Supplementary methods

To profile the piwi protein expression in the stomach, we used microarray and immunohistochemistry technologies.

Microarray. Tissue microarray recipient blocks containing 181 gastric cancer tissues and 181 normal adjacent tissues were constructed from formalin-fixed paraffin-embedded specimens. We located the appropriate tissue of the normal and tumor tissues under the microscope. Then three tissue cores (1.5-mm in diameter) were transferred to a new recipient paraffin block using a microarray instrument, according to established methods. One cylinder of normal gastric mucosa adjacent to each tumor was also transferred to the recipient block. Sections (3 mm thick) were cut the day before use and stained according to standard protocol.

Immunohistochemistry. Immunostaining was conducted on 5-μm paraffin-embedded tissue sections using antigen retrieval with EDTA buffer and the EliVision Plus horseradish peroxidase. Staining was performed using an UltraSensitive S-P (goat) kit (Lab Vision Corp, Kalamazoo, MI, USA), following the manufacturer's recommendations. The sections were incubated overnight at 4°C with PIWIL4 antibodies (1/200; cat no. ab111714; Abcam, Cambridge, UK). The results were reviewed independently by two pathologists. Immunostaining was assessed semi-quantiatively by measuring both the intensity of the staining (score A = 0, 1, 2 or 3) and extent of staining (score B=0, 0%; 1, 1-10%; 2, 11-50%; 3, 51-80% or 4, 81-100%). The scores for the intensity and extent of staining were multiplied (possible maximum A x B=12) to give a weighted score (-, 0-1; 1+, 1-2; 2+, 3-4; or 3+, 6-12) for each case (1). The weighted scores were grouped in two categories where scores of ≤1+ were considered as negative expression and ≥2+ as positive expression. Further, the weighted score distribution was compared between cases and controls using the extended 2 by 4 Fisher Exact Test.

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Figure S1. The distributions of intensities from all samples.

