1.00	0.72
	AT	64	114	1.15(0.82–1.61)		1.07(0.75–1.52)	
	TT	2	8	0.51 (0.11–2.42)		0.7212(0.14–3.97)	
	AT/TT	66	122	1.11(0.80–1.54)	0.55	1.05(0.74–1.49)	0.79
Positive	rs2071165						
	GG	423	167	1.00	0.75	1.00	0.97
	AG	288	102	0.90 (0.67–1.20)		0.96 (0.71–1.30)	
	AA	45	18	1.01 (0.57–1.80)		0.99 (0.54–1.80)	
	AG/AA	333	120	0.91 (0.69–1.20)	0.51	0.96 (0.72–1.28)	0.8
	rs4530741						
	CC	99	250	1.00	0.98	1.00	0.72
	AC	138	350	0.99 (0.73–1.35)		1.06(0.77–1.46)	
	AA	49	156	0.80(0.538–1.18)		0.80 (0.53–1.21)	
	AC/AA	187	506	0.93 (0.70–1.24)	0.64	0.98(0.73–1.32)	0.88
	rs6874309						
	AA	245	634	1.00	0.63	1.00	0.41
	AT	40	114	0.91(0.62–1.34)		0.84 (0.57–1.26)	
	TT	2	8	0.65(0.14–3.07)		0.62 (0.12–3.21)	
	AT/TT	42	122	0.89 (0.61–1.30)	0.55	0.83 (0.56–1.23)	0.36
Clinical stage [a]							
Early	rs2071165						
	GG	71	423	1.00	0.22	1.00	0.10
	AG	61	288	1.26 (0.87–1.83)		1.39(0.94–2.05)	
	AA	9	45	1.19 (0.56–2.54)		1.17(0.53–2.57)	
	AG/AA	70	333	1.25 (0.87–1.80)	0.22	1.35(0.93–1.87)	0.12
	rs4530741						
	CC	38	250	1.00	0.13	1.00	0.12
	AC	74	350	1.39(0.91–2.12)		1.42(0.91–2.21)	
	AA	28	156	1.18(0.70-2.00)		1.23(0.71–2.13)	
	AC/AA	102	506	1.33(0.89–1.98)	0.17	1.36(0.90–2.07)	0.15
	rs6874309						
	AA	112	634	1.00	0.16	1.00	0.32

[1]:adjusted by gender;[2]:adjusted by age and gender; [3]:adjusted by age

[a]: Patient numbers may not add up to 100% of available subjects because of missing clinical data.

	Genotype	Control	Case	OR (95% CI)	*p*	OR (95% CI)	p^2
	AT	28	114	1.39(0.88–2.20)		1.27(0.79–2.06)	
	TT	0	8	NA		NA	
	AT/TT	28	122	1.30(0.82–2.052)	0.26	1.2(0.74–1.94)	0.45
Middle	rs2071165						
	GG	272	423	1.00	0.43	1.00	0.62
	AG	168	288	0.91(0.71–1.16)		0.94(0.73–1.21)	
	AA	25	45	0.86 (0.52–1.44)		0.85 (0.50–1.45)	
	AG/AA	193	333	0.90 (0.71–1.14)	0.38	0.93(0.73–1.18)	0.53
	rs4530741						
	CC	166	250	1.00	0.60	1.00	0.67
	AC	217	350	0.93 (0.72–1.21)		0.94(0.72–1.24)	
	AA	82	156	0.79 (0.57–1.10)		0.77 (0.55–1.09)	
	AC/AA	299	506	0.89(0.70–1.13)	0.35	0.89(0.69–1.15)	0.37
	rs6874309						
	AA	395	634	1.00	0.73	1.00	0.49
	AT	67	114	0.94 (0.68–1.31)		0.89(0.63–1.25)	
	TT	4	8	0.80 (0.24–2.68)		0.93 (0.26–3.38)	
	AT/TT	71	122	0.93 (0.68–1.28)	0.67	0.89 (0.64–1.24)	0.49
Late	rs2071165						
	GG	32	423	1.00	0.77	1.00	0.98
	AG	20	288	0.92(0.51–1.64)		1.01(0.55–1.83)	
	AA	3	45	0.88 (0.26–2.99)		0.76(0.21–2.67)	
	AG/AA	23	333	0.91 (0.52–1.59)	0.75	0.97(0.54–1.71)	0.90
	rs4530741						
	CC	19	250	1.00	0.96	1.00	0.66
	AC	27	350	1.02(0.55–1.87)		1.15 (0.61–2.18)	
	AA	9	156	0.76(0.34–1.72)		0.90 (0.39–2.10)	
	AC/AA	36	506	0.94(0.53–1.67)	0.82	1.08(0.59–1.97)	0.81
	rs6874309						
	AA	46	634	1.00	0.82	1.00	0.88
	AT	9	114	1.09(0.52–2.28)		0.94 (0.44–2.03)	
	TT	0	8	NA		NA	
	AT/TT	9	122	1.02(0.49–2.13)	0.96	0.89(0.41–1.91)	0.75
Tumor size [a]							
≥ 5 cm	rs2071165			1.00		1.00	
	GG	423	145	1.00	0.44	1.00	0.44

