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Genome-wide association study of gastric adenocarcinoma in Asia: A comparison of associations between cardia and noncardia tumors

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

CONTRIBUTIONS

Study concept and design: NH, ZW, XS, LW, BSK, NDF, KS, LDW, DL, SJC, AMG, PRT, CCA. Acquisition of data: All authors. Analysis and interpretation of data: NH, ZW, XS, LW, BSK, NDF, SJC, AMG, PRT, CCA. Drafting of the manuscript: NH, ZW, XS, LW, BSK, NDF, AMG, PRT, CCA. Critical revision for important intellectual and final approval of the manuscript: All authors. Study Supervision: KS, LDW, DL, SJC, AMG, PRT, CCA.

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Abstract

Objective—Genome wide association studies (GWAS) of gastric cancer have reported differences in SNP associations for tumor subtypes, particularly when divided by location into the gastric cardia versus the noncardia.

Design—Here we present results for a GWAS using 2350 East Asian gastric cancer cases divided as 1189 gastric cardia and 1027 gastric noncardia cases and 2708 controls. We also included up to 3042 cardia cases, 4359 noncardia cases, and 7548 controls for replication from two Chinese studies and one from Korean. From the GWAS we selected 12 top SNPs for each gastric cancer subtype, 4 top SNPs for total gastric cancer, and 1 SNP in *MUC1* for replication testing.

Results—We observed genome-wide significant associations for rs10074991 in *PRKAA1* at 5p13.1 for cardia ($p = 2.77\times10^{-12}$) and noncardia cancers ($p = 3.95\times10^{-21}$) with per allele OR (95% CI) for the combined endpoint of 0.80 (0.77–0.83). At 6p21.1, rs2294693 near *UNC5CL* was significantly associated with gastric noncardia cancer risk ($p = 2.50\times10^{-8}$), with OR (95% CI) of 1.18 (1.12–1.26), but there was only a nominal association for cardia cancer ($p = 1.47\times10^{-2}$). We also confirmed a previously reported association for rs4072037 in *MUC1* with $p = 6.59\times10^{-8}$ for total GC and similar estimates for cardia and noncardia cancers. Three SNPs in *PSCA* previously reported to be associated with gastric noncardia cancer showed no apparent association for cardia cancer.

Conclusion—Our results suggest that associations for SNPs with gastric cancer show some different results by tumor location in the stomach.

Keywords

GWAS; gastric cancer; East Asia

INTRODUCTION

Despite reductions in gastric cancer incidence rates coinciding with economic development, gastric cancer remains the third leading cause of cancer death worldwide and continues to be a major public health problem (1). As a consequence of aging populations, IARC projects that the number of incident cases of gastric cancer will continue to increase for several decades. About 90% of all gastric tumors present as adenocarcinomas, which can be further classified by location. Etiologic studies have found numerous differences between gastric cardia adenocarcinomas occurring in the top few centimeters of the stomach and noncardia

adenocarcinomas occurring elsewhere in the stomach, including distinct results for *Helicobacter pylori* infection (2;3), BMI (4), and other risk factors. Risk factors for gastric cardia adenocarcinomas also differ between Eastern and Western populations, including *Helicobacter pylori* (5).

Recently, we published a genome-wide association study that examined the associations between common genetic variants and risk of gastric adenocarcinoma and esophageal squamous cell carcinoma (ESCC) risk in ethnic Chinese subjects (6). We reported that the strongest association for gastric cardia adenocarcinoma and ESCC were SNPs in a locus on chromosome 10q23 in the *PLCE1* gene, but these SNPs showed no association with gastric noncardia adenocarcinoma. This study demonstrated that genetic susceptibility loci differ between the two main sub-locations of gastric cancer among ethnic Chinese, and therefore, each type should be investigated separately when possible.

Two other groups have published GWAS studies of gastric carcinoma in East Asians, each focusing on particular subtypes of gastric cancer. A GWAS of gastric adenocarcinoma from Japan reported significant associations for SNPs in prostate stem cell antigen (*PSCA*) (7) and for SNPs at 1q22 which were associated with gastric adenocarcinomas of diffuse but not intestinal histologic type, which are subtypes of adenocarcinoma defined in the Lauren histologic classification system (8). This study (7) did not report tumor location within the stomach, but other studies report that most gastric cancers in Japan are located in the noncardia, especially those of the intestinal subtype. A GWAS of noncardia gastric adenocarcinoma from China reported significant associations with SNPs at 5p13.1 and 3q13.31 with the strongest associations at rs13361707 and rs9841504, respectively. When the authors tested these SNPs using an independent set of 905 subjects with gastric cardia cancer, these SNPs were not significantly associated with risk (9). This study, like most studies conducted in China, did not report associations by Lauren subtype because that histologic system is not widely implemented clinically.

Here we extend our previous work by examining additional potential associations for gastric cardia, gastric noncardia, and total gastric adenocarcinoma using our gastric adenocarcinoma GWAS data and three large replication sets from China and Korea.