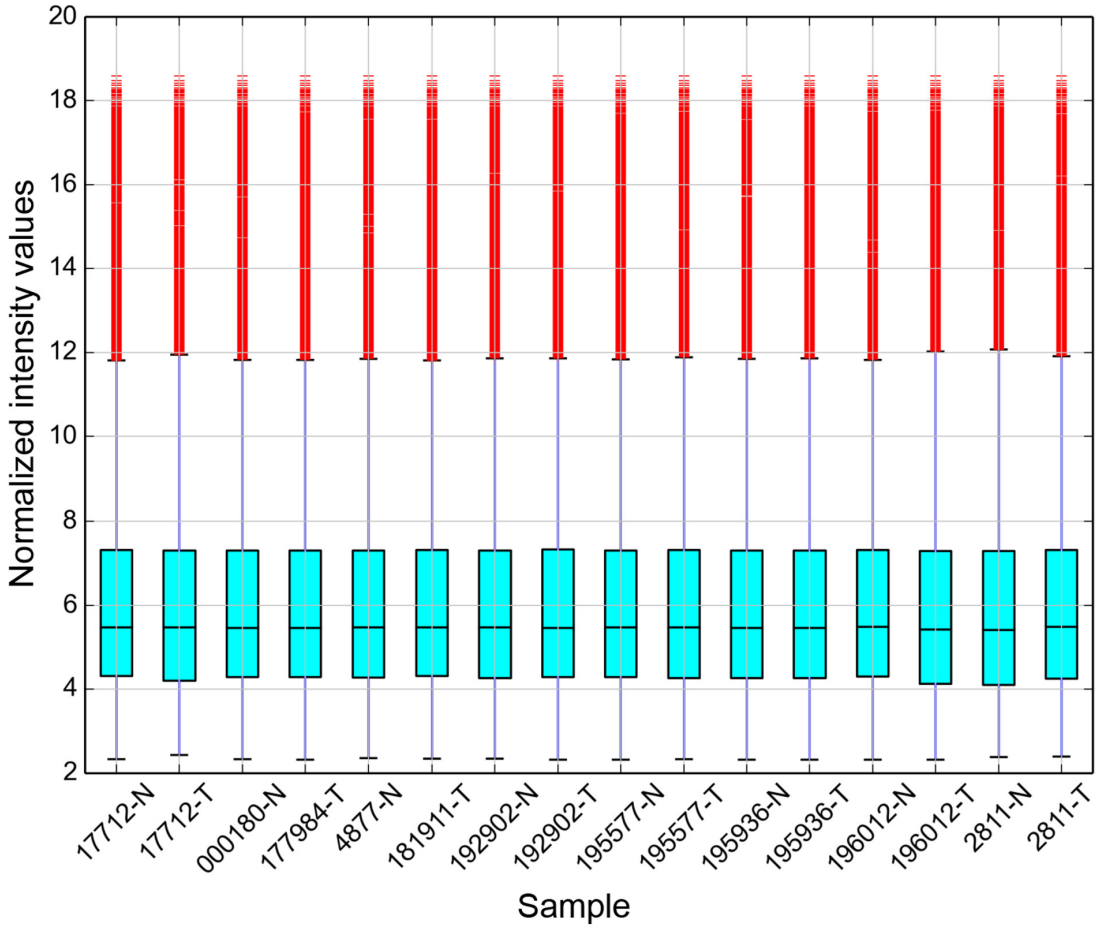

Figure S2. The Scatter-plot for the intensity reproducibility between cases and controls.

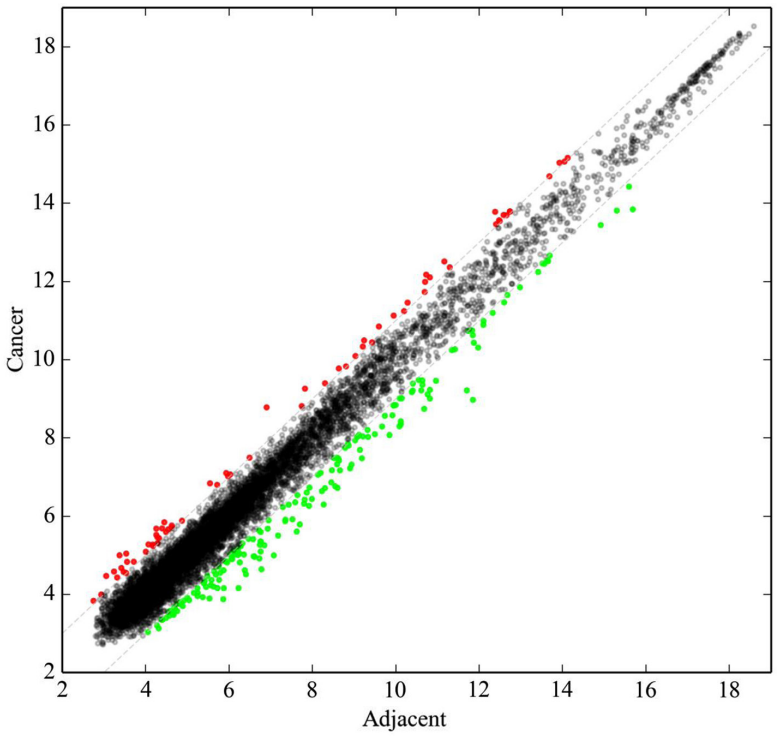

Figure S3. Illustration for the pathways underlying piRNA-GC association. Solid lines: Directly evidenced by our study; dash lines: Indirectly evidenced by the literature. ❶ piRNA expression is correlated with the risk SNPs (by eQTL analysis). ❷ piRNAs may regulate the expression of the nearest protein-coding genes by sequence complementarity via non-TE pathway. ❸ mRNAs/proteins of the risk protein-coding genes are expressed in the stomach (by RNA-Seq, RNA microarray and mass spectrometry-based proteomics microarray analyses). ❹ RNAs/proteins expressed in the stomach are assumed to have potential physiological functions. ❺ Many physiological functions are assumed to be related to the development of GC. ❻ piRNAs are hypothesized to suppress RNA retrotransposons that might regulate transcription of proximate genes. ❼ piRNAs are hypothesized to suppress DNA transposons that might regulate transcription of proximate genes. ❽ Many genes have been associated with GC in the literature. ❾ Some genes regulated by piRNAs exert physiological functions in the stomach. ❿ piRNA expression in the stomach is detected by microarray analysis. ⓫ piRNAs are associated with GC (by differential expression analysis), which is the main goal of the present study. ⓬ Associations between SNPs and GC are identified by GWAS. SNPs, single nucleotide polymorphisms; GC, gastric cancer; GWAS, genome-wide association study.

