Original Article

Association study between *KCNQ1* and *KCNQ1OT1* genetic polymorphisms and gastric cancer susceptibility and survival in a Chinese Han population: a case-control study

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Background: The present study analyzed gene polymorphisms in the potassium voltage-gated channel KQT-like subfamily member 1 (*KCNQ1*) and the long noncoding RNA, *KCNQ1OT1*, and their impacts on genetic susceptibility and survival in a Chinese Han population with gastric cancer (GC).

Methods: We designed a case-control study that included 681 patients with GC and 756 healthy controls. Three single-nucleotide polymorphisms (SNPs) in the *KCNQ1* gene region and eight SNPs in the *KCNQ1OT1* gene region were selected for further research.

Results: Among the 11 SNPs, we found no significant differences in the genotype and allele frequencies between GC patients and the healthy population. Hierarchical analysis by the log-additive model indicated that the *KCNQ1* rs231348 CT genotype was significantly associated with an increased GC risk in individuals aged ≥55 years, regardless of gender. The *KCNQ1OT1* rs231352 CC and rs7128926 AA genotypes increased the risk of GC in individuals with stage III/IV tumors larger than 5 cm in diameter. On evaluating the genotype polymorphism and survival analysis, we detected that the AA genotypes of the *KCNQ1OT1* rs7128926 and rs7939976 polymorphisms presented a significant survival advantage over the GA/GG genotypes, especially in patients with the following characteristics: age >55, *Helicobacter pylori* infection, BMI >24, tumor in the non-cardia region with a diameter greater than 5 cm, clinical stage II, and postoperative adjuvant chemotherapy.

Conclusions: Our results suggest that the KCNQ1 rs231348 and KCNQ1OT1 rs231352 polymorphisms might be independent predictors of the risk of GC susceptibility depending on certain factors, such as the age of the individual and the tumor stage and diameter. Simultaneously, genotype polymorphism of the rs7128926 and rs7939976 loci of the KCNQ1OT1 gene independently predicted the recurrence-free survival (RFS) and overall survival (OS) of GC patients.

Keywords: Polymorphisms; potassium voltage-gated channel KQT-like subfamily member 1 (*KCNQ1*); *KCNQ1OT1*; gastric cancer (GC); genetic susceptibility; survival; Chinese Han population

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Introduction

Gastric cancer (GC), a common malignancy with a 5-year survival rate of <25%, is the second leading cause of cancer mortality worldwide (1). The highest GC incidence rate and mortality rate in both sexes are found in East Asia, with approximately 679,100 new cancer cases and 498,000 cancer deaths reported in 2018 in China (2). Carcinogenesis is a complex multistep process resulting from both genetic and environmental factors (3). The development of GC is caused by individual genetic susceptibility, potential environmental components, and/or dietary habits (4,5), such as tobacco smoking, alcohol use, water intake, and daily consumption of meat broth (6,7). Furthermore, genetic factors, among which single-nucleotide polymorphisms (SNPs) are the most common, also play an important role in the development and progression of tumors, including GC. With the continuous development of genetic research in recent years, especially the application of genome-wide association studies (GWAS), more GC susceptibility genes have been discovered (8). Thus far, all GWAS data are from East Asians, including Japanese, Korean, and Chinese populations. However, results from other populations are expected in the next few years (9).

The *KCNQ1* gene is located on chromosome 11 and consists of 17 exons of different lengths, ranging from 47 bp (exon 14) to 1,122 bp (exon 16). *KCNQ1* encodes the Q1 subfamily of the voltage-dependent potassium channel, a type of membrane protein ubiquitous in the body, that plays an important role in controlling gastric acid secretion and stabilizing resting potential (10). The KCNQ1 locus includes 8–10 maternal allele-encoded protein-coding genes and 1 long noncoding RNA (lncRNA), KCNQ1OT1 (11), which is an imprinted gene that is expressed from the paternal allele. The *KCNQ1OT1* transcript regulates the silencing of other imprinted genes in the imprinted gene cluster at position 11p15.5. The *KCNQ1* gene is highly expressed in peripheral blood leukocytes, the heart, prostate, inner ear blood vessels, stomach, small intestine, kidney, and pancreas, expressed in tissues that are critical for ion homeostasis (12,13). Humans carrying germline mutations in *KCNQ1* develop a range of pathologies, most notably cardiac arrhythmia (long and short QT, Jervell and Lange-Nielsen syndrome), but also hearing loss, elevated gastrin levels, gastric hyperplasia, and in some cases gastric neoplasia (14-17). These phenotypes have been modeled in *KCNQ1* knockout mice which develop inner ear defects, imbalance, chronic gastritis, gastric hyperplasia, and gastric metaplasia (18).

Because the transcription of the *KCNQ1OT1* gene overlaps with most of the *KCNQ1* transcription unit on the anti-strand, it is possible to affect the transcription of *KCNQ1* and other non-overlapping genes through transcriptional interference (19). Meanwhile, *KCNQ1OT1* can cause transcriptional silencing in chromosomal regions and can serve as an example of lncRNA-mediated gene transcription silencing (20); it has also been associated with poor patient survival in several gastrointestinal cancers, including colorectal cancer (CRC) (21), esophageal cancer (22), and hepatocellular carcinoma (HCC) (23). lncRNAs are closely related to the occurrence and development of tumors (24). Multiple polymorphic sites in the KCNQ1 and KCNQ1OT1 gene region are related to the occurrence and outcome of GC, and genetic variations are also associated with increased risk and overall survival (OS). *KCNQ1OT1* dysregulation participates in carcinogenesis and progression of human cancers (25,26). However, the expression and potential functions of this gene region in GC are largely unknown. Therefore, this study selected SNP loci from the *KCNQ1* and *KCNQ1OT1* gene region and observed the relationship between SNP genotypes and the susceptibility and survival prognosis in Chinese GC patients.