[1]:adjusted by gender;[2]:adjusted by age and gender; [3]:adjusted by age

[a]: Patient numbers may not add up to 100% of available subjects because of missing clinical data.

	Genotype	Control	Case	OR (95% CI)	*p*	OR (95% CI)	p^2
	AG	288	106	1.07 (0.80–1.44)		1.14 (0.84–1.55)	
	AA	45	22	1.43 (0.83–2.46)		1.40 (0.79–2.48)	
	AG/AA	333	128	1.12 (0.85–1.48)	0.42	1.18 (0.88–1.58)	0.27
	rs4530741						
	CC	93	250	1.00	0.86	1.00	0.69
	AC	134	350	1.03(0.75–1.40)		1.07(0.77–1.48)	
	AA	45	156	0.78(0.52–1.17)		0.81 (0.53–1.24)	
	AC/AA	179	506	0.95 (0.71–1.27)	0.74	0.99(0.73–1.34)	0.94
	rs6874309						
	AA	239	634	1.00	0.21	1.00	0.15
	AT	33	114	0.77(0.51–1.16)		0.73(0.47–1.12)	
	TT	1	8	0.33 (0.04–2.67)		0.37 (0.04–3.31)	
	AT/TT	34	122	0.74(0.49–1.11)	0.15	0.71(0.46–1.08)	0.11
< 5 cm	rs2071165						
	GG	423	224	1.00	0.28	1.00	0.36
	AG	288	140	0.92 (0.71–1.19)		0.97 (0.74–1.27)	
	AA	45	15	0.63 (0.34–1.15)		0.64 (0.34–1.20)	
	AG/AA	333	155	0.88 (0.68–1.13)	0.31	0.92 (0.71–1.20)	0.55
	rs4530741						
	CC	126	250	1.00	0.86	1.00	0.89
	AC	181	350	1.03(0.78–1.36)		1.02(0.76–1.37)	
	AA	72	156	0.92(0.64–1.30)		0.89 (0.63–1.29)	
	AC/AA	253	506	0.99 (0.76–1.29)	0.95	0.98 (0.75–1.29)	0.89
	rs6874309						
	AA	306	634	1.00	0.15	1.00	0.38
	AT	70	114	1.27(0.92–1.77)		1.16(0.83–1.64)	
	TT	3	8	0.78(0.20–2.95)		0.88(0.21–3.66)	
	AT/TT	73	122	1.24(0.90–1.71)	0.19	1.15(0.82–1.61)	0.42
Position [a]							
Cardia	rs2071165						
	GG	423	78	1.00	0.14	1.00	0.34
	AG	288	39	0.73 (0.49–1.11)		0.80 (0.51–1.27)	
	AA	45	7	0.84 (0.37–1.94)		0.75(0.30–1.87)	
	AG/AA	333	46	0.75(0.51–1.11)	0.15	0.79 (0.51–1.23)	0.30
	rs4530741						
	CC	38	250	1.00	0.59	1.00	0.66

[1]:adjusted by gender;[2]:adjusted by age and gender; [3]:adjusted by age

[a]: Patient numbers may not add up to 100% of available subjects because of missing clinical data.