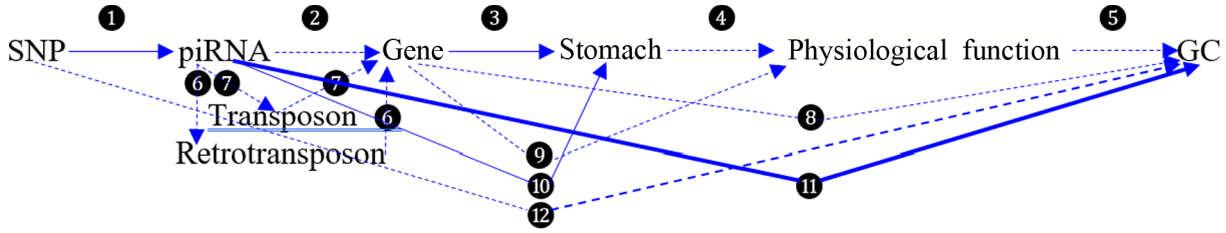

Figure S4. HeatMap and hierarchical clustering. (x-axis, individuals; y-axis, piRNAs; color: Expression levels).

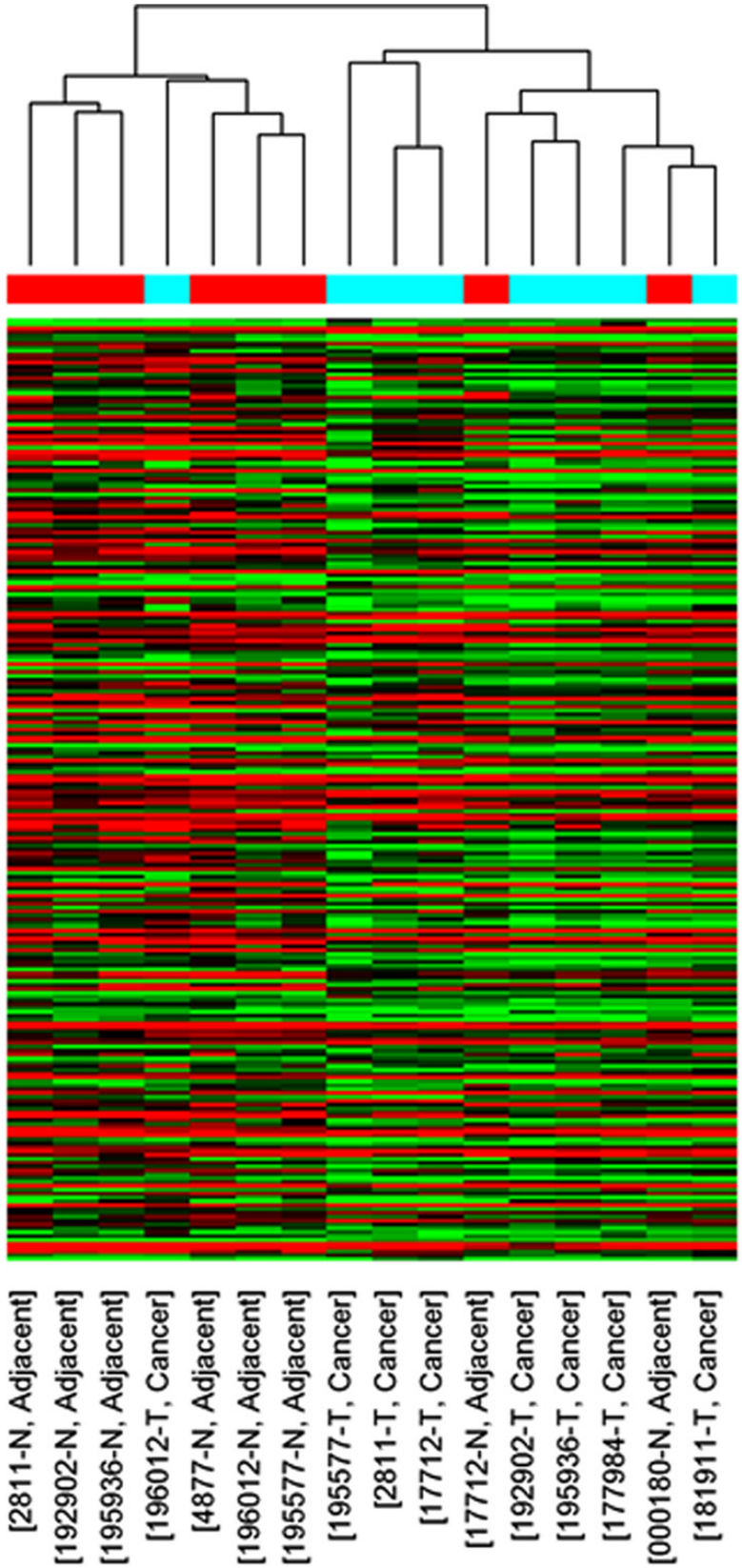

Figure S5. Representative images of PIWIL4 protein expression in gastric cancer and adjacent normal tissues. (A and B) High expression of PIWIL4 in gastric