MATERIALS & METHODS

Gastric GWAS

For the NCI GWAS, subjects were drawn from four prospective cohort studies and one large case-control study as reported in Abnet *et al.* (6) and all subjects used in replication in the original paper were subsequently genotyped using the Illumina 660W-Quad microarray, which included scanning 725 additional gastric cancer cases and 608 additional controls. Similar genotype filtering was applied to those additional genotyped samples. The final analytic data set included 2350 gastric cancer cases and 2708 controls with genotypes for a total of 556,896 SNPs. Demographic characteristics are presented in Supplementary Table 1.

GWAS analysis and replication

We used the final analytic dataset to complete full GWAS analysis for three endpoints, cardia cancer, noncardia cancer, and total gastric cancer (the two prior end points combined plus a modest number of overlapping subsite and NOS cases) using the models described in the statistical analysis section. We ordered all results by p-value and selected a total of 29 SNPs for replication testing after excluding SNPs tagged to *PLCE1*, because these were studied in a prior publication (6). All 29 SNPs had a stage one p-value $<5 \times 10^{-5}$ and we distributed the 29 tests among the three end points as the 12 top SNPs based on the cardia gastric cancer model, the 12 top SNPs based on the noncardia gastric cancer model, and the 4 top SNPs from the total gastric model. The last SNP was selected as the lowest p-value SNP tagged to *MUC1* because of the strong prior probability given other recent publications (10). TaqMan assays were designed and optimized at the Cancer Genomics Research Laboratory. For the assays that failed to design, LD surrogates rs6717108, rs6768588, rs61364777, and rs10881372 were used for the originally selected SNPs rs11884368, rs2035265, rs3935714, and rs12403232, respectively. A total of 25 SNPs were genotyped on 3716 gastric cancer cases (1877 cardia and 1839 noncardia) and 3912 controls in the Beijing study. A total of 24 SNPs were successfully genotyped using Sequenom platform on 2896 gastric cancer cases (1796 cardia and 1100 noncardia) and 2826 controls in the Henan study. All 29 SNPs (23 were designed as Sequenom assays plus six were supplemented with TaqMan) were genotyped on 796 gastric cancer cases (65 cardia, 724 noncardia, and 7 NOS) and 810 controls in the Korean study. The modest proportion of gastric cardia cancer cases in Korea limits power for independent testing in this study.

Statistical analysis

For stage 1, logistic regression was performed to analyze the association between each SNP (genetic trend effect) and the case-control status with adjustments for study, gender, age, and significant eigenvectors, if any. To adjust for population stratification, we used the first eigenvector from a PCA analysis of ancestry informative SNPs for total gastric and cardia cancer models only, because this vector was nominally significant ($p<0.05$) in both baseline risk models. No eigenvector adjustment was needed for the noncardia only model to control for population stratification because no vectors were significantly associated with case status. Quantile-quantile plots for each outcome show no evidence of inflation with a lambda of 1.01 for each outcome (Supplementary Figure 1). In each replication study, we adjusted for gender and age (not available in the Korean study), and analyzed the total gastric as well as cardia or noncardia only models. Fixed-effect meta-analysis was subsequently applied to combine the association results for stage 1 and three stage 2 studies together. Data analysis and management were performed with GLU (https://code.google.com/p/glu-genetics/), a suite of tools available as an open-source application for management, storage, and analysis of GWAS data.

RESULTS

Search for novel associations

Using GWAS data on 2350 subjects with gastric adenocarcinoma, which included 1189 cardia, 1027 noncardia, and 134 gastric cancer cases not otherwise specified, and 2708

controls (Table 1), we selected 29 SNPs with the lowest *p*-values after LD pruning (r^2>0.6) and removal of previously identified *PLCE1* SNPs, because of their known association with risk for gastric cardia cancer. The 29 SNPs (Supplementary Table 2) included 12 SNPs with the lowest p-values each for cardia and noncardia, and four additional SNPs with the lowest p-values for total gastric cancer, plus rs4072037 near *MUC1* because it appeared to be strongly associated with gastric cancer risk in many previous candidate gene studies. Replication testing used three independent case-control sets from Henan Province China, Beijing China, and Korea that provided a total of 7408 cases and 7548 controls (Table 1). Because of past differences in associations between cardia and noncardia gastric cancers, we tested all 29 SNPs for both anatomic subtypes in the replication phase.

Supplementary Tables 3–5 provide complete results from the GWAS and the replication testing for cardia, noncardia, and total gastric cancer for all 29 SNPs. Table 2 highlights three SNPs with associations at or near genome-wide significance ($p < 5\times10^{-8}$).

At 5p13.1, rs10074991 showed genome-wide significant associations for both cardia and noncardia cancers with p-values of 7.6×10^{-12} and 2.42×10^{-23}, respectively. The odds ratios were similar in magnitude and the overall per allele OR (95% CI) for total gastric cancer was 0.80 (0.77–0.83), $p = 4.83 \times 10^{-26}$. This SNP localizes to an intron in *PRKAA1 (*protein kinase AMP-activated alpha 1 catalytic subunit) (Figure 1a).

At 6p21.1, rs2294693 we observed nominal associations with each gastric cancer subsite, but the association was genome-wide significant for only noncardia cancer risk ($p = 2.50 \times10^{-8}$), with OR (95% CI) of 1.18 (1.12–1.26). For cardia cancer the OR (95% CI) was 1.08 (1.01–1.15) ($p=1.47\times10^{-2}$), suggesting either a modest or null association with risk at that subsite. rs2294693 is an intronic SNP in *UNC5CL* (unc-5 homolog C (C. elegans)-like) (Figure 1b).

