Association Analysis between SNPs in *LATS1* and *LATS2* and Non-Cardia Gastric Cancer

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Abstract

Background: Many studies have found that large tumor suppressor kinase 1 (LATS1) and LATS2 play important roles in many diseases, but studies have been rare on the relationship between these genes and non-cardia gastric cancer (GC). We performed a case-control association study to investigate the associations between single nucleotide polymorphisms (SNPs) in LATS1 and LATS2 genes and Helicobacter pylori infection as well as the risk of non-cardia GC.

Methods: First, H. pylori infection was determined by an enzyme-linked immunoassay. Then genotyping of SNPs was performed for 808 samples by the Taqman method. Finally, appropriate statistical methods were used to analyze the relationship between the SNPs of LATS1 and LATS2 genes and H. pylori infection, the risk of non-cardia GC, and the level of protein expression.

Results: The statistical results showed that LATS2 rs9552315 was associated with H. pylori infection, and that the CC+CT genotype could reduce the risk of H. pylori infection (odds ratio [OR]: 0.549, 95% confidence interval [CI]: 0.339–0.881, P<0.05) compared with the TT genotype in a dominant model. LATS1 rs9393175 was associated with risk of non-cardia GC, and the AG genotype reduced the risk of non-cardia GC (OR: 0.702, 95% CI: 0.516–0.952, P<0.05) compared with the GG+AA genotype in an overdominant model. LATS2 rs9509492 was associated with the risk of GC in an additive model. No associations were found between five SNPs and expression of LATS1 and LATS2 proteins.

Conclusions: LATS2 rs9552315 CT genotype may be a protective factor against infection of H. pylori. LATS1 rs9393175 AG genotype and LATS2 rs9509492 GG genotype may be protective factors for non-cardia GC.

Introduction

Gastric cancer (GC) is one of the most common malignant tumors with high morbidity, high mortality, and a poor prognosis. In 2018, there were more than 1 million new cases of GC worldwide, and 783,000 deaths caused by GC. The morbidity and mortality rate ranked fifth and third among all malignant tumors, respectively, and it was one of the malignant tumors that seriously affected human health [1]. *Helicobacter pylori* infection is a main cause of GC. According to epidemiological investigation, about 78% of GC patients have been infected with *H. pylori [*2]. It is closely related to the pathogenesis of GC, and was defined as a class I carcinogen of the stomach by the International Agency for Research on Cancer in 1994 [3]. It has been reported in the literature that about 74.7–89.0% GC is associated with *H. pylori [*4]. However, although about 50% of the world's population is infected with *H. pylori,* only 1–3% eventually develop GC. This suggests that individual genetic factors of the host play important roles in the development of GC [5,6]. Many literature reports and previous studies from our research group found that the single nucleotide polymorphisms (SNPs) of some genes are associated with *H. pylori* infection and GC [7].

Large tumor suppressor kinase 1 (LATS1) and LATS2 are tumor suppressor-producing factors that have been discovered in recent years [8]. They are the core components of the Hippo signaling pathway and regulate a series of biological behaviors through phosphorylation reactions with components upstream and downstream of the pathways including cell proliferation, differentiation, apoptosis, and regulation of organ size [9–11]. Studies have reported that the expression levels of LATS1 and LATS2 proteins in malignant tumor cells are significantly lower than those in normal tissues [12,13]. Previous studies from our group confirmed that the expression levels of LATS1 and LATS2 proteins in GC tissues are significantly lower than those in normal gastric tissues, with statistically significant differences [14]. Therefore, we speculated that *LATS1* and *LATS2* gene polymorphisms may be involved in the occurrence and development of GC. However, the association of *LATS1* and *LATS2* gene polymorphisms with non-cardiac GC carcinogenesis has not been reported.

Therefore, this case-control association study was performed in the Baotou Han population to investigate the association between five SNPs of *LATS1* and *LATS2* genes and *H. pylori* infection and non-cardia GC.