We present the following article in accordance with the MDAR reporting checklist (available at http://dx.doi.org/10.21037/atm-20-8052).

Methods

Study participants

From May 2010 to June 2016, 681 patients with GC were enrolled from the Second Affiliated Hospital of the Air Force Medical University and 756 healthy subjects were recruited as controls through strict physical examinations in the same hospital. All 681 patients were confirmed as having primary GC by endoscopic and histopathological analysis. Patients with other types of cancers, gastritis, or gastric ulcers, or those who underwent radiotherapy or chemotherapy were excluded. In addition, all participants were Chinese who were not directly related within the past three generations. Demographic and lifestyle habit data of all the participants were collected through a detailed questionnaire, including residence, age, ethnicity, sex, dietary habits, and previous disease history.

The study was conducted in accordance with the

Declaration of Helsinki (as revised in 2013). The current study was approved by the institutional ethics committees of the Second Affiliated Hospital of the Air Force Medical University (No. K201009-03). All the participants provided signed informed consent documents and a donation of approximately 5 mL of blood as part of this research.

Genomic DNA extraction and genotyping

Approximately 5 mL of peripheral blood were collected from each subject. Genomic DNA from whole blood samples was extracted using the TIANamp Blood DNA Purification Kit (Gold Mag Co. Ltd., Xi'an City, China) according to the manufacturer's instructions. Extracted DNA was stored at –20 ℃. The concentration and purity of the genomic DNA were determined using a NanoDrop Spectrophotometer (ND-1000, Thermo Fisher Scientific). The KCNQ1 and KCNQ1OT1 gene polymorphisms was genotyped on Agena Mass ARRAY RS1000 platform according to the standard protocol.

The associations between the functional SNPs of the *KCNQ1* and *KCNQ1OT1* genes and GC development were evaluated. The tag SNPs that represent the polymorphisms of a block were included in our study. Finally, three SNPs (rs6578283, rs231348, and rs760419) in *KCNQ1*, and eight SNPs (rs10832514, rs231361, rs231359, rs7128926, rs231356, rs231354, rs231352, and rs7939976) in *KCNQ1OT1* were selected for further research. The characteristics of the sequences in this study are summarized in Table S1. Then, Agena Typer 4.0 software (Agena Bioscience) was used to analyze and manage our data.

Statistical analysis

Continuous variables, such as demographic variables, risk factors, and *KCNQ1* and *KCNQ1OT1* genotype distribution between the case and control groups, are shown as the mean ± standard deviation (SD) and were compared by Student's *t*-test. Categorical variables are presented as frequencies with percentages (%) and were compared with the χ^2 test or Fisher's exact test when appropriate. The χ^2 test was also used to assess whether the distribution of genotypes was consistent with the Hardy-Weinberg equilibrium (HWE). Univariate and multivariate logistic regression analyses were used to test the association between the SNP genotypes and the progression of GC based on the generated odds ratios (ORs) and 95% confidence intervals (18). Adjusted ORs were calculated using multivariate analysis adjusting for age and gender. The Kaplan-Meier method was used to estimate the OS and recurrence-free survival (RFS), the log-rank test was used to compare survival distributions, and the Cox proportional hazards model was used to determine the hazards ratio (HR). All statistical analyses were performed using SAS 9.4 software (IBM Corp.). Statistical significance was defined as a P value <0.05 with a two-tailed test.

Results

Characteristics of the participants

This study contained 681 GC patients and 756 healthy controls. Overall, the variable distribution of the selected demographic data did not differ between GC patients and controls. *Table 1* shows the distributions of age, gender, and clinical stages of the study subjects. There were no significant statistical differences between the groups in terms of gender and age (P<0.001). The mean age was 57.57±10.826 years for GC patients and 52.58±8.709 years for the controls. The proportion of male subjects was significantly higher in both groups (77.4% *vs.* 64.7%, respectively). A follow-up of all patients was carried out according to our standard protocol, the median follow-up period for GC patients was 6.04 years (range, 0.12–10.68 years) and 6.15 years (range, 0.92–10.68 years) for the control cases. The latest follow-up data in this analysis was obtained in October 2019.

Associations between KCNQ1 and KCNQ1OT1 SNPs and GC risk

The basic data on the three *KCNQ1* SNP genotype frequencies (rs6578283, rs231348, and rs760419) and eight *KCNQ1OT1* SNP genotype frequencies (rs10832514, rs231361, rs231359, rs7128926, rs231356, rs231354, rs231352, and rs7939976) are shown in Table S1, which contains the position, alleles, minor allele frequency (MAF) distribution, HWE P value, ORs, and 95% CIs of all the candidate SNPs. The MAF values for each SNP in the controls were similar to the values for the Chinese population in the database (0.208 *vs.* 0.195, 0.115 *vs.* 0.106, 0.335 *vs.* 0.332, 0.118 *vs.* 0.111, 0.214 *vs.* 0.217, 0.213 *vs.* 0.219, 0.090 *vs.* 0.092, 0.217 *vs.* 0.225, 0.123 *vs.* 0.133, 0.122 *vs.* 0.132, and 0.087 *vs.* 0.089, respectively). The HWE P values of the 11 SNPs were more than 0.05, and none showed a significant departure from the HWE. Using the Pearson χ^2 test, we compared the SNP genotype and

Table 1 Characteristics and clinical features of the GC group and the control group

Variables	GC (%) N=681	Controls (%) N=756	P[a]	Variables	GC (%) N=681
Age (years)			<0.001	Stage[b]	
M ± SD	57.57±10.826	52.58±8.709		0/I/II	458 (67.25)
≥55	251 (36.86)	429 (56.75)		III/ IV	204 (29.96)
<55	430 (63.14)	327 (43.25)		R/M[b]	
Gender			<0.001	No	287
Male	527 (77.4)	489 (64.7)		Yes	377
Female	154 (22.6)	267 (35.3)		Family history[b]	
BMI			<0.001	No	282
<24	460 (67.5)	432 (57.2)		Yes	45
≥24	221 (32.5)	324 (42.8)		ACT[b]	
Diameter[b]				Yes	430
<5 cm	380 (55.8)			No	233
≥5 cm	273 (40.8)			Position[b]	
H. pylori[b]				Cardia	125 (18.34)
Yes	392			No-cardia	425(62.41)
No	187				

