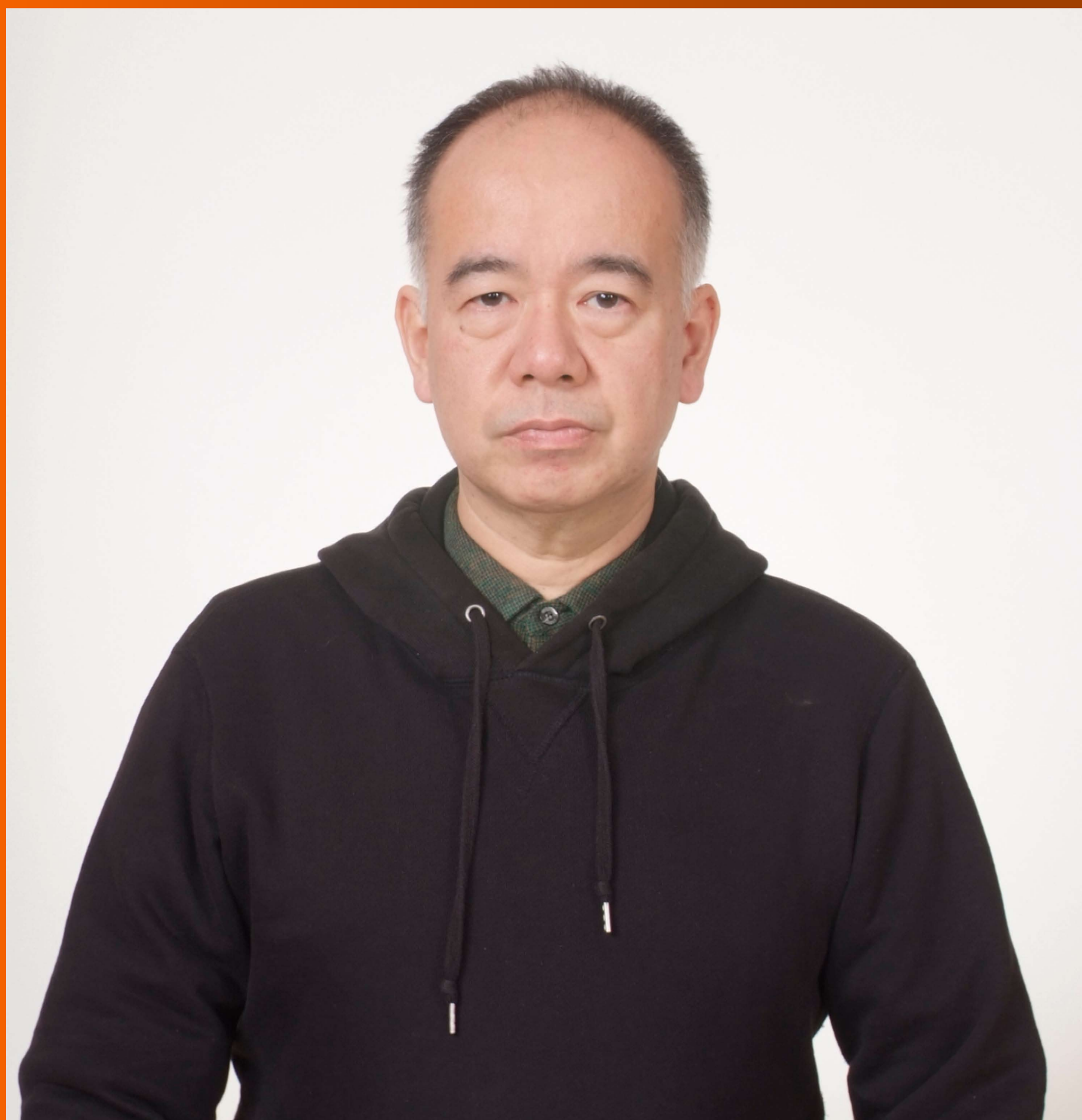


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Case Control Study

Association of twelve polymorphisms in three onco-lncRNA genes with hepatocellular cancer risk and prognosis: A case-control study