Materials And Methods

Clinical samples

We collected 381 blood samples from non-cardia GC patients from Baotou Cancer Hospital (Inner Mongolia, China) from 2008 to 2017, of which 288 cases were collected from June 2008 to December 2010, and the remaining 93 cases were collected from 2015 to 2017. During the same period the patients were recruited, our group collected 427 blood samples from normal medical examinations in the First Affiliated Hospital of Baotou Medical College and Inner Mongolia Baotou Steel Hospital. The inclusion criteria for the cases were as follows. The patients had to be of Han descent, and the three generations had no history of intermarriage with other ethnic groups and had been living in Baotou for more than 5 years at the time of onset. Secondary cases, relapse cases, and patients who had not received chemotherapy or radiotherapy were excluded. All cases were confirmed by pathology examination. The normal control inclusion criteria were as follows. Medical examination was required to confirm Han descent, and the three generations had no history of marriage with other ethnic groups and had been living in Baotou for more than 5 years with no individual history of cancer or identifiable gastric or genetic disease. At recruitment, informed consent was obtained from each subject, and the study was approved by the institutional Review Board of Baotou Medical College.

H. pylori infection test

The serological status of *H. pylori* infection was determined by an enzyme-linked immunosorbent assay (ELISA) using the “Human Helicobacter pylori antibody (HP-Ab) ELISA Kit (96-well plate),” which was purchased from Suzhou Ailesa Bio Technology Co., Ltd. (Suzhou, China).

Screening for SNPs

SNPs of the *LATS1* and *LATS2* genes were screened at the National Center for Biotechnology Information database, and the tag SNPs of the study genes were screened according to the Chinese Han genetic polymorphism data provided by the HapMap database (http://hapmap.ncbi.nlm.nih.gov/). The SNP minority allele frequency was required to be greater than 5%, and the linkage disequilibrium (LD) (r^2) cut-off was required to be 0.8. A total of five SNPs were screened including *LATS1* rs9393175, *LATS2* rs558614, rs9552315, rs7317471, and rs9509492.

Genotyping assay

Genomic DNA was extracted using the "TIANamp Blood DNA Kit, spin column type (200 servings)", which was purchased from Tiangen Biotech (Beijing) Co., Ltd. Genotyping was performed by the TaqMan method. Primers and probes were designed by ABI Scientific Inc. (Sterling, VA, USA). The genotyping success rates of five SNPs were all more than 90%. In the experiment, 5% DNA samples with good quality and quantity were randomly selected for repeated experiments to verify the accuracy of the results. The consistency of genotyping results in all repeated samples was 100%.

Statistical analysis

R software (version 3.5.0) was used for statistical analysis. Age did not conform to normal distribution, so the non-parametric rank sum test was adopted. Enumeration data such as gender were evaluated using the chi-square test. The Pearson's chi-square test of the genetics package with R software was used for Hardy Weinberg Equilibrium (HWE) in the case and control groups. Unconditional logistic regression was used to estimate the odds ratio (OR) and 95% confidence intervals (CIs) after adjustment for age and gender. Haploview 4.2 software was used to conduct LD and haplotype block on the four SNPs of *LATS2,* calculate limit of detection value and linkage unbalance coefficient D', and construct haplotype by the D' confidence interval method.

Results

General description of the samples

A total of 808 samples were included in this study, including 381 samples of non-cardia GC (case group) and 427 samples of healthy individuals (control group). The statistical results showed that the age distribution between the case group and the control group had statistical significance. There was no significant difference in gender distribution between the case group and control group (Table 1).

Table 1 Comparison of general conditions of 808 samples

Variable		Group		Statistics	*P*
		Case(n=381)	Control(n=427)		
Age(median (IQR))		60(52-69)	57(50-65)	W=65012	<0.001
Age group	<65	237(62.2%)	313(73.3%)	$\chi 2$=11.408	<0.001
	≥65	144(37.8%)	114(26.7%)		
Genger	female	95(24.9%)	107(25.1%)	$\chi 2$=0.002	0.968
	male	286(75.1%)	320(74.9%)		

Association between *LATS1* and *LATS2* SNPs and risk of *H. pylori* infection

Among the 427 normal subjects, 225 cases were negative for *H. pylori* infection and 202 were positive for *H. pylori* infection, with a positive rate of 47.3%. The statistical results showed that there were no significant differences in the age and gender distribution between the *H. pylori* negative and *H. pylori* positive infection groups (Table 2). The genotype distribution of all SNPs was consistent with HWE in the control group. The results showed that *LATS2* rs9552315 was associated with infection of *H. pylori* in codominant and dominant models. The dominant genetic model was more suitable with a lower Akaike Information Criterion (AIC) . No association was found between other SNPs and infection of *H. pylori* (Table.3). Furthermore, no haploid blocks were formed between the four SNPs of *LATS2*.