[a], based on a two-sided χ^2 test for distributions between gastric cancer and cancer-free controls; [b], patient numbers may not add up to 100% of available subjects because of missing clinical data. P<0.05 indicates statistical significance. GC, gastric cancer; ACT, adjuvant chemotherapy; R/M, recurrence/metastasis.

allele frequencies of *KCNQ1* and *KCNQ1OT1* between the casegroup and the control group and calculated ORs to evaluate associations with the GC risk. However, there were no statistically significant differences in genotype and allele frequencies between GC cases and controls in the Chinese population (P>0.05, Table S1). To further assess the possible association between the *KCNQ1* and *KCNQ1OT1* polymorphisms and the risk of GC under different genetic models, we applied logistic regression analysis and assumed four genetic models (codominant, dominant, recessive, and log-additive) with adjustments for age and gender (shown in Table S2). Again, we observed no statistically significant differences between patients and controls (P>0.05, Table S2).

We next performed a stratified analysis according to age, gender, clinical stage and tumor diameter to evaluate the effect of these 11 SNPs on GC risk. Stratified analysis by age revealed significant associations between the rs231348 genotype and the risk of GC, as displayed in Table S3. The rs231348 CT genotype in *KCNQ1* was identified to increase the risk of GC in individuals aged ≥55 years using the log-additive model (OR =1.48, CI: 1.01–2.16, P=0.042). No significant associations with GC risk were observed in either females or males (Table S3). Stratified analysis by clinical stage revealed significant associations between the *KCNQ1OT1* rs231352 genotype and the risk of GC, as displayed in https://cdn.amegroups.cn/static/public/10.21037atm-20-8052-1.pdf. The rs231352 CC genotype in *KCNQ1OT1* was identified to decrease the risk of GC in individuals at stages I–II as opposed to stages III–IV according to the recessive model (OR =0.31, CI: 0.08–1.12, P=0.048). In addition, stratified analysis by tumor diameter revealed a significant association between the *KCNQ1OT1* rs7128926 genotype and the risk of GC, as displayed in https://cdn.amegroups.cn/static/public/10.21037atm-20-8052-1.pdf. The rs7128926 AA genotype in *KCNQ1OT1* was identified to decrease the risk of GC in individuals with a tumor diameter <5 cm as opposed to ≥5 cm according to the recessive

model (P=0.026) (https://cdn.amegroups.cn/static/public/10.21037atm-20-8052-1.pdf).

Recurrence risk evaluation and survival analysis

Recurrent and mortality events were recorded, and the RFS was calculated for the prognosis assessment. Of the 681 patients diagnosed with GC, more than half were classified as the most common stages 0 [26], I [126], and II [316]. Most patients showed a tumor diameter less than 5 cm [380], and during the entire observation period, 377 patients experienced recurrence. To further estimate the correlation between the *KCNQ1* and *KCNQ1OT1* polymorphisms and the recurrence or metastasis risk and survival analysis of GC, univariate analysis, multivariate analysis, and multiple inheritance models (dominant, recessive, and additive models) were applied to analyze potential associations by a logistic regression analysis adjusted for age and gender. As shown in https://cdn.amegroups.cn/static/public/10.21037atm-20-8052-2.pdf, after adjusting for age and gender, rs7128926 in *KCNQ1OT1* decreased the GC recurrence and metastasis risk in both the codominant model (P=0.047) and the recessive model (P=0.026). Moreover, according to the recessive model, the *KCNQ1OT1* rs7939976 GG genotype was associated with a decreased recurrence and metastasis risk of GC (P=0.026) compared with the rs7939976 AA/AG genotypes (https://cdn.amegroups.cn/static/public/10.21037atm-20-8052-2.pdf).

The results of the survival analysis in relation to the SNPs are listed in *Table 2*. Among the 11 SNPs, 2 *KCNQ1OT1* SNPs, rs7939976 and rs7128926, were significantly associated with survival. Three genotypes, AA, GA and GG, were detected at the rs7939976 and rs7128926 loci of the *KCNQ1OT1* gene. Compared with patients with the GG and GA genotype of the *KCNQ1OT1* SNP rs7939976, we found that patients with the AA genotypes had longer OS and RFS after 1 year (*Figure 1A*,*B*), and patients carrying the A alleles had a substantially higher median OS compared with patients with no A allele (OR =20.749, CI: 2.68–160.616, P=0.004) (*Table 2*). Among all the cases, the MST was 57 months for those with the rs7939976 AA genotype (two A alleles), 47.8 months for those with the GA genotype (one A allele), and 4 months for those with the GG genotype (no A allele). This trend was also similar for the MST with RFS, with 32 months for AA, 11.2 months for GA, and 4 months for GG (P<0.01) (*Table 2*).

Meanwhile, patients with the AA genotype of the *KCNQ1OT1* rs7128926 SNP had longer OS and RFS after 1 year compared with patients with the GG and GA genotypes (*Figure 1C*,*D*), although there was no statistically significant difference (log-rank P=0.185 and 0.197, respectively). Meanwhile, as shown in *Table 2*, patients carrying the A allele of rs7128926 had a substantially higher OS (OR =0.863, CI: 0.553–1.346, P=0.012) and RFS (OR =0.946, CI: 0.647–1.385, P=0.01) compared with patients without the A allele. Among all the cases, the median survival time (MST) was 57 months for those with the rs7128926 AA genotype (two A alleles), 47 months for those with the GA genotype (one A allele), and only 4 months for those with the GG genotype (no A allele). This trend was similar for the MST with RFS, with 32 months for AA, 11.2 months for GA, and 2 months for GG (P<0.01). The other six SNP loci (rs10832514, rs231361, rs231359, rs231356, rs231354, and rs231352) of *KCNQ1OT1* and the three SNP loci (rs6578283, rs231348 and rs760419) of *KCNQ1* showed no significant correlation with OS and RFS in patients with GC (*Table 2*).