cancer. (C and D) Low expression of PIWIL4 in matched adjacent normal tissues. A and C: IHC; magnification x100; scale bars, 200 μm. B and D: IHC, magnification x 400; scale bars, 50 μm. IHC, immunohistochemistry.

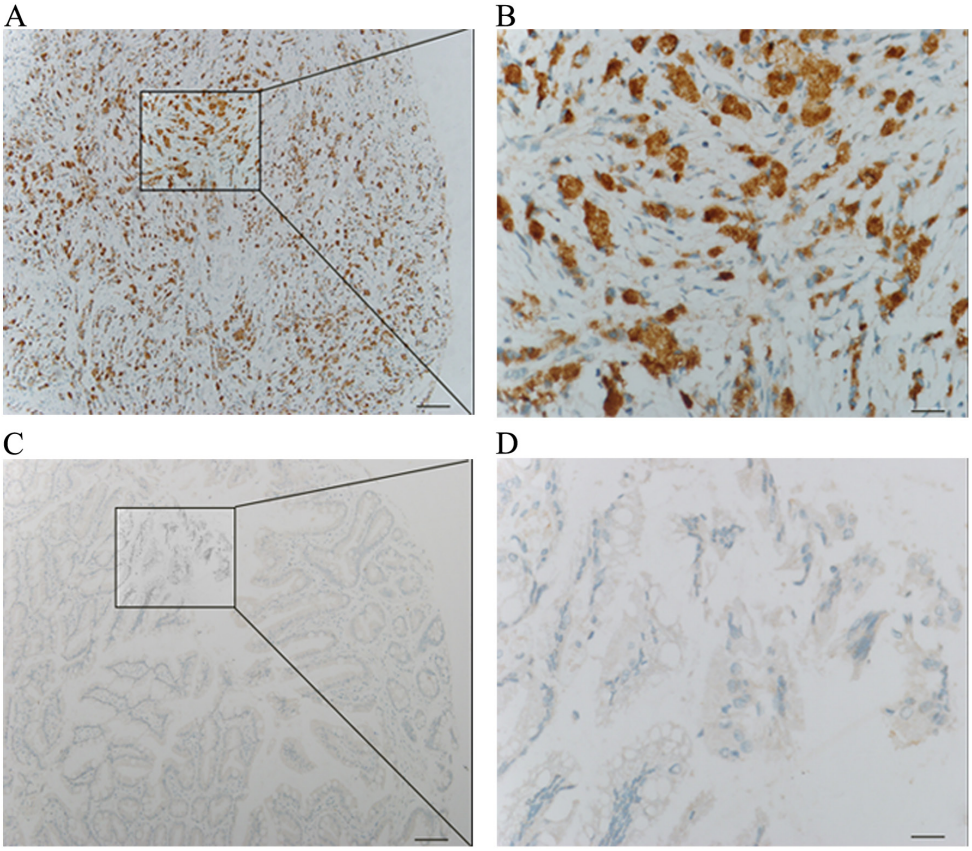

Table SI. All stomach piRNAs significantly differentially expressed between cases and controls.