Table 2 General comparison in negative and positive cases of H. pylori infection

Variable		H. pylori infection of control group		Statistics	*P*
		negative(n=225)	positive(n=202)		
Age(median (IQR))		54 (50-66)	53(49-64)	W=24220	0.24
Age group	<65	160(71.1%)	153(75.7%)	$\chi 2$=1.167	0.280
	≥65	65(28.9%)	49(24.3%)		
Genger	female	56(24.9%)	51(25.2%)	$\chi 2$=0.007	0.932
	male	169(75.1%)	151(74.8%)		

Table 3 Association between 5 SNPs and risk of *H. pylori* infection under different genetic models

Locus	Model	Genotype	Control [n(%)]	Case [n(%)]	OR(95%CI)[a]	AIC	BIC
LATS1	Codominant	G/G	125(55.56)	128(64.00)	1	1092.33	1115.76
		A/G	88(39.11)	61(30.50)	0.671(0.443-1.010)		
rs9393175		A/A	12(5.33)	11(5.50)	0.916(0.383-2.175)		
	Dominant	G/G	125(55.56)	128(64.00)	1	591.691	607.899
		A/A+A/G	100(44.44)	72(36.00)	0.700(0.472-1.035)		
	Recessive	G/G+A/G	213(94.67)	189(94.50)	1	594.873	611.081
		A/A	12(5.33)	11(5.50)	1.062(0.449-2.487)		
	overdominant	G/G+A/A	137(60.89)	139(69.50)		591.254	607.462
		A/G	88(39.11)	61(30.50)	0.675(0.449-1.011)		
	additive	-	-	-	0.792(0.570-1.093)	592.876	609.084
LATS2	Codominant	T/T	63(29.30)	60(30.46)	1	579.405	599.511
		C/T	106(49.30)	91(46.19)	0.900(0.572-1.416)		
rs558614		C/C	46(21.40)	46(23.35)	1.042(0.606-1.794)		
	Dominant	T/T	63(29.30)	60(30.46)	1	577.742	593.826
		C/C+C/T	152(70.70)	137(69.54)	0.943(0.617-1.442)		
	Recessive	T/T+C/T	169(78.60)	151(76.65)	1	577.614	593.698
		C/C	46(21.40)	46(23.35)	1.112(0.698-1.772)		
	overdominant	T/T+C/C	109(50.70)	106(53.81)	1	577.428	593.512
		C/T	106(49.30)	91(46.19)	0.884(0.599-1.303)		
	additive	-	-	-	1.012(0.773-1.326)	577.807	593.891
LATS2	Codominant	T/T	45(20.18)	60(30.00)	1	588.160	608.397
		C/T	119(53.36)	88(44.00)	0.549(0.339-0.881)		
rs9552315		C/C	59(26.46)	52(26.00)	0.650(0.377-1.114)		
	Dominant	T/T	45(20.18)	60(30.00)	1	586.672	602.862
		C/C+C/T	178(79.82)	140(70.00)	0.582(0.370-0.909)		
	Recessive	T/T+C/T	164(73.54)	148(74.00)	1	592.331	608.521
		C/C	59(26.46)	52(26.00)	0.970(0.626-1.499)		
	overdominant	T/T+C/C	104(46.64)	112(56.00)	1	588.616	604.805
		C/T	119(53.36)	88(44.00)	0.685(0.466-1.005)		
	additive	-	-	-	0.811(0.618-1.061)	590.018	606.207
LATS2	Codominant	C/C	177(80.09)	173(85.64)	1	590.953	611.190
		C/T	39(17.65)	28(13.86)	0.746(0.435-1.266)		
rs7317471		T/T	5(2.26)	1(0.50)	0.206(0.011-1.230)		
	Dominant	C/C	177(80.09)	173(85.64)	1	590.590	606.780
		C/T+T/T	44(19.91)	29(14.36)	0.684(0.405-1.143)		
	Recessive	C/C+C/T	216(97.74)	201(99.50)	1	590.126	606.316
		T/T	5(2.26)	1(0.50)	0.217(0.011-1.362)		
	overdominant	C/C+T/T	182(82.35)	174(86.14)	1	591.689	607.879
		C/T	39(17.65)	28(13.86)	0.764(0.446-1.295)		
	additive	-	-	-	0.667(0.413-1.057)	589.722	609.912
LATS2	Codominant	A/A	87(39.01)	74(36.82)	1	595.106	615.355
		A/G	98(43.95)	96(47.76)	1.147(0.754-1.746)		
rs9509492		G/G	38(17.04)	31(15.42)	0.964(0.544-1.699)		
	Dominant	A/A	87(39.01)	74(36.82)	1	593.488	609.687
		A/G+G/G	136(60.99)	127(63.18)	1.096(0.739-1.627)		
	Recessive	A/A+A/G	185(82.96)	170(84.58)	1	593.516	609.715
		G/G	38(17.04)	31(15.42)	0.894(0.529-1.500)		
	overdominant	A/A+G/G	125(56.05)	105(52.24)	1	593.123	609.322
		A/G	98(43.95)	96(47.76)	1.160(0.790-1.702)		
	additive	-	-	-	1.013(0.772-1.329)	593.687	609.886