To further investigate the relationship between the *KCNQ1OT1* rs7128926 and rs7939976 SNPs and survival time in GC patients, we carried out a stratified analysis of the correlation between the two SNP loci in patients with GC, and the effect of age, gender, BMI, *Helicobacter pylori* infection status, clinical stage, tumor diameter, and chemotherapy status on OS and RFS were evaluated using a codominant model (*Tables 3*,*4*). The analysis revealed that MST and OS were the lowest in patients with the GG genotype at the *KCNQ1OT1* rs7128926 locus, especially in females over 60 years of age, followed by *H. pylori* infection, BMI >24, tumor in the non-cardia region with a diameter greater than 5 cm, clinical stage II, and postoperative adjuvant chemotherapy. This trend was similar for the MST and RFS among patients with the GG genotype at the *KCNQ1OT1* rs7939976 locus (*Table 3*). We also found that patients carrying the GG genotype at the *KCNQ1OT1* rs7939976 locus had a poorer MST with OS and RFS (*Table 4*).

Discussion

We collected data from 681 GC patients and 756 normal controls, detected 3 functional SNPs in the *KCNQ1* gene and 8 functional SNPs in the *KCNQ1OT1* gene, and assessed their associations with GC risk and survival in a Chinese population. There were no significant differences

Table 2 Genotypes of *KCNQ1* and *KCNQ1OT1* polymorphisms with clinical outcome of gastric cancer patients

SNP ID	Genotype	Total/ event	OS				Total/ event	RFS			
			Log-rank P	MST	HR (95% CI)	P		Log-rank P	MST	HR (95% CI)	P
rs6578283	AA	421/140		62		0.804	421/179		41		0.503
	GA	211/77	0.773	57	0.958 (0.696–1.32)	0.795	211/94	0.986	31	0.880 (0.660–1.174)	0.386
	GG	32/9		47.3	1.234 (0.594–2.565)	0.573	32/14		29	1.223 (0.670–2.231)	0.512
	Dominant	243/86	0.781	57	0.985 (0.725–1.339)	0.925	243/108	0.87	30	0.918 (0.699–1.207)	0.542
rs231348	CC	520/173		57		0.781	520/221		37		0.621
	TC	131/48	0.766	57	1.001 (0.704–1.451)	0.953	131/59	0.343	32	0.996 (0.722–1.374)	0.981
	TT	12/5		41.039	1.436 (0.524–3.937)	0.481	12/7		17	1.561 (0.635–3.836)	0.331
	Dominant	143/53	0.754	57	1.040 (0.735–1.473)	0.824	143/66	0.675	29	1.032 (0.757–1.406)	0.842
rs760419	AA	304/105		62		0.174	304/131		31		0.302
	GA	281/90	0.517	59	0.787 (0.565–1.096)	0.157	281/117	0.609	41	0.845 (0.632–1.128)	0.253
	GG	79/31		39	1.165 (0.743–1.825)	0.507	79/39		22	1.127 (0.752–1.687)	0.563
	Dominant	360/121	0.88	57	0.866 (0.638–1.176)	0.358	360/156	0.953	37	0.904 (0.690–1.183)	0.462
r231356	TT	406/138		57		0.827	406/172		40		0.358
	TA	228/79	0.961	57	1.038 (0.758–1.421)	0.818	228/102	0.864	31	1.063 (0.806–1.403)	0.664
	AA	30/9		46.776	1.289 (0.561–2.959)	0.55	30/12		26	1.637 (0.827–3.241)	0.157
	Dominant	258/88	0.986	57	1.056 (0.778–1.433)	0.726	258/115	0.613	31	1.102 (0.843–1.441)	0.478
rs231354	CC	507/172		57		0.917	507/213		40		0.556
	TC	150/52	0.961	57	1.043 (0.740–1.470)	0.812	150/71	0.636	29	1.150 (0.854–1.550)	0.356
	TT	7/2		47.7	0.714 (0.099–5.167)	0.739	7/3		17	0.582 (0.081–4.193)	0.591
	Dominant	157/54	0.925	57	1.032 (0.734–1.450)	0.858	157/74	0.342	29	1.132 (0.842–1.521)	0.413
rs231352	CC	509/172		57		0.914	509/214		40		0.545
	TC	148/52	0.936	57	1.045 (0.741–1.473)	0.803	148/70	0.634	26	1.154 (0.857–1.555)	0.346
	TT	7/2		47.7	0.714 (0.099–5.169)	0.739	7/3		17	0.582 (0.081–4.195)	0.591
	Dominant	155/54	0.826	57	1.034 (0.736–1.453)	0.848	155/73	0.34	26	1.135 (0.844–1.526)	0.401
rs7939976	AA	550/193		57		0.014	550/243		32		0.010
	GA	112/31	0.048	47.832	0.929 (0.595–1.449)	0.745	112/42	<0.001	11.258	1.030 (0.704–1.508)	0.878
	GG	2/2		4	20.749 (2.680–160.616)	0.004	2/2		2	23.238 (3.026–178.479)	0.002
	Dominant	114/33	0.263	47.06	0.972 (0.628–1.504)	0.897	114/44	0.322	40.59	1.063 (0.730–1.548)	0.750
rs10832514	AA	517/174		57		0.155	517/219		37		0.081
	GA	139/49	0.809	41.823	1.359 (0.955–1.933)	0.088	139/64	0.812	29	1.346 (0.984–1.840)	0.063
	GG	8/3		36.964	1.821 (0.574–5.783)	0.309	8/4		20	2.041 (0.750–5.558)	0.163
	Dominant	147/52	0.517	41.778	1.383 (0.982–1.949)	0.064	147/68	0.522	29	1.379 (1.017–1.870)	0.039