One other SNP showed an association with gastric cancer risk, but did not reach genome-wide significance. The exonic SNP rs4072037, in *MUC1* at 1q22, showed a similar OR (95% CI) for cardia and noncardia gastric cancer and a combined per allele OR (95% CI) of 0.76 (0.69–0.84), $p = 6.59 \times 10^{-8}$ (Figure 1c).

Finally, two other SNPs showed some evidence for an association with gastric cardia cancer, but had inconsistencies between studies. The point estimates for rs3935714 at 16p11.2 were consistent in data from the Beijing and Korean studies, but was not assayable in the Henan replication set and the SNP did not reach genome-wide significance in the combined estimate ($p = 1.27 \times 10^{-6}$). Similarly, rs12922317 at 16p13.13 replicated in the Beijing set, but not in the other two studies (combined $p = 2.62 \times 10^{-6}$, Supplemental Table 3)

Previously reported variants from the literature

In Table 3, we present results from our stage 1 GWAS data, without attempted replication, for six SNPs at four loci that were gleaned from previously published gastric cancer GWAS and two SNPs from a GWAS for *Helicobacter pylori* seropositivity. Notably, we confirm prior independent GWAS reports (7) of an association between multiple SNPs in *PSCA* at 8q24.3 and risk of noncardia gastric cancer, but find no evidence for an association with

cardia cancer. Shi *et al.* reported a novel association for rs9841504 in *ZBTB20* with noncardia gastric cancer, but we saw no evidence of that association in our data. Furthermore, results were mixed for two SNPs reported in a previous pleiotropy analysis that included gastric, lung, and esophageal cancer. A nominally significant association was found for rs2285947, but no association for rs2494938. We also looked up the association for two SNPs reported to be associated with *Helicobacter pylori* seropositivity in Europeans (11), without regard to development of gastric cancer, because *H. pylori* is an important cause of gastric adenocarcinoma. We found one locus (rs368433) to be nearly monomorphic in our population and no evidence for an association with gastric cancer risk at the other locus (rs10004195).

DISCUSSION

From our GWAS analysis of gastric cancer in Chinese subjects, we selected and tested associations between 29 SNPs and risk of cardia and noncardia gastric cancer using replication data from up to 9758 total cases and 10256 controls. One SNP, rs10074991 in *PRKAA1* at 5p13.1, reached genome-wide significance for both cardia- and noncardia gastric cancers, while rs2294693 at 6p21.1 showed genome-wide significance for only noncardia gastric cancer.

An intronic SNP in *PRKAA1*, rs13361707, was recently reported to be associated with risk of noncardia but not cardia gastric cancer (9). Here we found significant associations with ORs of similar magnitude for both gastric cancer subsites for rs10074991, a SNP in perfect LD with rs13361707. Shi *et al.* (9) reported a genome-wide significant association for this SNP in a scan of noncardia cancer and also tested the association using DNA samples from 905 cardia cancer patients. Other reports relating this SNP to gastric cancer from Korea have also confirmed an association (12), with one study reporting that the association did not differ by location in the stomach (13). Overall, there appears to be consistent evidence for an association with gastric noncardia cancer, but the results for cardia are mixed. *PRKAA1* is a catalytic subunit of the 5′- AMP-activated protein kinase (AMPK), which is an energy sensor that is highly conserved across eukaryotic species. Supplementary table 6 provides additional biological information on rs10074991 and SNPs in linkage disequilibrium with it showing numerous potential changes in altered binding motifs.

An association between rs2294693 at 6p21.1 and risk of noncardia gastric cancer reached genome-wide significance, but not for gastric cardia cancer alone or the combined endpoint. This intronic SNP in *UNC5CL* falls in a genomic region with two prior GWAS hits for upper gastrointestinal cancers. Two SNPs, rs10484761 and rs2494938, are 200 kb and 500 kb telomeric to rs2294693, respectively, and have been associated with esophageal squamous cell carcinoma (14) and noncardia gastric cancer in Chinese populations (15). However, the pairwise r-squared values for these three SNPs were low (≤0.015), and rs2494938 is not associated with gastric cancer risk in our GWAS data (Table 3). rs2294693 and SNPs in high LD with it (Supplementary Table 6), including a synonymous change in the coding sequence, lead to alterations in numerous protein binding and other motifs, but there is only limited evidence for alterations predicted to alter gene regulation.