	Genotype	Control	Case	OR (95% CI)	*p*	OR (95% CI)	p^2
	AC	60	350	1.13(0.73–1.75)		1.12(0.68–1.83)	
	AA	27	156	1.14(0.67–1.94)		1.38(0.76–2.50)	
	AC/AA	87	506	1.13 (0.75–1.71)	0.56	1.19 (0.75–1.89)	0.46
	rs6874309						
	AA	107	634	1.00	0.66	1.00	0.25
	AT	17	114	0.88(0.51–1.53)		0.70(0.38–1.30)	
	TT	1	2	0.74(0.09–5.98)		0.83(0.067–10.18)	
	AT/TT	18	333	0.87(0.51–1.49)	0.62	0.70 (0.38–1.29)	0.26
Non-cardia	rs2071165						
	GG	423	238	1.00	1.00	1.00	0.79
	AG	288	162	1.00(0.78–1.28)		1.04(0.80–1.34)	
	AA	45	25	0.99(0.59–1.65)		0.98(0.58–1.66)	
	AG/AA	333	187	1.00(0.79–1.27)	0.99	1.03(0.80–1.31)	0.83
	rs4530741						
	CC	142	250	1.00	0.82	1.00	0.70
	AC	205	350	1.03 (0.79–1.35)		1.06(0.80–1.40)	
	AA	76	156	0.86(0.61–1.21)		0.85 (0.60–1.21)	
	AC/AA	281	506	0.98(0.76–1.26)	0.86	0.99 (0.76–1.29)	0.95
	rs6874309						
	AA	350	634	1.00	0.47	1.00	0.80
	AT	71	114	1.13(0.82–1.56)		1.04(0.75–1.46)	
	TT	3	8	0.68(0.18–2.58)		0.75(0.18–3.04)	
	AT/TT	74	122	1.10(0.80 – 0.58)	0.56	1.03(0.74–1.43)	0.87

[1]:adjusted by gender;[2]:adjusted by age and gender; [3]:adjusted by age

[a]: Patient numbers may not add up to 100% of available subjects because of missing clinical data.

Table 3
Stratification analyses for the association between *GJA1* rs2071165 G > A polymorphism and GC susceptibility in females

	Model	Genotype	case	control	OR(95%CI)	*p*	OR(95%CI)	*p*[1]
Age								
≥ 55	Co-dominant	GG	38	105	1.00	0.26	1.00	0.25
		AG	33	66	1.38 (0.79–2.42)		1.42(0.78–2.56)	
		AA	6	9	1.84(0.61–5.52)		2.15(0.67–6.88)	
	Dominant	GG	38	105	1.00	0.19	1.00	0.16
		AA/AG	39	75	1.44(0.84–2.46)		1.50(0.85–2.64)	
	Recessive	AG/GG	71	171	1.00	0.39	1.00	0.28
		AA	6	9	1.61(0.55–4.68)		1.86(0.60–5.75)	
< 55	Co-dominant	GG	39	56	1.00	0.11	1.00	0.10
		AG	33	28	1.69(0.88–3.24)		1.85 (0.88–3.88)	
		AA	5	3	2.39 (0.54–10.60)		4.52(0.93-22.00)	
	Dominant	GG	39	56	1.00	0.08	1.00	**0.046**
		AA/AG	38	31	1.76(0.94–3.93)		**2.06(1.01–4.21)**	
	Recessive	AG/GG	72	84	1.00	0.37	1.00	0.11
		AA	5	3	1.94(0.45–8.42)		3.51(0.75–16.53)	
Tumor size [a]								
≥ 5 cm	Co-dominant	GG	32	161	1.00	0.07	1.00	0.08
		AG	31	94	1.66(0.95–2.89)		1.66(0.95–2.89)	
		AA	6	12	2.52(0.88–7.20)		2.53(0.88–7.23)	
	Dominant	GG	32	161	1.00	**0.04**	1.00	**0.04**
		AA/AG	37	106	**1.76(1.03–2.99)**		**1.753(1.03–2.99)**	
	Recessive	AG/GG	63	255	1.00	0.17	1.00	0.17
		AA	6	12	2.02 (0.73–5.60)		2.04(0.73–5.64)	
< 5 cm	Co-dominant	GG	41	161	1.00	0.17	1.00	0.21
		AG	34	94	1.42(0.84–2.39)		1.42(0.82–2.46)	
		AA	5	12	1.64(0.55–4.91)		2.01(0.64–6.34)	
	Dominant	GG	41	161	1.00	0.15	1.00	0.15
		AA/AG	39	106	1.45(0.87–2.39)		1.48(0.87–2.51)	
	Recessive	AG/GG	75	255	1.00	0.52	1.00	0.33
		AA	5	12	1.42(0.48–4.15)		1.75(0.57–5.36)	
Clinical stage [a]								
0/I/II*	Co-dominant	GG	56	161	1.00	0.26	1.00	0.19
		AG	43	94	1.32(0.82–2.11)		1.38 (0.85–2.23)	