Table 1 (*continued*)

Table 2 (*continued*)

SNP ID	Genotype	Total/ event	OS				Total/ event	RFS			
			Log-rank P	MST	HR (95% CI)	P		Log-rank P	MST	HR (95% CI)	P
rs231361	AA	409/142		57		0.975	409/179		35		0.608
	GA	225/76	0.832	57	1.031 (0.752–1.413)	0.849	225/96	0.981	37	1.038 (0.787–1.371)	0.791
	GG	29/8		48.286	1.066 (0.432–2.633)	0.89	29/12		38.76	1.437 (0.700–2.952)	0.323
	Dominant	254/84	0.768	44.71	1.034 (0.761–1.405)	0.832	254/108	0.856	37	1.066 (0.814–1.395)	0.642
rs231359	AA	410/143		57		0.943	410/176		40		0.617
	CA	224/75	0.788	57	0.950 (0.692–1.303)	0.749	224/99	0.986	31	1.029 (0.780–1.357)	0.840
	CC	29/8		48.286	1.038 (0.420–2.562)	0.936	29/12		38.76	1.433 (0.698–2.945)	0.327
	Dominant	253/83	0.611	45.069	0.956 (0.703–1.300)	0.775	253/111	0.865	31	1.056 (0.808–1.381)	0.690
rs7128926	AA	547/192		57		0.012	547/242		32		0.010
	GA	115/32	0.05	47.667	0.863 (0.553–1.346)	0.515	115/43	<0.001	11.293	0.946 (0.647–1.385)	0.777
	GG	2/2		4	20.585 (2.659–159.37)	0.004	2/2		2	22.981 (2.992–176.541)	0.003
	Dominant	117/34	0.277	46.924	0.902 (0.583–1.395)	0.642	117/45	0.315	40.64	0.976 (0.670–1.421)	0.899

KCNQ1, potassium voltage-gated channel KQT-like subfamily member 1; OS, overall survival; RFS, recurrence-free survival; MST, median survival time;

to the genotype and allele frequencies between the GC cases and risk in the healthy population; however, in the stratification analyses, the log-additive model indicated that the CT genotype at the *KCNQ1* rs231348 locus was significantly associated with a decreased risk of GC in individuals aged ≥55 years. The CC genotype at the *KCNQ1OT1* rs231352 locus also decreased the risk of GC in individuals at stages I–II as opposed to stages III–IV. In addition, a stratified analysis by tumor diameter revealed significant associations between the *KCNQ1OT1* rs7128926 AA genotype and a decreased risk of GC for individuals with a tumor diameter <5 cm.

Consistent with our research, another recent study showed that *KCNQ1* mutant mice are a powerful new tool for investigating the connection between acid balance, *Helicobacter* infection, and mucin disruption in the progression to GC, and that *KCNQ1* mutations predispose mutant mice to metaplastic and pre-neoplastic changes in the stomach (27). In our study, *KCNQ1* rs231348 and *KCNQ1OT1* rs231352 independently predicted the risk of GC susceptibility under certain patient conditions, including the individual's age, tumor stage, and tumor diameter. Simultaneously, polymorphism of the rs7128926 and rs7939976 loci of the *KCNQ1OT1* gene independently predicted the OS and RFS of GC patients. One possible mechanism for this was that these genes for GC act as multiple DNA transposon-based forward genetic screens in patients (28). Than *et al.* (17) found that *KCNQ1* was a potential tumor suppressor gene, and low expression of *KCNQ1* was significantly associated with poor OS in patients with CRC. However, the relationship between *KCNQ1* rs231348 and GC has not been reported previously, and this study provides the first report of an association between the *KCNQ1* rs231348 polymorphism and the risk of GC susceptibility.

We also identified associations between the *KCNQ1OT1* gene polymorphisms, rs7128926 and rs7939976, and OS and RFS, even after adjustment for other clinical factors. These represent novel associations that have not been identified previously. Because the transcription of the *KCNQ1OT1* gene overlaps with most of the *KCNQ1* transcription unit on the anti-strand, the transcription of *KCNQ1* and other non-overlapping genes can be affected by transcriptional interference. In the evaluation of genotype polymorphism and survival analysis, we discovered that as the number of A alleles of the rs7128926 and rs7939976 loci of the *KCNQ1OT1* gene increased, the MST with OS and RFS of GC cases showed an increasing trend, and that