- adjusted for gender and age

Association between *LATS1* and *LATS2* SNPs and risk of non-cardia GC

Results showed that *LATS1* rs9393175 was associated with risk of non-cardia GC in codominant, dominant, and overdominant models. The overdominant genetic model was more suitable with the lowest AIC and BIC. *LATS2* rs9509492 was associated with risk of non-cardia GC in the codominant, dominant, recessive, and additive models. The additive genetic model was more suitable with the lowest AIC and BIC. No associations were found between other SNPs and non-cardia GC (Table 4). Furthermore, no haploid blocks were formed between the four SNPs of *LATS2*.

Table 4 Association between 5 SNPs and risk of non-cardia gastric cancer under different genetic models

Locus	Model	Genotype	Control [n(%)]	Case [n(%)]	OR(95%CI)[a]	AIC	BIC
LATS1	Codominant	G/G	253(59.53)	253(67.29)	1	1092.33	1115.76
		A/G	149(35.06)	101(26.86)	0.696(0.509-0.949)		
rs9393175		A/A	23(5.41)	22(11.26)	0.906(0.486-1.683)		
	Dominant	G/G	253(59.53)	253(67.29)	1	1090.969	1109.713
		A/A+A/G	172(40.47)	123(32.71)	0.725(0.540-0.972)		
	Recessive	G/G+A/G	402(94.59)	354(94.15)	1	1095.593	1114.337
		A/A	23(5.41)	22(5.85)	1.018(0.551-1.877)		
	overdominant	G/G+A/A	276(64.94)	275(73.14)	1	1090.429	1109.173
		A/G	149(35.06)	101(26.86)	0.702(0.516-0.952)		
	additive	-	-	-	0.814(0.641-1.030)	1092.663	1111.406
LATS2	Codominant	T/T	123(29.85)	90(23.81)	1	1081.499	1104.859
		C/T	197(47.82)	192(50.79)	1.287(0.916-1.812)		
rs558614		C/C	92(22.33)	96(25.40)	1.375(0.923-2.052)		
	Dominant	T/T	123(29.85)	90(23.81)	1	1079.635	1098.323
		C/C+C/T	289(70.15)	288(76.19)	1.315(0.955-1.815)		
	Recessive	T/T+C/T	320(77.67)	282(74.60)	1	1081.613	1100.301
		C/C	92(22.33)	96(25.40)	1.168(0.838-1.628)		
	overdominant	T/T+C/C	215(52.18)	186(49.21)	-	1081.954	1100.642
		C/T	197(47.82)	192(50.79)	1.107(0.834-1.470)		
	additive	-	-	-	1.176(0.964-1.436)	1079.912	1098.6
LATS2	Codominant	T/T	105(24.82)	100(26.46)	1	1096.314	1119.743
		C/T	207(48.94)	195(51.59)	1.034(0.735-1.456)		
rs9552315		C/C	111(26.24)	83(21.96)	0.812(0.544-1.212)		
	Dominant	T/T	105(24.82)	100(26.46)	1	1096.153	1114.896
		C/C+C/T	318(75.18)	278(73.54)	0.956(0.693-1.321)		
	Recessive	T/T+C/T	312(73.76)	295(78.04)	1	1094.35	1113.094
		C/C	111(26.24)	83(21.96)	0.795(0.570-1.104)		
	overdominant	T/T+C/C	216(51.06)	183(48.41)	1	1095.351	1114.095
		C/T	207(48.94)	195(51.59)	1.144(0.863-1.516)		
	additive	-	-	-	0.903(0.740-1.102)	1095.226	1113.97
LATS2	Codominant	C/C	350(82.74)	302(79.89)	1	1097.992	1121.421
		C/T	67(15.84)	69(18.25)	1.188(0.816-1.729)		
rs7317471		T/T	6(1.42)	7(1.85)	1.386(0.449-4.402)		
	Dominant	C/C	350(82.74)	302(79.89)	1	1096.061	1114.804
		C/T+T/T	73(17.26)	76(20.11)	1.204(0.839-1.729)		
	Recessive	C/C+C/T	417(98.58)	371(98.15)	1	1096.804	1115.547
		T/T	6(1.42)	7(1.85)	1.345(0.437-4.264)		
	overdominant	C/C+T/T	356(84.17)	309(81.75)	1	1096.322	1115.065
		C/T	67(15.84)	69(18.25)	1.180(0.812-1.717)		
	additive	-	-	-	1.185(0.861-1.633)	1095.993	1114.736
LATS2	Codominant	A/A	161(37.97)	180(47.24)	1	1094.648	1118.102
		A/G	194(45.75)	161(42.26)	0.747(0.552-1.010)		
rs9509492		G/G	69(16.27)	40(10.50)	0.525(0.333-0.818)		
	Dominant	A/A	161(37.97)	180(47.24)	1	1095.087	1113.85
		A/G+G/G	263(62.03)	201(52.76)	0.688(0.518-0.915)		
	Recessive	A/A+A/G	355(83.73)	341(89.50)	1	1096.241	1115.004
		G/G	69(16.27)	40(10.50)	0.609(0.397-0.923)		
	overdominant	A/A+G/G	230(54.25)	220(57.74)	1	1100.815	1119.578
		A/G	194(45.75)	161(42.26)	0.871(0.657-1.156)		
	additive	-	-	-	0.731(0.594-0.897)	1092.686	1111.449