[1]:adjusted by age

*: stage 0 was added to the Clinical stage I/II

[a]: Patient numbers may not add up to 100% of available subjects because of missing clinical data.

	Model	Genotype	case	control	OR(95%CI)	*p*	OR(95%CI)	*p*[1]
		AA	5	12	1.20(0.40–3.55)		1.28(0.42–3.85)	
	Dominant	GG	56	161	1.00	0.26	1.00	0.17
		AA/AG	48	106	1.30(0.82–2.06)		1.37(0.86–2.18)	
	Recessive	AG/GG	99	255	1.00	0.90	1.00	0.84
		AA	5	12	1.07 (0.37–3.13)		1.12(0.38–3.32)	
III/IV	Co-dominant	GG	20	161	1.00	0.01	1.00	**0.01**
		AG	22	94	1.88 (0.98–3.63)		1.83(0.94–3.54)	
		AA	6	12	4.03(1.36–11.91)		4.19(1.41–12.45)	
	Dominant	GG	20	161	1.00	0.02	1.00	**0.02**
		AA/AG	28	106	2.13(1.14–3.97)		**2.09(1.12–3.91)**	
	Recessive	AG/GG	42	255	1.00	0.04	1.00	**0.03**
		AA	6	12	3.036(1.08–8.53)		**3.21(1.14–9.08)**	
Recurrence/ Metastasis[a]								
negative	Co-dominant	GG	35	161	1.00	0.04	1.00	**0.03**
		AG	36	94	1.76(1.04–2.99)		**1.82(1.06–3.10**)	
		AA	7	12	2.68(0.99–7.30)		**2.84(1.03–7.80)**	
	Dominant	GG	35	161	1.00	0.02	1.00	**0.01**
		AA/AG	43	106	1.87(1.12–3.105)		**1.93(1.16–3.23**)	
	Recessive	AG/GG	71	255	1.00	0.13	1.00	0.12
		AA	7	12	2.095(0.795–5.52)		2.18(0.82–5.80)	
positive	Co-dominant	GG	41	161	1.00	0.49	1.00	0.58
		AG	29	94	1.21(0.71–2.08)		1.17(0.68–2.03)	
		AA	4	12	1.31(0.40–4.27)		1.41(0.43–4.63)	
	Dominant	GG	41	161	1.00	0.45	1.00	0.51
		AA/AG	33	106	1.22 (0.3–2.06)		1.20(0.70–2.03)	
	Recessive	AG/GG	70	255	1.00	0.74	1.00	0.64
		AA	4	12	1.21 (0.38–3.88)		1.32 (0.41–4.27)	

[1]:adjusted by age

*: stage 0 was added to the Clinical stage I/II

[a]: Patient numbers may not add up to 100% of available subjects because of missing clinical data.