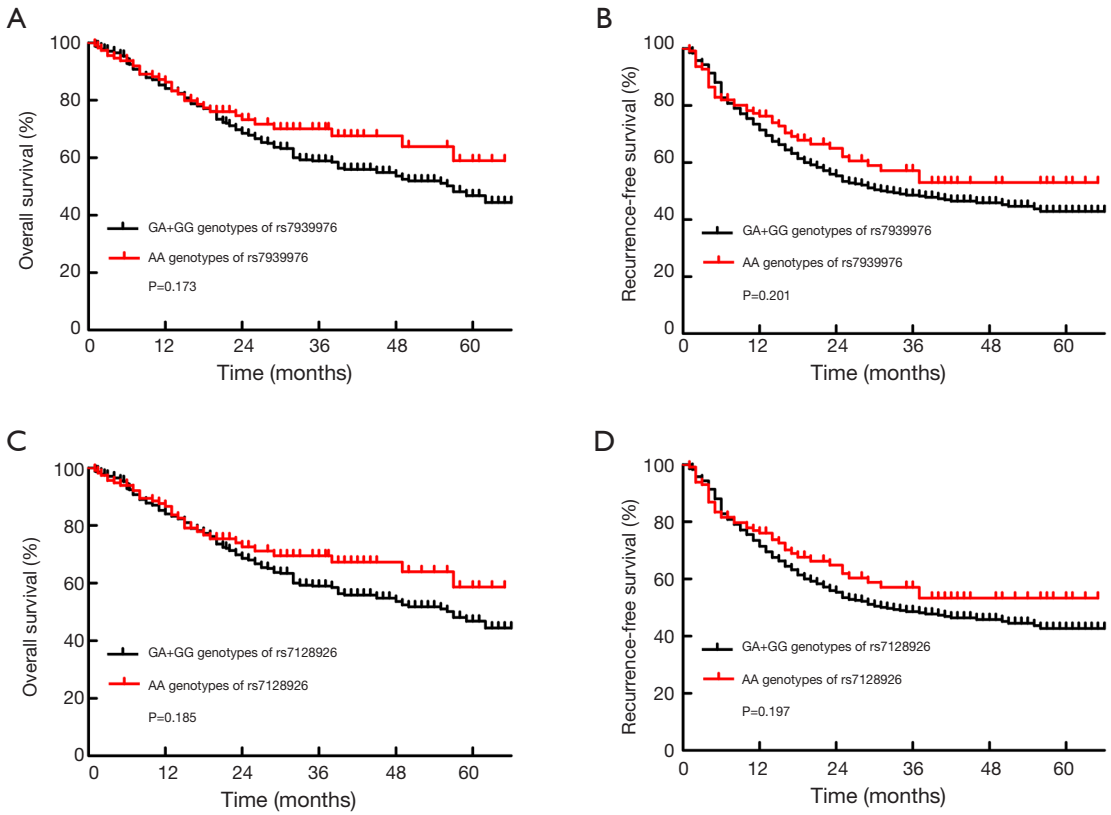

Figure 1 Kaplan-Meier curves of OS and RFS in patients with different KCNQ1OT1 rs7939976 and rs7128926 genotypes. (A,B) Median OS and RFS were longer in patients with *KCNQ1OT1* rs7939976 AA genotypes than in those with GA + GG genotypes after 1 year (log-rank P=0.173 and 0.201, respectively). (C,D) Median OS and RFS were longer in patients with *KCNQ1OT1* rs7128926 AA genotypes than in those with GG and GA genotypes after 1 year (log-rank P=0.185 and 0.197, respectively). OS, overall survival; RFS, recurrence-free survival. *KCNQ1*, potassium voltage-gated channel KQT-like subfamily member 1; OS, overall survival; RFS, recurrence-free survival.

the AA plus GA genotypes presented a significant survival advantage over the GG genotypes. A further stratified investigation also showed that the AA/GA genotypes of the rs7128926 and rs7939976 polymorphisms improved survival in those with the following characteristics: age over 55, the presence of *H. pylori* infection, BMI >24, tumor in the non-cardia region with a diameter greater than 5 cm, clinical stage II, and postoperative adjuvant chemotherapy.

The *KCNQ1* gene plays an important role in encoding the Q1 subfamily of the voltage-dependent potassium channel, and includes one paternally expressed lncRNA, *KCNQ1OT1*. The functions of ion channels influence a variety of cellular processes, many of which overlap heavily with these hallmarks of cancer (29). For these reasons, cancer has been described as a channelopathy (30). K^+ channels play a major role in the maintenance of plasma membrane (PM) potential (29). With 77 genes coding for K^+ channels, they are the largest and most diverse group of ion channels in the human genome. There is increasing evidence that K^+ channels are implicated in a variety of cellular and tissue functions, including cell proliferation, differentiation, invasion, migration, and metastasis. *KCNQ1* downregulation has also been observed in CRC, where *KCNQ1* expression is associated with improved RFS at stages II–IV of the disease (29). Meanwhile, in agreement with our findings, previous studies found a significant association between a common *KCNQ1OT1* promoter polymorphism (rs11023840) and the risk of symptomatic prolonged QT interval (31). The Previous study also examined the expression levels of *KCNQ1OT1*, which showed no significant alterations in early GC tissues compared with normal adjacent tissues by reverse

Table 3 Stratified analysis of the KCNQ1OT1 rs7128926 polymorphism with gastric cancer OS and RFS

Variables	Genotype	OS				RFS			
		Total/event	MST	HR (95% CI)	P	Total/event	MST	HR (95% CI)	P
Age[1]									
≥55	AA	244/89	56	1	0.033	244/109	26	1	0.012
	GA	43/13	46.124	1.182 (0.622–2.243)	0.61	43/17	40.207	1.282 (0.731–2.248)	0.386
	GG	2/2	4	16.444 (1.976–136.829)	0.01	2/2	2	23.626 (2.808–198.769)	0.004
<55	AA	303/103	57	1		303/133	38	1	
	GA	72/19	46.867	0.759 (0.407–1.416)	0.386	72/26	40.437	0.798 (0.473–1.3484)	0.399
	GG	NA				NA			
Gender[3]									
Male	AA	423/145	57	1		423/182	34	1	
	GA	88/22	49.604	0.760 (0.448–1.290)	0.309	88/30	43.837	0.937 (0.597–1.470)	0.776
	GG	1/1	32			1/1	5		
Female	AA	124/47	49	1	0.029	124/60	28	1	0.025
	GA	27/10	57	1.111 (0.483–2.555)	0.805	27/13	18	0.912 (0.429–1.941)	0.812
	GG	1/1	4	20.590 (2.226–190.458)	0.008	1/1	2	20.027 (2.225–180.28)	0.008
BMI[a]									
<24	AA	142/42	44.062	1		142/55	42	1	0.18
	GA	21/4	53.505	0.664 (0.233–1.891)	0.443	21/5	49.591	0.493 (0.175–1.387)	0.18
	GG	NA				NA			
≥24	AA	338/114	45.062	1	0.026	338/140	50	1	0.012
	GA	77/20	46.393	0.926 (0.566–1.515)	0.761	77/29	37	1.082 (0.715–1.638)	0.709
	GG	1/1	4	16.775 (2.129–132.171)	0.007	1/1	2	22.835 (2.891–180.37)	0.003
H. pylori infection[a]									
Yes	AA	331/108	46.099	1	0.028	331/128	41.846	1	0.017
	GA	60/17	47.416	0.946 (0.556–1.608)	0.837	60/20	44.019	0.963 (0.593–1.565)	0.879
	GG	1/1	4	16.661 (2.099–132.243)	0.008	1/1	2	20.207 (2.547–160.309)	0.004
No	AA	149/48	35.121	1	0.329	149/67	25	1	0.706
	GA	38/7	36.069	0.661 (0.288–1.517)	0.329	38/14	37	0.886 (0.471–1.665)	0.706
	GG	NA				NA			
	GA	70/18	47.349	0.796 (0.427–1.486)	0.457	70/25	40.684	0.857 (0.507–1.448)	0.564
	GG	NA				NA			
ACT[a]									
No	AA	190/51	62	1	0.145	190/55	45.538	1	0.092
	GA	43/7	50.692	0.520 (0.216–1.252)	0.145	43/8	49.297	0.495 (0.218–1.122)	0.092
	GG	NA				NA			