piRNA	Alias	Length (nt)	Chr	Normalized intensity		Cancer vs. control		Potential TE target [type]	Gene	Associated phenotypes
				Cancer	Control	FC	P-value			
DQ580689	piR-hsa-10915	28	chr1	180	90	2.0 ↑	0.016	MIRc [SINE]	*NBPF3*[S]	
DQ600515	piR-hsa-30715	29	chr1	4,071	1,668	2.4 ↑	0.041	AluY [SINE]	*ATAD3B*[S]	Breast cancer (2), cancer cells (3)
DQ571419	piR-hsa-1742	28	chr1	1,443	605	2.4 ↑	0.032	AluJr [SINE]	*RPS8*[S]	Phylogeny of *Babesia* and *Theileria* (4,5)
DQ588779	piR-hsa-19076	29	chr1	14,194	6,844	2.1 ↑	0.037	AluSz6 [SINE]	*SKI*[S]	Gastric cancer (6,7), pancreatic cancer (8), prostate cancer (9), lung cancer (10,11), cervical cancer cells (12), breast cancer (13)
DQ601419	piR-hsa-30907	27	chr1	16	8	2.1 ↑	0.038	AluSz [SINE]	*FAM163A*	
DQ575884[E]	piR-hsa-6147	32	chr2	1,393	691	2.0 ↑	0.017	L1M4 [LINE]	to *EPCAM*[S]	Metastatic colorectal carcinoma (14), colon cancer (15,16), lung cancer (17), hepatic tumors (18,19), epithelial cancer (20)
DQ594797	piR-hsa-25103	26	chr2	14	7	2.1 ↑	0.042	L1MCa [LINE]	to *TEKT4*	Breast cancer (21)
DQ578739[E,C]	piR-hsa-8966	31	chr2	1,709	3,422	2.0 ↓	0.007	L1PA8 [LINE]	to *LOC100507334*	
DQ571556[E,C]	piR-hsa-1879	27	chr2	10	21	2.0 ↓	0.023	MSTA [LTR]	to *SPATA31C1*	
DQ595533[E,C]	piR-hsa-25780	29	chr3	13,314	6,148	2.2 ↑	0.035	L1MD [LINE]	*COLQ*[S]	Congenital myasthenia [>30 studies: e.g. (22)]
DQ575557[C]	piR-hsa-5835	29	chr3	25	83	3.4 ↓	0.003	L2b [LINE]	to *IQSEC1*[S]	
DQ594440[C]	piR-hsa-24659	31	chr3	60	164	2.7 ↓	0.004	L2b [LINE]	to *IQSEC1*[S]	
DQ593293[E,C]	piR-hsa-23556	31	chr5	710	1,595	2.2 ↓	0.049	AluSq2 [SINE]	to *C5orf52*	
DQ573237[E,C]	piR-hsa-3530	32	chr6	33	71	2.2 ↓	0.038	L1MB7 [LINE]	*SAYSD1*[S]	Blood pressure [dbGaP]
DQ587262[C]	piR-hsa-17553	31	chr6	97	233	2.4 ↓	0.003	-	to *LOC100507584*	
DQ580665[E,C]	piR-hsa-10891	26	chr7	2,349	5,133	2.2 ↓	0.041	AluSq2 [SINE]	*POLR2J*[S]	Lung cancer (23)
DQ594511	piR-hsa-24730	29	chr8	22	45	2.0 ↓	0.004	AluY [SINE]	to *LOC100287846*	
DQ572848[C]	piR-hsa-3171	30	chr9	22	8	2.7 ↑	0.024	-	to *TLE4*[S]	Colorectal cancer (24), myeloid leukemia (25)
DQ590922[C]	piR-hsa-21201	29	chr9	32	10	3.1 ↑	0.036	-	to *TLE4*[S]	Colorectal cancer (24), myeloid leukemia (25)
DQ583443[E,C]	piR-hsa-13723	30	chr9	1,582	3,683	2.3 ↓	0.015	-	*FAM225A*	
DQ583442[C]	piR-hsa-13722	29	chr9	704	2,000	2.8 ↓	0.039	-	*FAM225A*	
DQ580779	piR-hsa-11005	28	chr9	61	184	3.0 ↓	0.035	MER58A [DNA]	*TMOD1*[S]	Oral cancer (26)
DQ598137	piR-hsa-28352	28	chr10	15	58	4.0 ↓	0.017	-	*NUTM2A*	
DQ600670	piR-hsa-30958	30	chr11	4,410	1,805	2.4 ↑	0.032	AluJb [SINE]	*EED*[S]	Colorectal cancer (27,28)
DQ573078[C]	piR-hsa-3386	30	chr11	28	62	2.2 ↓	0.032	MER61A [LTR]	to *CHST1*[S]	Glucose [dbGaP]
DQ571073[E,C]	piR-hsa-231	26	chr12	9	19	2.1 ↓	0.02	HERV9-int [LTR]	to *CLLU1*[S]	Chronic lymphocytic leukemia [>10 studies: e.g. (29)]