We previously reported a borderline significant association for rs4072037 (*MUC1*) for total gastric cancer using a subset of the current data (6). Our original published findings for rs4072037 included about 2240 gastric cancer cases, while the total here includes about 3146 cases. Although the current p-value falls just short of genome-wide significance ($p = 6.59 \times 10^{-8}$) Saeki *et al.* (16) reported that rs4072037 was associated with both diffuse type gastric cancer (OR 1.66, 95% CI 1.44–1.93) and intestinal type gastric cancer (1.23, 1.02–1.48). We do not have information on diffuse versus intestinal type gastric cancer in our study, so we cannot directly investigate the specificity of the association by Lauren classification. Further, a recent meta-analysis of 6580 cases and 10324 controls including data from both the Saeki *et al.* study and our previous publication (6) found a summary estimate for rs4072037 of 0.72 (0.68–0.77), $p = 7.82 \times 10^{-25}$ (10). The choice of referent allele has differed in prior publications because the G allele predominates in populations of European descent, while the A allele predominates in populations of East Asian descent, but studies consistently find that the A allele elevates risk compared to the G allele. *MUC1* is a member of the mucin family that collectively forms the protective mucous barrier on epithelial surfaces. rs4072037 seems to be functionally important because it altered transcriptional regulation and determined splice variants in *MUC1* (16).

Using our GWAS data, we observed significant associations between variants at 8q24.3 (*PSCA*) and risk of noncardia gastric cancer, which has been reported in several prior publications (Table 3) (7). Jin *et al.* also showed evidence for an association between rs2285947 at 7p15.3 and noncardia gastric cancer risk (15). This SNP does not appear on our array so we examined a proxy, rs976516 ($r^2 = 0.85$) and found further evidence for an association with noncardia and cardia cancer, with p-value (9.42×10^{-3}) for total gastric cancer. We saw no association with either of two loci reported to be associated with *H. pylori* seropositivity in Europeans (11), but note that *H. pylori* seropositivity is highly prevalent in our populations, and we did not directly re-assess the previously reported association.

Regardless of which sub-location of gastric cancer provided the initial signal from the GWAS analysis, we completed replication testing in both cardia and noncardia gastric adenocarcinoma cases to more deeply explore how associations for the selected SNPs differed between gastric cancer locations. Our overall results showed that rs10074991 was associated with risk of gastric cardia adenocarcinoma ($p = 7.36 \times 10^{-12}$) despite little evidence for an association in our GWAS subjects ($p = 1.27 \times 10^{-2}$). Finally, when added to the known consistent differences between cardia and noncardia gastric cancer for the associations in common variants for *PSCA* and *PLCE1*, our results suggest that the clearest picture of the association of common genetic variants with gastric cancer in the future will come from studies that include both gastric cancer sub-locations studied independently whenever possible. Studies in Western populations have noted major differences in the risk factors for cardia and noncardia gastric cancers, many of which suggest that cardia adenocarcinomas in the West are more similar to esophageal adenocarcinomas. The current study coupled with previous reports on other risk factors that showed either similar (5) or dissimilar results (6) in China highlight the apparent differences between these tumor types in Asian versus Western countries.

In summary, our replication study found associations with variants in *PRKAA1* and *MUC1* for cardia and noncardia gastric cancers. We also report a novel association with variants in *UNC5CL* at 6p21.1. There was some heterogeneity between our studies and those in the literature, resolution of which will require additional data.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Non-standard abbreviations

ESCC	Esophageal squamous cell carcinoma
NCI	National Cancer Institute

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SUMMARY BOX

What is already known about this subject?

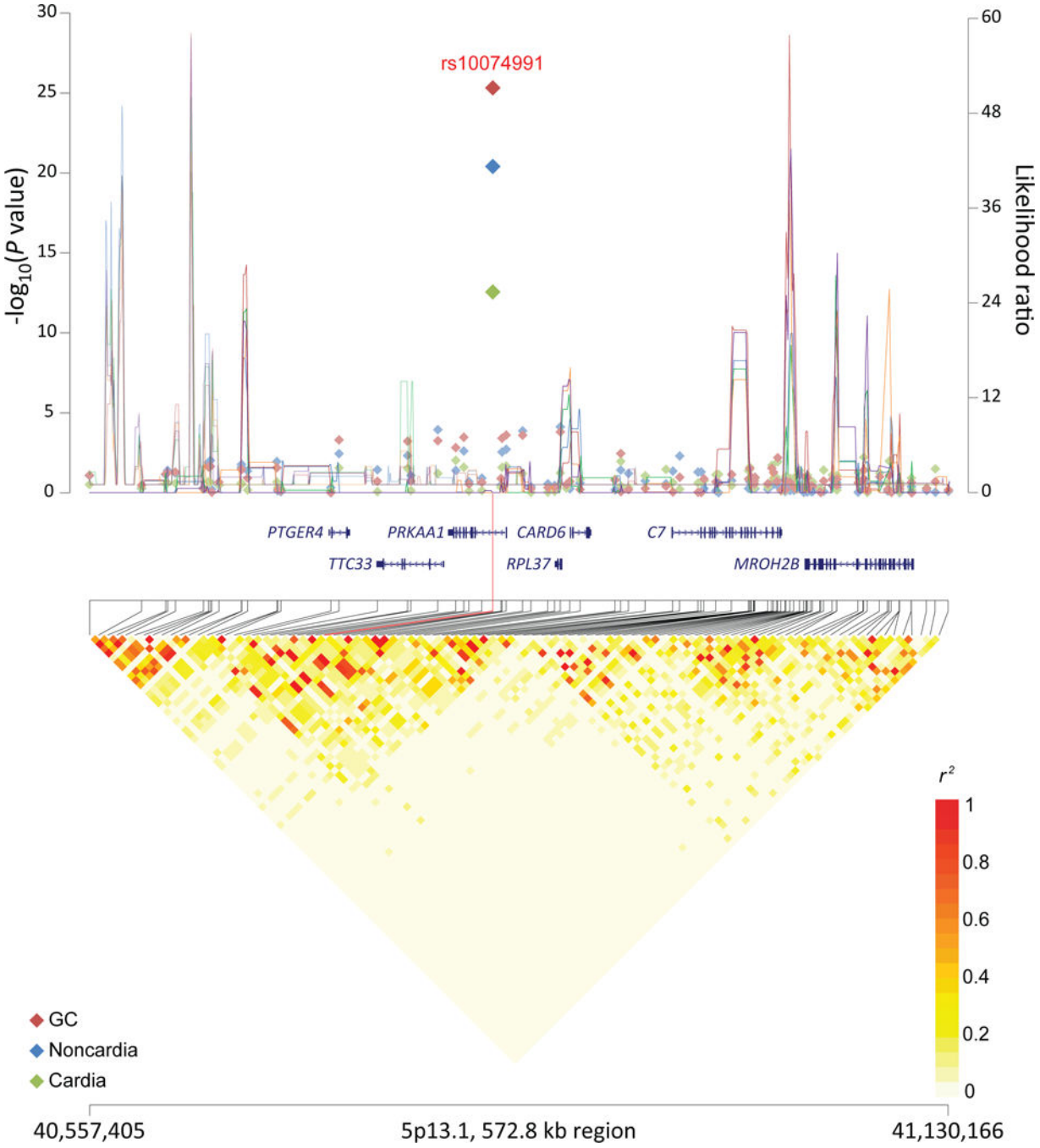
- There are almost one million new cases of gastric cancer each year and Eastern Asia has the highest rates of any geographic region
- Several previous GWAS studies of gastric cancer in subjects of East Asian ethnicities have reported a modest number of associations for common single nucleotide polymorphisms
- These studies have reported that many SNPs have different results when analyzed by location of the tumor within the stomach – cardia versus noncardia