Table 3 (*continued*)

Table 3 (*continued*)

Variables	Genotype	OS				RFS			
		Total/event	MST	HR (95% CI)	P	Total/event	MST	HR (95% CI)	P
Yes	AA	357/141	48	1	<0.001	357/187	24	1	0.002
	GA	71/25	57	1.184 (0.702–1.997)	0.527	71/35	26	1.179 (0.763–1.822)	0.458
	GG	1/1	4	21.275 (2.295–197.256)	0.007	1/1	2	20.576 (2.282–185.538)	0.007
Tumor site[a]									
Cardia	AA	106/44	39	1	0.696	106/54	18	1	0.56
	GA	19/6	44.485	0.836 (0.340–2.055)	0.696	19/8	37	0.794 (0.366–1.722)	0.56
	GG	NA				NA			
Non-cardia	AA	348/103	47.599	1	0.005	348/130	42.709	1	0.005
	GA	76/16	50.944	0.879 (0.514–1.504)	0.638	76/25	43.566	1.086 (0.695–1.697)	0.716
	GG	1/1	4	32.242 (3.866–268.872)	0.001	1/1	2	30.802 (3.815–248.709)	0.001
Tumor diameter[a]									
<5	AA	309/82	48.422	1	0.307	309/107	43.251	1	0.617
	GA	68/11	54.953	0.701 (0.354–1.386)	0.307	68/21	46.036	1.138 (0.686–1.889)	0.617
	GG	NA				NA			
≥5	AA	227/106	33	1	0.019	227/131	18	1	0.005
	GA	44/20	38	1.005 (0.551–1.833)	0.987	44/20	31	0.709 (0.383–1.311)	0.273
	GG	2/2	4	20.254 (2.481–165.381)	0.005	2/2	2	26.207 (3.200–214.648)	0.002
Clinical stage[a]									
Early	AA	110/11		1	0.98	110/14	57.535	1	0.416
	GA	30/0		0	0.98	30/1	62.87	0.421 (0.052–3.383)	0.416
	GG	NA				NA			
Middle	AA	384/143	48	1	0.036	384/184	25	1	0.035
	GA	78/27	57	0.882 (0.538–1.446)	0.618	78/38	26	0.920 (0.609–1.390)	0.692
	GG	2/2	4	14.270 (1.810–112.511)	0.012	2/2	2	14.416 (1.859–111.822)	0.011
Late	AA	49/36	13	1	0.269	49/41	7	1	0.336
	GA	6/5	15	0.530 (0.172–1.635)	0.269	6/4	6	0.531 (0.146–1.930)	0.336
	GG	NA				NA			

[1], adjusted by gender; [3], adjusted by age. [a], patient numbers may not add up to 100% of available subjects because of missing clinical data. *KCNQ1*, potassium voltage-gated channel KQT-like subfamily member 1; OS, overall survival; RFS, recurrence-free survival; MST, median survival time; ACT, adjuvant chemotherapy; R/M, recurrence/metastasis.

Table 4 Stratified analysis of the *KCNQ1OT1* rs7939976 polymorphism with gastric cancer OS and RFS