Ben-Gang Wang, Qian Xu, Zhi Lv, Xin-Xin Fang, Han-Xi Ding, Jing Wen, Yuan Yuan

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Abstract

AIM

To evaluate the association of 12 tag single nucleotide polymorphisms (tagSNPs) in three onco-long non-coding RNA (lncRNA) genes (*HOTTIP*, *CCAT2*, *MALAT1*) with the risk and prognosis of hepatocellular cancer (HCC).

METHODS

Twelve tagSNPs covering the three onco-lncRNAs were genotyped by the KASP method in a total of 1338 samples, including 521 HCC patients and frequency-matched 817 controls. The samples were obtained from an unrelated Chinese population at the First Hospital of

China Medical University from 2012-2015. The expression quantitative trait loci (eQTL) analyses were conducted to explore further the potential function of the promising SNPs.

RESULTS

Three SNPs in *HOTTIP*, one promoter SNP in *MALAT1*, and one haplotype of *HOTTIP* were associated with HCC risk. The *HOTTIP* rs17501292, rs2067087, and rs17427960 SNPs were increased to 1.55-, 1.20-, and 1.18-fold HCC risk under allelic models ($P = 0.012$, 0.017 and 0.049 , respectively). *MALAT1* rs4102217 SNP was increased to a 1.32-fold HCC risk under dominant models ($P = 0.028$). In addition, the two-way interaction of *HOTTIP* rs17501292-*MALAT1* rs619586 polymorphisms showed a decreased effect on HCC risk ($P_{\text{interaction}} = 0.028$, OR = 0.30) and epistasis with each other. *HOTTIP* rs3807598 variant genotype showed significantly longer survival time in HBV negative subgroup ($P = 0.049$, HR = 0.12), and *MALAT1* rs591291 showed significantly better prognosis in female and HBV negative subgroups ($P = 0.022$, HR = 0.37; $P = 0.042$, HR = 0.25, respectively). In the study, no significant effect was observed in eQTL analysis.

CONCLUSION

Specific lncRNA (*HOTTIP* and *MALAT1*) SNPs have potential to be biomarkers for HCC risk and prognosis.

Key words: Hepatocellular cancer; Single nucleotide polymorphism; Long non-coding RNA; Risk; Prognosis

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Core tip: We aim to evaluate the association of twelve tag single nucleotide polymorphisms (tagSNPs) in three onco-lncRNA genes (*HOTTIP*, *CCAT2*, *MALAT1*) with the risk and prognosis of hepatocellular cancer (HCC). Twelve tagSNPs covering the three onco-lncRNAs were genotyped by the KASP method in a total of 1338 samples. We found three SNPs in *HOTTIP*, one promoter SNP in *MALAT1* and one haplotype of *HOTTIP* gene were associated with HCC risk. In addition, *HOTTIP* rs3807598 variant genotype showed significantly longer survival time in hepatitis B virus (HBV) negative subgroup, and *MALAT1* rs591291 showed significantly better prognosis in female and HBV negative subgroups.

Wang BG, Xu Q, Lv Z, Fang XX, Ding HX, Wen J, Yuan Y. Association of twelve polymorphisms in three onco-lncRNA genes with hepatocellular cancer risk and prognosis: A case-control study. *World J Gastroenterol* 2018; 24(23): 2482-2490 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v24/i23/2482.htm> DOI: <http://dx.doi.org/10.3748/wjg.v24.i23.2482>

INTRODUCTION

Hepatocellular cancer (HCC) is a common malignant

tumor with high incidence and mortality, and it is the main histologic type of primary liver cancer^[1,2]. Similar to most other solid tumors, HCC patients are considered to be incurable due to the extensive heterogeneity in the clinical manifestations and biological characteristics^[3]. HCC heterogeneity can be manifested via diverse genetic, epigenetic, and histogenic features, as well as ethnic differences in patients^[4]. Knowledge of genetic and epigenetic variations could aid the early detection and personalized management of HCC. To date, the research hotspots regarding genetic and epigenetic variations are not only coding genes but also noncoding RNAs.