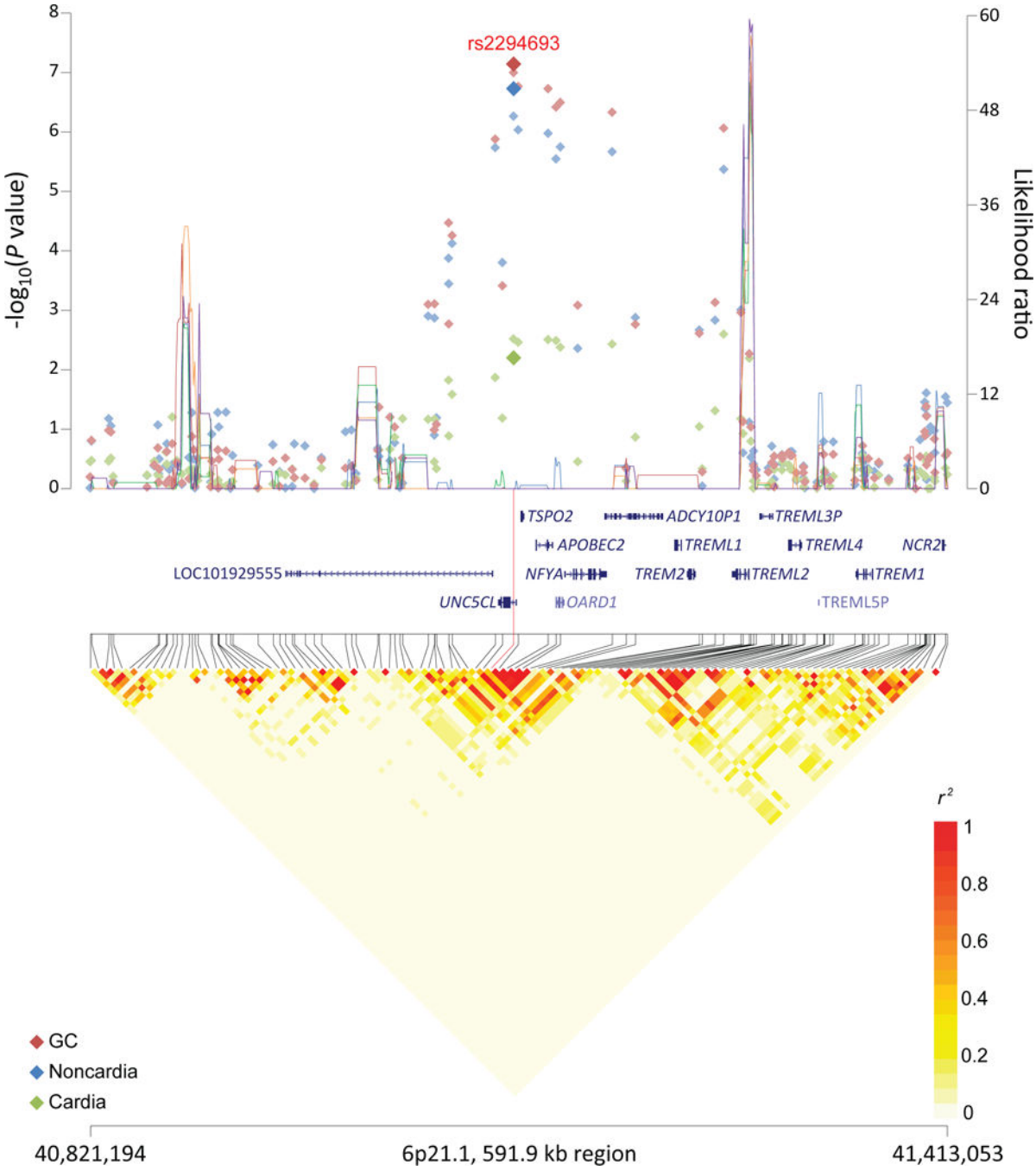
What are the new findings?