Variables	Genotype	Total/event	OS			Total/event	RFS		
			MST	HR (95% CI)	P		MST	HR (95% CI)	P[2]
Age[1]									
≥55	AA	245/89	56	1	0.031	245/109	26	1	0.009
	GA	42/13	45.762	1.221 (0.643–2.32)	0.542	42/17	37	1.378 (0.784–2.424)	0.265
	GG	2/2	4	16.54 (1.988–137.641)	0.009	2/2	2	24.131 (2.866–203.164)	0.003
<55	AA	305/104	57	1		305/134	38	1	
	GA	70/18	47.349	0.796 (0.427–1.486)	0.457	70/25	40.684	0.857 (0.507–1.448)	0.564
	GG	NA				NA			
Gender[3]									
Male	AA	424/145	57			424/182	34		
	GA	87/22	49.503	0.800 (0.470–1.360)	0.41	87/30	43.725	1.018 (0.646–1.604)	0.938
	GG	1/1	32			1/1	5		
Female	AA	126/48	49	1	0.025	126/61	28	1	0.026
	GA	25/9	57	1.272 (0.552–2.929)	0.572	25/12	18	1.025 (0.482–2.179)	0.949
	GG	1/1	4	21.275 (2.295–197.256)	0.007	1/1	2	20.576 (2.282–185.538)	0.007
BMI[a]									
<24	AA	140/42	43.675	1		140/55	42	1	
	GA	23/4	54.558	0.594 (0.209–1.687)	0.328	23/5	51.132	0.439 (0.156–1.229)	0.117
	GG	NA				NA		0.439 (0.156–1.229)	0.117
≥24	AA	343/115	45.225	1	0.027	343/141	50	1	0.008
	GA	72/19	45.961	1.043 (0.638–1.706)	0.866	72/28	37	1.239 (0.818–1.876)	0.313
	GG	1/1	4	16.941 (2.151–133.427)	0.007	1/1	2	23.274 (2.948–183.783)	0.003
H. pylori infection[a]									
Yes	AA	333/109	46.116	1	0.028	333/129	41.865	1	0.017
	GA	58/16	47.68	1.028 (0.605–1.747)	0.918	58/19	43.953	1.026 (0.632–1.666)	0.916
	GG	1/1	4	16.764 (2.113–133.028)	0.008	1/1	2	20.401 (2.572)	0.004
No	AA	150/448	35.046	1	0.382	150/67	25	1	
	GA	37/7	36.294	0.689 (0.299–1.589)	0.382	37/14	37	0.974 (0.512–1.850)	0.935
	GG	NA				NA			
ACT[a]									
No	AA	192/51	62	1	0.233	192/55	45.801	1	0.144
	GA	41/7	50.023	0.587 (0.244–1.410)	0.233	41/8	48.662	0.544 (0.240–1.230)	0.144
	GG	NA				NA			

Table 4 (*continued*)

Table 4 (*continued*)

Variables	Genotype	Total/event	OS			Total/event	RFS		
			MST	HR (95% CI)	P		MST	HR (95% CI)	P[2]
Yes	AA	358/142	48	1	<0.001	358/188	23	1	0.001
	GA	70/24	57	1.268 (0.750–2.143)	0.375	70/34	29	1.296 (0.837–2.007)	0.244
	GG	2/2	4	89.316 (9.807–813.41)	<0.001	2/2	2	42.558 (5.243–345.483)	<0.001
Tumor site[a]									
Cardia	AA	105/44	35	1	0.383	105/54	18	1	0.331
	GA	20/6	45.681	0.656 (0.254–1.693)	0.383	20/8	37	0.667 (0.295–1.510)	0.331
	GG	NA				NA			
Non-cardia	AA	351/103	47.847	1	0.006	351/130	42.963	1	0.004
	GA	73/16	50	0.993 (0.581–1.697)	0.98	73/25	42.314	1.233 (0.789–1.924)	0.357
	GG	1/1	4	32.587 (3.909–271.665)	0.001	1/1	2	31.240 (3.870–252.142)	0.001
Tumor diameter[a]									
<5	AA	308/82	48.354	1	0.261	308/107	43.174	1	0.692
	GA	69/11	55.114	0.675 (0.341–1.338)	0.261	69/21	46.241	1.108 (0.666–1.844)	0.692
	GG	NA				NA			
≥5	AA	230/106	33	1	0.017	230/131	18	1	0.008
	GA	41/20	38	1.159 (0.634–2.119)	0.631	41/20	23	0.852 (0.458–1.585)	0.613
	GG	2/2	4	20.426 (2.503–166.657)	0.005	2/2	2	26.846 (3.278–219.865)	0.002
Clinical stage[a]									
Early	AA	109/11		1	0.976	109/14	57.497	1	0.378
	GA	31/0		0	0.976	31/1	62.958	0.393 (0.049–3.146)	0.378
	GG	NA				NA			
Middle	AA	387/143	49	1	0.04	387/184	25	1	0.038
	GA	75/27	57	0.959 (0.584–1.576)	0.87	75/38	25	0.999 (0.661–1.511)	0.997
	GG	2/2	4	14.354 (1.821–113.143)	0.011	2/2	2	14.494 (1.869–112.392)	0.011
Late	AA	50/37	13	1	0.269	50/42	7	1	0.336
	GA	5/4	17	0.530 (0.172–1.635)	0.269	5/3	4	0.531 (0.146–1.930)	0.336
	GG	NA				NA			

[1], adjusted by gender; [3], adjusted by age. [a], patient numbers may not add up to 100% of available subjects because of missing clinical data. *KCNQ1*, potassium voltage-gated channel KQT-like subfamily member 1; OS, overall survival; RFS, recurrence-free survival; MST, median survival time; ACT, adjuvant chemotherapy; R/M, recurrence/metastasis.

transcription-quantitative polymerase chain reaction (RT-qPCR) (32).

The limitations of our study included its relatively small sample size and retrospective nature. Furthermore, the mechanisms whereby the identified SNPs influence the risk of GC susceptibility and GC survival were not elucidated. Further prospective studies with larger sample sizes are needed to clarify the correlations between the KCNQ1 and KCNQ1OT1 genes and GC. More basic studies using GC cells are also needed to identify the molecular mechanisms

responsible for the effects of the *KCNQ1* and *KCNQ1OT1* genes on the susceptibility, risk, and survival of GC patients.

Conclusions

Our study showed that polymorphisms in the *KCNQ1* and *KCNQ1OT1* genes might have predictive or prognostic value in determining the susceptibility, risk, and survival of Chinese Han patients with GC. However, these results were only demonstrated to be good predictors in a specific population as a result of the heterogeneity of the tumor population and the relatively small sample size included in this study. Furthermore, the association between genetic factors and environmental factors was not fully investigated because of a lack of data regarding traits such as drinking and dietary habits. Further results are expected to clarify the influence and specific mechanisms by which *KCNQ1* and *KCNQ1OT1* gene polymorphisms affect the susceptibility, risk, and/or survival of GC patients.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The authors state that they have obtained appropriate institutional review board approval (No. K201009-03) and have followed the principles outlined in the Declaration of Helsinki (as revised in 2013) for all human experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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