Long non-coding RNAs (lncRNAs) are a type of noncoding RNA with a length of 200 bp, which can function as miRNA sponges to compete with mRNAs by acting as so-called competing endogenous RNAs (ceRNAs)^[5]. Genetic variations such as single-nucleotide polymorphisms (SNPs) can alter the expression of coding genes and lncRNAs^[6]. To date, several lncRNAs have been reported to be involved in carcinogenesis, such as *H19*, *HOTAIR*, *HOTTIP*, *CCAT2*, and *MALAT1*. Regarding studies of genetic variation, only *H19* and *HOTAIR* SNPs have been well investigated. For example, several meta-analyses showed that *H19* and *HOTAIR* SNPs were associated with cancer risk^[7-9], and the *HOTAIR* rs920778 SNP was found to be associated with ovarian cancer prognosis^[10]. Only four studies have focused on the polymorphisms of the onco-lncRNAs *HOTTIP*, *CCAT2*, and *MALAT1* (Gene ID: 100316868, 101805488, 378938, respectively)^[11-14]. Among them, Gong *et al.*^[11] found that these SNPs were significantly associated with lung cancer susceptibility or platinum-based chemotherapy response. However, no SNPs in the above-mentioned lncRNAs have been reported to be associated with HCC risk, and few comprehensive and systematic analyses have been performed on polymorphisms in these three onco-lncRNAs. It thus remains unclear whether the promising SNPs in these lncRNAs have potential to be used as biomarkers for HCC risk and prognosis.

In the present study, we adopted a candidate gene association study strategy with the selected 12 potentially functional tagSNPs covering the three onco-lncRNAs *HOTTIP*, *CCAT2*, and *MALAT1* to determine whether these SNPs are associated with HCC risk and prognosis and whether promising SNPs could affect the expression of corresponding lncRNAs. We aimed to identify predictive biomarkers for HCC risk and prognosis, establish experimental basis for the comprehension of the HCC etiology, and improve our understanding of the pathogenesis and disease progression of HCC.

MATERIALS AND METHODS

Patients and study design

This research project was approved by the Ethical Committee of the First Hospital of China Medical University and written informed consent was obtained from each subject at the time of recruitment. The study

was designed to be composed of two parts: risk and prognosis. In the risk study, a total of 1338 participants were recruited, including 521 patients who underwent surgical operation for HCC at the First Hospital of China Medical University between 2012 and 2015. The inclusion and exclusion criteria were as follows: (1) The participants who underwent surgical operation were diagnosed with HCC by pathological confirmation, in accordance with the World Health Organization (WHO) classification; and (2) removal of other pathological types of liver cancer (gallbladder cell carcinoma, mix-type liver cancer, and hepatosarcoma). A total of 817 frequency-matched controls were also recruited, some of whom were from a health screening program from the Zhuanghe area, Liaoning Province, China, performed between 2002 and 2012, while others were from a health screening program at the First Hospital of China Medical University performed between 2012 and 2015.

To investigate further the association of these lncRNA polymorphisms with clinicopathological parameters and overall survival of HCC patients, we used data of 351 HCC cases for which information on death or survival was available. Patients with (1) distant metastasis found preoperatively or (2) incomplete pathological data entries were excluded from the survival analysis. Follow-up was completed by July 1st, 2017. For the promising SNPs, lncRNA expression was investigated to explore the possible mechanism by which they exerted their effects, according to our experimental and bioinformatic data. The study design is shown in Figure 1. This research project was approved by the Ethical Committee of the First Hospital of China Medical University and written informed consent was obtained when the patients and controls were recruited.