- Using a GWAS with subjects of Asian ethnicity and more than 1000 cases from each sub-location within the stomach, we found that rs10074991 in *PRKAA1* at 5p13.1 showed genome-wide significant associations for cardia and noncardia cancers, with the finding for cardia being novel. Furthermore, we observed that rs2294693 near UNC5CL at 6p212.1 was genome-wide significant for gastric noncardia cancer.
- A SNP in MUC1 (rs4072037) showed near genome-wide significance, with similar associations for cardia and noncardia tumors
- Three SNPs in *PSCA* previously reported to be associated with gastric noncardia cancer showed subsite specific findings with some evidence for an association in the noncardia, but no association for cardia cancer.

How might this impact clinical practice in the foreseeable future?

- These GWAS findings highlight the importance of studying gastric cardia and noncardia cancer in parallel to assess differences in etiology by location within the stomach
- The results from this GWAS increase our understanding of the pathophysiology of gastric cancer and support better understanding of the etiology of this common cancer





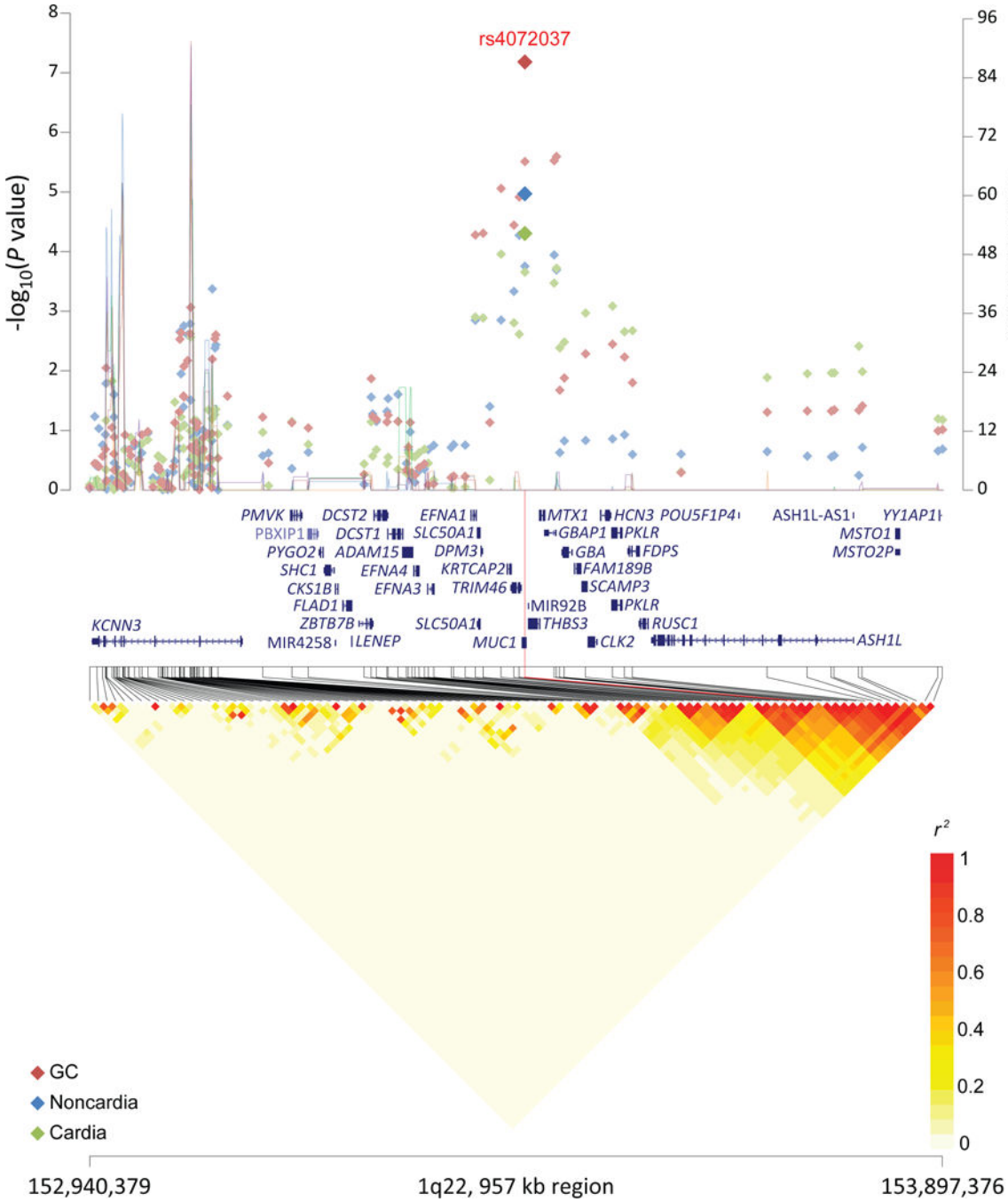


Figure 1.