- adjusted for gender and age

Association between five SNPs and expression of LATS1 and LATS2 proteins

We evaluated the expression of LATS1 and LATS2 proteins by immunohistochemistry among the 93 cases of non-cardia GC tissue and normal tissue adjacent to cancer in our pre-study [14]. The results showed that the expression of LATS1 and LATS2 in non-cardia GC tissue was significantly lower than that in normal gastric tissue adjacent to cancer. We analyzed the association between five SNPs and expression of LATS1 and LATS2 proteins in non-cardia GC tissue by the logistic regression method in five different genetic models. The results showed that no associations were found (Table 5). Furthermore, no haploid blocks were formed between the four SNPs of *LATS2*.

Table 5 Association between 5 SNPs and expression of LATS1 and LATS2 under different genetic models

Locus	Model	Genotype	Positive expression N(%)	Negative expression N(%)	OR(95%CI)[a]	AIC	BIC
LATS1 rs9393175	Codominant	G/G	30(62.50)	40(65.57)	1	157.896	171.353
		A/G	15(31.25)	16(26.23)	1.208(0.508-2.869)		
		A/A	3(6.25%)	5(8.20)	0.795(0.152-3.535)		
	Dominant	G/G	30(62.50)	40(65.57)	1	156.162	166.927
		A/A+A/G	18(37.50)	21(34.43)	1.110(0.497-2.467)		
	Recessive	G/G+A/G	45(93.75)	56(91.80)	1	156.082	166.847
		A/A	3(6.25)	5(8.20)	0.750(0.146-3.258)		
	overdominant	G/G+A/A	33(68.75)	45(73.77)	1	155.985	166.751
		A/G	15(31.25)	16(26.23)	1.237(0.527-2.897)		
	additive	-	-	-	1.012(0.544-1.863)	156.225	166.991
LATS2 rs558614	Codominant	T/T	20(26.67)	6(17.14)	1	144.846	158.348
		C/T	35(46.67)	21(60.00)	0.505(0.163-1.407)		
		C/C	20(26.67)	8(22.86)	0.739(0.208-2.522)		
	Dominant	T/T	20(26.67)	6(17.14)	1	143.431	154.233
		T/C+C/C	55(73.33)	29(82.86)	0.570(0.190-1.513)		
	Recessive	T/T+C/T	55(73.33)	27(77.14)	1	144.519	155.321
		C/C	20(26.67)	8(22.86)	1.200(0.478-3.229)		
	overdominant	C/C+T/T	40(53.33)	14(40.00)	1	143.079	153.881
		C/T	35(46.67)	21(60.00)	0.593(0.258-1.336)		
	additive	-	-	-	0.882(0.491-1.572)	144.483	155.285
LATS2 rs9552315	Codominant	T/T	25(33.33)	7(20.59)	1	141.158	154.615
		C/T	31(41.33)	20(58.82)	0.409(0.139-1.100)		
		C/C	19(25.33)	7(20.59)	0.716(0.207-2.451)		
	Dominant	T/T	25(33.33)	7(20.59)	1	140.308	151.073
		T/C+C/C	50(66.67)	27(79.41)	0.489(0.174-1.244)		
	Recessive	T/T+C/T	56(74.67)	27(79.41)	1	142.279	153.044
		C/C	19(25.33)	7(20.59)	1.283(0.493-3.632)		
	overdominant	C/C+T/T	44(58.67)	14(41.18)	1	139.447	150.213
		C/T	31(41.33)	20(58.82)	0.478(0.205-1.089)		
	additive	-	-	-	0.836(0.473-1.468)	142.140	152.905