Table SI. Continued.

piRNA	Alias	Length (nt)	Chr	Normalized intensity		Cancer vs. control		Potential TE target [type]	Gene	Associated phenotypes
				Cancer	Control	FC	P-value			
DQ600254[E,C]	piR-hsa-30454	29	chr14	144	354	2.5 ↓	0.027	MamGyp-int [LTR]	*PNMA1*[S]	Pancreatic ductal, adenocarcinoma (30), paraneoplastic CNS disease (31-33)
DQ598301[C]	piR-hsa-28516	30	chr15	22	10	2.2 ↑	0.031	-	to *TARSL2*[S]	
DQ570858	piR-hsa-1109	31	chr15	30	106	3.5 ↓	0.005	L1ME2 [LINE]	*HERC2P7*	
DQ572562[E,C]	piR-hsa-2798	29	chr15	592	1,356	2.3 ↓	0.011	-	*DNM1P46*	
DQ570015	piR-hsa-339	30	chr15	429	1,642	3.8 ↓	0.036	MIR1_Amn [SINE]	*GOLGA8A*[S]	
DQ595214[C]	piR-hsa-25475	31	chr15	11	24	2.2 ↓	0.037	AluJo [SINE]	*DNM1P46*	
DQ590386[E,C]	piR-hsa-18709	29	chr16	11,953	5,766	2.1 ↑	0.046	L1MB7 [LINE]	*VAC14*[S]	Neurodegeneration (34)
DQ595534[E,C]	piR-hsa-25781	30	chr16	11,307	5,429	2.1 ↑	0.038	L1MB7 [LINE]	*VAC14*[S]	Neurodegeneration (34)
DQ571813[E,C]	piR-hsa-2107	31	chr16	12,123	5,710	2.1 ↑	0.046	L1MB7 [LINE]	*VAC14*[S]	Neurodegeneration (34)
DQ590827	piR-hsa-21123	30	chr16	179	367	2.0 ↓	0.037	AluJb [SINE]	*DHODH*[S]	Melanoma (35)
DQ583301	piR-hsa-13610	26	chr17	18	53	3.0 ↓	0.018	AluJb [SINE]	*LRRC37A4P*[S]	
DQ588880	piR-hsa-19177	30	chr17	30	67	2.2 ↓	0.032	-	to *HOXB5*[S]	Gastric carcinoma (36), breast cancer (37), bladder cancer (38), oral squamous cell carcinoma (39), ovarian carcinomas (40), obesity (41)
DQ579739	piR-hsa-9994	30	chr19	1,844	774	2.4 ↑	0.029	AluSc8 [SINE]	*CXCL17*[S]	Colon cancer (42), hepatocellular carcinoma (43), lung macrophages (44), tumor progression (45), pancreatic carcinogenesis (46)
DQ576821	piR-hsa-7157	28	chr19	28	77	2.7 ↓	0.004	FLAM_A [SINE]	*ZNF490*	
DQ577343[E,C]	piR-hsa-7633	29	chr19	515	1,807	3.5 ↓	0.023	THE1D [LTR]	to *LOC400685*	
DQ577344[E,C]	piR-hsa-7634	30	chr19	555	1,740	3.1 ↓	0.006	THE1D [LTR]	to *LOC400685*	
DQ577345[E,C]	piR-hsa-7635	31	chr19	383	969	2.5 ↓	0.003	THE1D [LTR]	to *LOC400685*	
DQ583043[E,C]	piR-hsa-13366	30	chr19	32	135	4.2 ↓	0.015	L1MDa [LINE]	to *LOC100652909*	
DQ570687	piR-hsa-952	28	chr22	910	448	2.0 ↑	0.012	Alu [SINE]	*RPL3*[S]	Colon cancer (47-49)
DQ574146[E,C]	piR-hsa-4408	30	chr22	49	197	4.1 ↓	0.012	AluSx3 [SINE]	*IGLL1*	Myocardial infarction [dbGaP]
DQ574145	piR-hsa-4407	30	chr22	18	75	4.2 ↓	0.01	AluSx3 [SINE]	*IGLL1*	Myocardial infarction [dbGaP]
DQ574148	piR-hsa-4410	30	chr22	25	110	4.4 ↓	0.012	AluSx3 [SINE]	*IGLL1*	Myocardial infarction [dbGaP]
DQ574147[E,C]	piR-hsa-4409	31	chr22	55	208	3.8 ↓	0.01	AluSx3 [SINE]	*IGLL1*	Myocardial infarction [dbGaP]
DQ580529[E,C]	piR-hsa-10755	30	chr22	13	30	2.3 ↓	0.022	MER52A [LTR]	to *WBP2NL*	Breast cancer (50-52)