Table 4
Association of genetic polymorphisms and GC prognosis

	Genotype	OS						RFS					
		Total	Event	Log-rank p	MST[1]	HR (95%CI)	*p*	Total	Event	Log-rank p	MST[1]	HR (95%CI)	*p*
rs2071165	GG	375	125	0.77	57	1.00		375	167	0.46	34	1.00	
	AG	250	85		62	1.03(0.75–1.41)	0.87	250	102		39.52	0.86(0.64–1.15)	0.30
	AA	38	15		40	1.01(0.54–1.87)	0.98	38	18		25	1.34(0.77–2.32)	0.30
	Dominant	288	100	0.94	62	1.02(0.76–1.39)	0.88	288	120	0.65	51	0.91(0.69–1.20)	0.50
rs4530741	CC	223	79	0.95	56	1.00		223	99	0.75	33	1.00	
	AC	319	110		59	1.05(0.75–1.48)	0.76	319	138		37	0.99(0.73–1.33)	0.93
	AA	120	36		43.12	1.03(0.66–1.60)	0.91	120	49		25	1.09(0.74–1.60)	0.67
	Dominant	439	146	0.80	62	1.05(0.76–1.44)	0.78	439	187	0.58	37	1.01(0.76–1.34)	0.93
rs6874309	AA	555	190	0.79	57	1.00		555	245	0.51	32	1.00	
	TA	104	35		42.985	1.14(0.75–1.71)	0.55	104	40		39.79	0.92(0.631–1.34)	0.67
	TT	4	1		55	0.56(0.08–1.09)	0.57	4	2		50	0.90(0.20–3.67)	0.88
	Dominant	108	36	0.86	57	1.10(0.73–1.65)	0.65	108	42	0.24	50	0.92(0.64–1.33)	0.66

[1]: Mean survival time was provided when MST could not be calculated

Further stratified analyses based on various female patient characteristics were performed. As shown in Table 3 (Supplementary Table 4), after adjusting for age, the dominant model demonstrated that rs2071165 combined genotype AA/AG was significantly associated with an increased risk of GC in female subjects aged < 55 years (OR = 2.06, 95% 95%CI = 1.01–4.21, $p = 0.046$), when compared to the rs2071165 GG genotype. Moreover, the AA/AG genotype was associated with an increased risk of GC for females with a tumor size of ≥ 5 cm (OR = 1.75, 95% 95%CI = 1.03–2.99, $p = 0.039$), females in tumor stage III/IV (OR = 2.09, 95% 95%CI = 1.12–3.91, $p = 0.021$), and females showing negative recurrence/metastasis (OR = 1.93, 95% 95%CI = 1.16–3.23, $p = 0.012$), compared to the rs2071165 GG genotype. Furthermore, the co-dominant model showed that the rs2071165 AA genotype had a significant association with an increased risk of GC in women with tumor stage III/IV (OR = 4.19, 95% 95%CI = 1.41–12.45, $p = 0.010$) and the rs2071165 AA and AG genotype was significantly associated with an increased risk of GC in women with negative recurrence/metastasis (OR = 2.84, 95% 95%CI = 1.03–7.796, $p = 0.029$; OR = 1.82, 95% 95%CI = 1.06–3.10, $p = 0.029$), respectively. The recessive model also showed that the rs2071165 AA genotype was associated with an increased risk of GC in females with stage III/IV tumors compared to the rs2071165 AG/GG genotype.

Discussion

The association of *GJA1* rs2071165 and *SCAMP1* rs4530741 A > C and rs6874309 T > A polymorphisms with GC risk and prognosis was investigated in this study. The *GJA1* gene rs2071165 AA/AG genotype significantly increased the risk of GC in the female Chinese population, which indicated that *GJA1* polymorphisms may contribute to GC susceptibility in females. Furthermore, the risk effect of rs2071165 was more evident in the subgroups of female patients with GC, stratified by age, clinical stage, tumor size, and recurrence/metastasis. Negative results were observed for *SCAMP1* rs4530741 A > C and rs6874309 T > A polymorphisms. To the best of our knowledge, this study reported the association between *GJA1* and *SCAMP1* gene polymorphisms and GC risk for the first time. Once validated, it may be used as a new marker for assessing GC risk in females, combined with traditional clinical risk factors.