Selected polymorphic sites

We selected polymorphisms using 1000G data (<http://www.internationalgenome.org/home>), as reported previously^[15-17]. The tagSNPs were selected separately using the following criteria: (1) Haploview with the Tagger function was used; (2) the population of the HapMap selected Chinese Han Beijing (CHB) population; (3) those for which pairwise tagging had r^2 of ≥ 0.8 ; and (4) those with a minor allele frequency of $\geq 5\%$. The selection area was enlarged by 10 kb both upstream and downstream for these three lncRNA genes. FastSNP and fSNP searches were used to predict the potential SNP function (<http://compbio.cs.queensu.ca/F-SNP/>)^[18,19]. A total of 12 SNPs from the three lncRNA genes were selected by integrating these two publicly available tools. Locations and characteristics of the selected SNPs are shown in Table 1.

Genotyping

Genomic DNA was extracted using a previously reported method^[20] and diluted to a working concentration of 20 ng/ μ L for genotyping. The genotyping assay was performed by Gene Company (Shanghai, China), using allele-specific PCR with KASPar (KASP) reagents (LGC

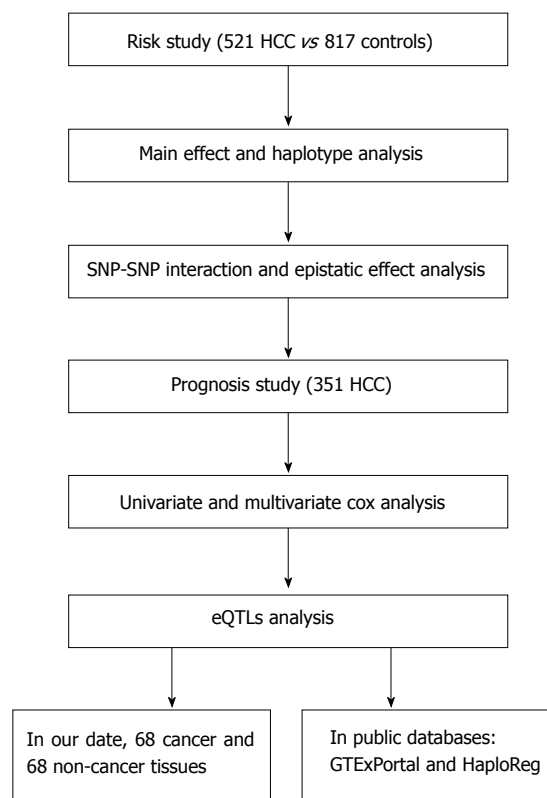


Figure 1 Flow chart of the study design.

Genomics, Hoddlesdon, United Kingdom). For quality control, we repeatedly genotyped 10% of the total samples at one time. The concordance rate of these repeated samples reached 100%, which demonstrated that the genotyping results were reliable.

eQTL analyses

The extraction of total RNA from 68 HCC specimens and corresponding samples from nearby noncancerous regions was performed as described previously^[15], and a total of 2.0 μ g of isolated RNA was converted into cDNA using Quantscript RT Kit (Tiangen Biotech, Beijing, China). The RNA expression levels of the promising lncRNA genes (*HOTTIP* and *MALAT1*) and an internal-control gene (*GAPDH*) were measured using SYBR Premix Ex Taq II (TaKaRa Biotech, Dalian, China) in an Eppendorf Mastercycler Gradient System (Eppendorf AG, Hamburg, Germany). Each reaction was performed in duplicate and controls without a template were also tested every time. The primers are summarized in Supplementary Table 1.

To perform functional candidate polymorphism and expression quantitative trait locus (eQTL) analyses on the promising genes, we mined the data from the following databases: GTExPortal (<https://www.gtexportal.org/home/>) and HaploReg (<http://www.broadinstitute.org/mammals/haploreg/haploreg.php>)^[21].