[E]These piRNAs with eQTL signals are nominally controlled by at least one of the genome-wide significant replicated risk variants for gastric cancer ($1.6x10^{-4}$≤P<0.05) (Table III). [C]These piRNAs are located in clusters. [S]These genes are expressed in stomach; ↑, upregulated; ↓, downregulated. FC, fold-change. P-values from t-test; 'to', proximate to; dbGaP, referring to dbGaP database (www.ncbi.nlm.nih.gov/gap).

Table SII. mRNA and protein expression levels of top risk genes in the stomach in three independent cohorts.

	UK Europeans (n=176)	American (n=262)	Germany (n=216)
Databases:	BioGPS	GTEx	ProteomicsDB
Age at death (years)	19-96 (45±16)	21-70 (41±14)	-
Values	Normalized intensity	TPM	Raw concentration value
Thresholds:	36	1	10 ppm
Expression levels:			
CXCL17	-	328.0	-
EPCAM	-	69.8	50
RPL3	-	1147.0	475
RPS8	-	539.6	286

n, the sample size; TPM, Transcripts Per Kilobase Million; '-', missing data. Databases: i) BioGPS: The numbers in these columns are intensity values from Affymetrix Human ST 1.0 exon arrays; ii) GTEx: The numbers in this column are TPM values from RNA-Seq; iii) ProteomicsDB: The numbers in this column are ppm values from mass spectrometry-based proteomics arrays.

Table SIII. Genome-wide significant and replicated risk variants for gastric carcinoma.

SNP	Allele	Location	Gene	Functional class	Splicing influence	Allele frequency			Study #1		Study #2		Study #3		Study #4	
						Allele	Europeans	Chinese	P-value	Refs.	P-value	Refs.	P-value	Ref.	P-value	Ref.
rs4072037	T/C	chr1:155192276	*MUC1*	splice_acceptor_variant	Yes	T	0.576	0.833	$7x10^{-8}$	(53)	$4x10^{-7}$	(54)	$6x10^{-17}$	(55)	$2x10^{-9}$	(56)
rs13361707	C/T	chr5:40791782	*PRKAA1*	intron_variant		C	0.768	0.500	$8x10^{-29}$	(57)	$1x10^{-10}$	(55)				
rs2294008	C/T	chr8:142680513	*PSCA*	5_prime_UTR_variant	Yes	C	0.576	0.738	$6x10^{-11}$	(55)	$2x10^{-7}$	(56)				