Connexin 43 is a member of the connexins known for its greater capacity for transporting macromolecules than other connexin proteins (19).Compelling evidence suggests that dysregulated Cx43 (*GJA1*) expression is associated with tumor development and progression (20–22), making Cx43 an attractive tumor biomarker. However, its role in cancer progression and metastasis remains controversial (14). Decreased

expression of Cx43 was found in primary gastric cancer, while increased Cx43 expression was found to contribute to lymph node metastasis (23). Increased Cx43 expression has been reported to be associated with poor prognosis in some cancer types (14, 20, 24), while the contrary has also been reported in breast cancer (25). However, the current consensus appeared to be that the loss of Cx43 gap junction intercellular communication is an early event in malignancy, with the possibility of gap junction restoration in the event of metastasis (26), which also enhanced the role of Cx43 in cancer development and prognosis.

Despite extensive investigations of Cx43(*GJA1*) expression and its corresponding activity in cancer evolution, few studies have focused on the effect of the SNPs in *GJA1* on cancer risk or prognosis. According to web-based SNP selection tools (https://manticore.niehs.nih.gov/snpinfo/snpfunc.html), two functional SNPs, rs2071165, were selected in the *GJA1* gene region for further analysis in our study. rs2071165 is located in the upstream-variant-2KB *GJA1* and was predicted to be a transcription factor binding site, which may influence the expression of Cx43 expression in GC patients. The correlation between rs2071165 and cancer risk has not yet been investigated. The SNP rs2071166 was removed from this study due to its strong linkage disequilibrium with the SNP rs2071165. However, the AA/AG genotypes of functional SNP rs2071165 were significantly associated with GC risk in females and the variant-containing (AA, AG, and AA/AG) genotypes showed a more prominent effect on subgroups of female GC patients, stratifying by age, clinical stages, tumor size, and recurrence/metastasis, supporting the important role of Cx43 in GC development. However, no significant association between rs2071165 polymorphisms and GC prognosis was observed in this study, even in females.

Sex disparity in GC has been proven (8). In the present study, it was observed that the *GJA1* rs2071165 AA/AG genotype was significantly associated with an increased risk of GC in females but not in males. Cx43 is hormone-responsive (27) and inhibition of estrogen receptors could reduce connexin 43 expression in breast cancers (28). Estrogen also has a preventive role in gastric cancer (29). Furthermore, a report suggested that hypothalamic Cx43 expression is regulated by steroid hormones in a brain-region-specific and sexually dimorphic manner (30). The interaction between estrogen and aberrant Cx43 expression might also contribute to GC development and progression. However, the expression of Cx43 in GC was also discussed in another cohort; decreased expression of Cx43 in gastric cancer was also observed, but no difference in Cx43 expression was observed between males and females (Fig. 1). Therefore, more evidence is needed to support this hypothesis.

Our study has several limitations. First, the exact mechanism of *GJA1* polymorphism needs to be further clarified, even though a correlation between rs2071165 polymorphisms and GC risk was observed. Second, the sample size was too small to have enough statistical power for the stratified analyses in females. Only two SNPs in *SCAMP1* were evaluated; other important SNPs may have been neglected. Third, the association between genetic and environmental factors, such as drinking and dietary habits, failed to account for the lack of these data. Moreover, the study was restricted to the Han Chinese population and, therefore, generalizability issues cannot be ruled out. Further studies in larger populations including other ethnicities are warranted.

Conclusions

The study suggests that *GJA1* rs2071165 polymorphisms are associated with increased GC risk in females, but no significant association between rs4530741 and rs6874309 polymorphisms in *SCAMP*1 and GC risk or prognosis was observed. Moreover, the *GJA1* rs2071165 polymorphisms may contribute to an increased risk of GC in women aged < 55 years. The present study showed potential clinical significance in predicting GC in women and a hypothesis for the sex difference in GC.

Abbreviations

Cx43
Connexin 43
GC
gastric cancer
OS
overall survival
RFS
recurrence-free survival
HR
hazard ratios
CIs
confidence intervals
SNP
single nucleotide polymorphism
MAF

minor allele frequency

Declarations

Ethics approval and consent to participate

Written permission was obtained from all participants, the study was approved by the Institutional Review Board of the Air Force Military Medical University (Xi`an, China). The procedures were performed according to the approved guidelines and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent for publication

All the authors listed have approved the enclosed manuscript for publication.