Regional plots of association results, recombination hotspots, and linkage disequilibrium for the (a) 5p13.1:40,557,405–41,130,166, (b) 6p21.1:40,821,194–41,413,053, and (c) 1q22:152,940,379–153,897,376 gastric cancer susceptibility loci. Association results from a trend test in –log10 p-values (y axis, left; red diamonds, gastric cancer association result; blue diamonds, noncardia gastric cancer association result; light green diamonds, cardia gastric cancer results) of the SNPs are shown according to their chromosomal positions (x axis). Linkage disequilibrium structure based on control data from the GWAS (n=1,660) was

visualized by snp.plotter software. The line graph shows likelihood ratio statistics (y axis, right) for recombination hotspots by SequenceLDhot software based on the background recombination rates inferred by PHASE v2.1 using 5 re-samplings of 100 controls. Physical locations are based on hg18. Gene annotation was based on the NCBI RefSeq genes from the UCSC Genome Browser.

Table 1

GWAS and replication subjects by type and study

Study	Cardia	Noncardia	All GC*	Controls
GWAS				
NCI	1189	1027	2350	2708
Replication sets				
Henan	1796	1100	2896	2826
Beijing	1877	1839	3716	3912
Korea	65	724	796	810
Combined	**4927**	**4690**	**9758**	**10256**

* Includes gastric cancers with overalpping or NOS locations

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Table 2

Three SNPs associated with gastric cancer risk at or near genome-wide significance

				Cardia			Noncardia			Total gastric cancer		
Cytoband	**NCBI dbSNP identifier, build 135 (referent, effect allele)**	**Gene Neighborhood**	**GROUP**	**OR**	**(95% CI)**	**P**	**OR**	**(95% CI)**	**P**	**OR**	**(95% CI)**	**P**
5p13.1	rs10074991	PRKAA1	NCI (GWAS)	0.88	(0.80–0.97)	1.27E-02	0.79	(0.71–0.88)	1.38E-05	0.83	(0.77–0.90)	5.52E-06
	(G, A)		Beijing	0.77	(0.71–0.84)	4.24E-10	0.70	(0.64–0.76)	1.40E-17	0.74	(0.69–0.79)	6.39E-20
			Henan	0.90	(0.82–0.99)	2.96E-02	0.85	(0.76–0.95)	3.67E-03	0.88	(0.81–0.96)	3.01E-03
			Korea	0.62	(0.42–0.89)	1.02E-02	0.80	(0.70–0.93)	3.34E-03	0.79	(0.68–0.91)	1.05E-03
			Combined	**0.83**	**(0.79–0.88)**	7.36E-12	**0.77**	**(0.73–0.81)**	**2.42E-23**	**0.80**	**(0.77–0.83)**	**4.83E-26**
6p21.1	rs2294693	UNC5CL,TSPO2	NCI (GWAS)	1.19	(1.06–1.34)	3.02E-03	1.36	(1.20–1.53)	5.44E-07	1.28	(1.17–1.41)	1.00E-07
	(T, C)		Beijing	1.02	(0.93–1.12)	7.24E-01	1.13	(1.03–1.23)	1.26E-02	1.07	(0.99–1.15)	7.58E-02
			Henan	1.09	(0.97–1.22)	1.31E-01	1.15	(1.01–1.30)	3.24E-02	1.13	(1.02–1.25)	1.52E-02
			Korea	0.79	(0.50–1.23)	2.97E-01	1.13	(0.96–1.33)	1.52E-01	1.09	(0.93–1.28)	2.90E-01
			Combined	**1.08**	**(1.01–1.15)**	1.47E-02	**1.18**	**(1.12–1.26)**	**2.50E-08**	**1.14**	**(1.09–1.20)**	**7.22E-08**
1q22	rs4072037	MUC1	NCI (GWAS)	0.76	(0.65–0.88)	2.21E-04	0.75	(0.65–0.87)	1.76E-04	0.76	(0.68–0.86)	3.08E-06
	(A, G)		Korea	0.46	(0.23–0.93)	2.60E-02	0.77	(0.62–0.96)	1.95E-02	0.74	(0.60–0.92)	5.68E-03
			Combined	**0.74**	**(0.64–0.86)**	**4.97E-05**	**0.76**	**(0.67–0.86)**	**1.07E-05**	**0.76**	**(0.69–0.84)**	**6.59E-08**

ORs and 95% CIs come from models adjusted for age and sex. Models for total and cardia gastric cancer were further adjusted for one Eigen vector to account for population stratification. Models for noncardia cancer required no adjustment (see methods).