LATS2 rs7317471		C/C	63(85.14)	26(74.29)	1	142.226	152.992
		C/T	11(14.86)	9(25.71)	0.509(0.186-1.413)		
LATS2 rs9509492	Codominant	A/A	34(45.33)	16(44.44)	1	147.894	161.441
		A/G	32(42.67)	18(50.00)	0.842(0.364-1.936)		
		G/G	9(12.00)	2(5.56)	2.138(0.478-15.146)		
	Dominant	A/A	34(45.33)	16(44.44)	1	147.305	158.143
		A/G+G/G	41(54.67)	20(55.56)	0.972(0.433-2.167)		
	Recessive	A/A+A/G	66(88.00)	34(94.44)		146.058	156.896
		G/G	9(12.00)	2(5.56)	2.332(0.559-15.911)		
	overdominant	A/A+G/G	43(57.33)	18(50.00)	1	146.805	157.644
		A/G	32(42.67)	18(50.00)	0.748(0.334-1.670)		
	additive	-	-	-	1.147(0.623-2.160)	147.118	157.956

- adjusted for gender and age

Discussion

GC is one of the most common malignant tumors with a large number of new cases and deaths every year globally. Asia is a region with a high incidence of GC, accounting for about half of the total number of cases worldwide, while China is one of the countries with a high incidence of GC in Asia. Although the incidence and mortality of GC have been decreasing in recent years, they are still in the forefront of all malignant tumors. According to its anatomical location, GC can be divided into cardia and non-cardia, which have big differences in mechanism, carcinogenesis, clinical manifestations, treatment, and prognosis. Cardia GC is similar to esophageal cancer regarding clinical characteristics, etiology, and pathology of epidemiology. So this experiment studied non-cardia GC in order to avoid sample clinical heterogeneity that could affect the results of the study.

The Hippo signaling pathway is a tumor inhibition pathway that was discovered in recent years, of which LATS1 and LATS2 kinase are two important components and have many important biological functions. LATS1 and LATS2 are involved in the occurrence and development of GC [15].

H. pylori infection is an important factor causing GC. Genome-wide scanning and case-control studies have confirmed that *H. pylori* infection is associated with individual genetic polymorphism [7]. In this study, we found that rs9552315 of *LATS2* gene was associated with *H. pylori* infection, and the dominant model was most suitable with the lowest AIC and BIC. Compared with the TT genotype, the CC+CT genotype can reduce the risk of *H. pylori* infection. The other four SNPs were not associated with *H. pylori* infection. At present, no correlation analysis between these five SNPs and *H. pylori* infection has been reported, so our results need to be further verified.