Availability of data and materials

Data are available from the authors upon reasonable request and with permission from the Air Force Military Medical University (Xi`an, China).

Competing interests

No conflict of interest exists in the submission of this manuscript, I would like to declare on behalf of my co-authors that the work described was original research that has not been published previously and is not under consideration for publication elsewhere, in whole or in part.

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Authors' contributions

LJY designed the work and drafted the article; GW and PY carried out experiments and collected data; ZYY and LY analyzed the experimental results; JGL and SJP assisted with data analysis; XLH and GQB reviewed the manuscript and gave final approval of the version to be published.

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Figures

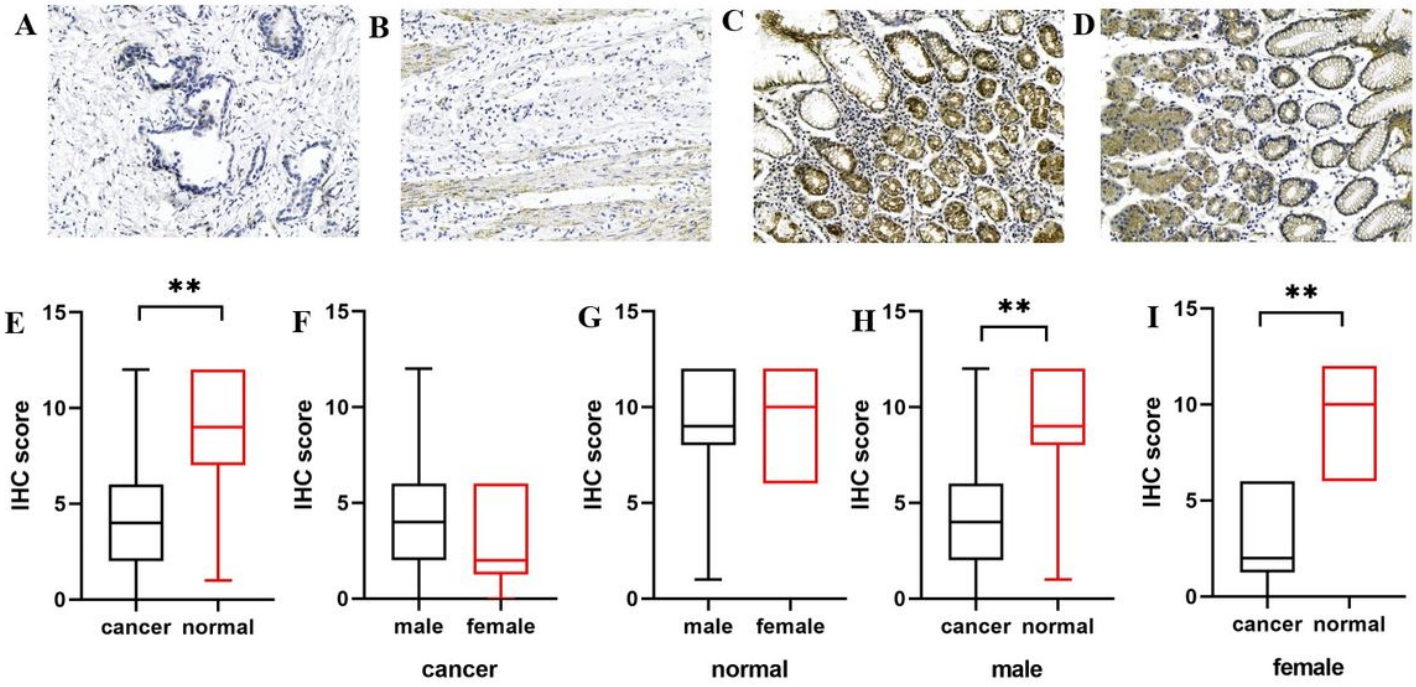

Figure 1

The interaction between estrogen and aberrant Cx43 expression might also contribute to GC development and progression. However, the expression of Cx43 in GC was also discussed in another cohort; decreased expression of Cx43 in gastric cancer was also observed, but no difference in Cx43 expression was observed between males and females (Figure 1).

Supplementary Files

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