Table 3

Associations from the Stage 1 GWAS data for SNPs from previously published GWAS studies

Cardia

Cytoband	NCBI dbSNP identifier build 135	Surrogate	R^2	Alleles	MAF Controls|Cases	P	OR	(95% CI)	Gene	GWAS target	Reference
8q24.3	rs2294008			C|T	0.280|0.286	9.92E-01	1.00	(0.89, 1.12)	PSCA	Gastric cancer	Sakamoto
8q24.3	rs2920297			T|C	0.281|0.285	8.55E-01	0.99	(0.89, 1.11)	PSCA	Gastric cancer	Sakamoto
8q24.3	rs2976392			T|C	0.281|0.285	8.55E-01	0.99	(0.89, 1.11)	PSCA	Gastric cancer	Sakamoto
3q13.31	rs9841504	rs16823078	0.94	T|C	0.129|0.131	5.66E-01	1.09	(0.82, 1.44)	ZBTB20	Noncardia gastric cancer	Shi
6p21.1	rs2494938	rs2494950	0.78	G|A	0.249|0.256	8.15E-01	0.99	(0.88, 1.11)	LRFN2	3 cancer pleiotropy	Jin
7p15.3	rs2285947	rs976516	0.85	A|G	0.347|0.336	9.44E-02	0.91	(0.82, 1.02)	DNAH11	3 cancer pleiotropy	Jin
1q23.3	rs368433	rs12744234	0.25	C|T	0.003|0.003				FCGR2A	*H. pylori* seropositivity	Mayerle
4p14	rs10004195	rs4543123	0.75	C|T	0.499|0.486	9.49E-01	1.00	(0.91, 1.11)	TLR	*H. pylori* seropositivity	Mayerle

Noncardia

Cytoband	NCBI dbSNP identifier build 135	Surrogate	R^2	Alleles	MAF Controls|Cases	P	OR	(95% CI)	Gene	GWAS target	Reference
8q24.3	rs2294008			C|T	0.280|0.307	5.86E-03	1.17	(1.05, 1.32)	PSCA	Gastric cancer	Sakamoto
8q24.3	rs2920297			T|C	0.281|0.309	5.46E-03	1.18	(1.05, 1.32)	PSCA	Gastric cancer	Sakamoto
8q24.3	rs2976392			T|C	0.281|0.309	5.46E-03	1.18	(1.05, 1.32)	PSCA	Gastric cancer	Sakamoto
3q13.31	rs9841504	rs16823078	0.94	T|C	0.129|0.143	3.87E-01	1.10	(0.88, 1.38)	ZBTB20	Noncardia gastric cancer	Shi
6p21.1	rs2494938	rs2494950	0.78	G|A	0.249|0.239	8.65E-01	0.99	(0.88, 1.12)	LRFN2	3 cancer pleiotropy	Jin
7p15.3	rs2285947	rs976516	0.85	A|G	0.347|0.305	1.40E-02	0.87	(0.78, 0.97)	DNAH11	3 cancer pleiotropy	Jin
1q23.3	rs368433	rs12744234	0.25	C|T	0.003|0.002				FCGR2A	*H. pylori* seropositivity	Mayerle
4p14	rs10004195	rs4543123	0.75	C|T	0.499|0.491	1.01E-01	0.92	(0.82, 1.02)	TLR	*H. pylori* seropositivity	Mayerle

All Gastric Cancer

Cytoband	NCBI dbSNP identifier build 135	Surrogate	R^2	Alleles	MAF Controls|Cases	P	OR	(95% CI)	Gene	GWAS target	Reference
8q24.3	rs2294008			C|T	0.280|0.295	8.21E-02	1.08	(0.99, 1.18)	PSCA	Gastric cancer	Sakamoto
8q24.3	rs2920297			T|C	0.281|0.296	1.02E-01	1.08	(0.99, 1.17)	PSCA	Gastric cancer	Sakamoto

Cardia

Cytoband	NCBI dbSNP identifier build 135	Surrogate	R^2	Alleles	MAF Controls|Cases	P	OR	(95% CI)	Gene	GWAS target	Reference
8q24.3	rs2976392			T|C	0.281|0.296	1.02E-01	1.08	(0.99, 1.17)	PSCA	Gastric cancer	Sakamoto
3q13.31	rs9841504	rs16823078	0.94	T|C	0.129|0.139	3.41E-01	1.09	(0.91, 1.31)	ZBTB20	Noncardia gastric cancer	Shi
6p21.1	rs2494938	rs2494950	0.78	G|A	0.249|0.245	7.63E-01	0.99	(0.90, 1.08)	LRFN2	3 cancer pleiotropy	Jin
7p15.3	rs2285947	rs976516	0.85	A|G	0.347|0.319	9.42E-03	0.90	(0.82, 0.97)	DNAH11	3 cancer pleiotropy	Jin
1q23.3	rs368433	rs12744234	0.25	C|T	0.003|0.002				FCGR2A	*H. pylori* seropositivity	Mayerle
4p14	rs10004195	rs4543123	0.75	C|T	0.499|0.493	3.20E-01	0.96	(0.89, 1.04)	TLR	*H. pylori* seropositivity	Mayerle

ORs and 95% CIs come from models adjusted for age and sex. Models for total and cardia gastric cancer were further adjusted for one Eigen vector to account for population stratification. Models for noncardia cancer required no adjustment (see methods).