Among the five selected SNPs, rs7317471 and rs9509492 were used to study the mortality of hepatocellular carcinoma (HCC) [16]. The results showed that rs7317471 was associated with mortality from HCC, and rs9509492 was considered to be an independent prognostic indicator of overall survival rate of HCC patients, while rs9509492 was not associated with the mortality of HCC. Moreover, Sebio [17] studied the association between rs558614 and rs9552315 and colorectal cancer, and the results showed that the two SNPs were not associated with the incidence risk of colorectal cancer. In this study, we analyzed the association between five SNPs of *LATS1* and *LATS2* genes and risk of non-cardia GC. The results showed that *LATS1* rs9393175 was associated with the risk of non-cardia GC in an overdominant model was most suitable with the lowest AIC and BIC. Compared with the GG+AA genotype, carrying the AG genotype may reduce the risk of non-cardia GC. So the AG genotype may be a protective factor against non-cardia GC in the Baotou Han population. In addition, *LATS2* rs9509492 was found to be associated with the risk of non-cardia GC. The additive genetic model is most suitable with the lowest AIC and BIC. Furthermore, no association were found between *LATS2* SNPs rs558614, rs9552315, rs7317471 and risk of non-cardia GC. To the best of our best knowledge, this is the first report of associations between these five SNPs and non-cardia GC, so our experimental results need further confirmation.

Furthermore, the relationship between polymorphisms in the *LATS1* and *LATS2* genes and their protein expression levels was analyzed. However, no correlation was found between these five SNPs and their protein expression levels, suggesting that gene mutations at five loci of the two genes may not affect their protein expression levels. It is also possible that these five SNPs had small effects on protein expression levels that were not detected due to the small sample size of only 111 non-cardia GC tissue samples. Therefore, our experimental results need to be further confirmed by expanding the sample size.

In this experiment, our group studied the association between these five SNPs and *H. pylori* infection, and explored the association between *LATS1* and *LATS2* SNPs and non-cardiac GC for the first time, to the best of our knowledge. The results of this study indicated that some SNPs of the *LATS1* and *LATS2* genes were involved in the pathogenesis of *H. pylori* infection and non-cardia GC, of which *LATS2* rs9552315 was associated with *H. pylori* infection. In addition, compared with the TT genotype, the CC+CT genotype appeared to reduce the risk of *H. pylori* infection, and may be a protective factor against *H. pylori* infection in the Baotou Han population. *LATS1* rs9393175 and *LATS2* rs9509492 were associated with risk of non-cardia GC, and AG and GG genotypes may be protective factors against GC in the Baotou Han population. These two SNPs may become biomarkers for GC screening and provide a new approach for the targeted therapy of GC. However, non-cardia GC patient and normal control samples were from the Han population in Baotou, Inner Mongolia, so the results only represent the genetic characteristics of the Han population in this area, and the sample size was also low. In the future, other regions and other ethnic groups need to be studied, and the sample size should be expanded to further clarify the relationship between these five SNPs and *H. pylori* infection and non-cardia GC.

Abbreviations

LATS1: large tumor suppressor kinase 1; LATS2: large tumor suppressor kinase 2; GC: gastric cancer; SNP: single nucleotide polymorphism; *H. pylori: Helicobacter pylori* ELISA: enzyme-linked immunosorbent assay; OR: odds ratio; CI: confidence interval; HWE: Hardy Weinberg Equilibrium; AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; HCC: hepatocellular carcinoma.

Declarations

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None

Authors' contributions

Conception and design: MLC, TXY, DT, JYB; data collection: MLC, TXY and DWJ; Molecular biology experiment: MLC, TXY, GF; data analysis and interpretation: MLC, TXY; manuscript writing: MLC, TXY; manuscript revision: JYB and DT; final approval of manuscript: All authors.

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Availability of data and materials

The datasets generated and analyzed during the present study are available from the corresponding author on reasonable request. All data generated or analysed during this study are included in this published article.

Ethics approval and consent to participate

At recruitment, written informed consent was obtained from each subject. Our study complies with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the study was approved by the institutional Review Board of Baotou Medical College.

Consent for publication

All data published here are under the consent for publication. Written informed consent was obtained from all individual participants included in the study. No personal or clinical details along with any

identifying images of the participants to be published in this study.

Competing interests

The authors declare that they have no competing interests.

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