Statistical analysis

Between-group differences in sex variability, as well as accordance with Hardy-Weinberg equilibrium, were

Table 1 Association of lncRNA gene single nucleotide polymorphisms and risk of hepatocellular cancer (*n*)

Gene	Chr. Pos.	SNP ¹	Loc.	Genotype	Controls (%)	Cases (%)	P ² value	OR (95%CI)	P _{HWE} value
<i>HOTTIP</i>	7p15.2	rs17501292	Exon	TT	732 (91.2)	453 (87.1)		1 (Ref.)	0.190
				TG	71 (8.8)	66 (12.7)	0.021	1.52 (1.06-2.17)	
				GG	0 (0)	1 (0.2)	NA	NA	
		rs2067087	Exon	TG + GG <i>vs</i> TT			0.017	1.54 (1.08-2.20)	0.674
				G <i>vs</i> T			0.012	1.55 (1.10-2.18)	
				GG	174 (21.7)	88 (16.9)		1 (Ref.)	
		rs17427960	Intron	GC	405 (50.6)	263 (50.7)	0.236	1.16 (0.90-1.49)	0.613
				CC	222 (27.7)	168 (32.4)	0.015	1.49 (1.08-2.08)	
				CC <i>vs</i> GG + GC			0.035	1.35 (1.02-1.82)	
		rs4102217	Promoter	C <i>vs</i> G			0.017	1.20 (1.03-1.41)	0.055
				CC	172 (21.7)	85 (16.7)		1 (Ref.)	
				CA	387 (48.8)	259 (50.9)	0.707	1.05 (0.81-1.35)	
<i>MALAT1</i>	22q13.2	rs4102217	Promoter	AA	234 (29.5)	165 (32.4)	0.032	1.78 (1.03-2.00)	0.028
				AA <i>vs</i> CC + CA			0.028	1.39 (1.03-1.85)	
				A <i>vs</i> C			0.049	1.18 (1.00-1.37)	
				GG	608 (75.1)	362 (69.6)		1 (Ref.)	
				GC	180 (22.2)	148 (28.5)	0.011	1.39 (1.08-1.79)	
				CC	22 (2.7)	10 (1.9)	0.481	0.76 (0.36-1.63)	
				GC + CC <i>vs</i> GG			0.028	1.32 (1.03-1.69)	0.097
				C <i>vs</i> G			0.097	1.20 (0.97-1.50)	

¹The sort order was according to the SNP location in its genes from 5' starting to 3' ends. ²P value was calculated by adjusted by age and gender. NA: Not available; Chr. Pos.: Chromosomal position; Loc.: Localisation; P_{HWE}: P value for Hardy-Weinberg Equilibrium.

compared by the χ^2 test and by analysis of variance for age variability. Multivariate logistic regression with adjustments for age and sex was used to show the association between selected lncRNA polymorphisms and HCC risk. The haplotypes of each gene were analyzed using SHesis software^[22]. The two-way pairwise interactions of lncRNA SNP-SNP were calculated using multivariate logistic regression. Univariate and multivariate survival analyses were carried out by the log-rank test and the Cox proportional hazards model. The differences of relative lncRNA levels between two groups were tested by Student's *t*-test. *P* value < 0.05 was considered to be significant.

RESULTS

The association of SNPs in lncRNA genes with HCC risk

The demographic characteristics of HCC cases and control subjects are shown in Supplementary Table 2. All polymorphism genotype distributions in cases and controls are shown in Table 1, including 12 SNPs in three lncRNA genes (*HOTTIP*: rs3807598, rs17501292, rs2067087, rs17427960, rs78248039; *CCAT2*: rs3843549, rs138947056, rs6983267; *MALAT1*: rs4102217, rs591291, rs11227209, and rs619586). Among them, most SNPs accorded with Hardy-Weinberg equilibrium, except for *CCAT2* rs6983267 (*P*_{HWE} = 0.029). This SNP was thus excluded from further association analysis.

Among these remaining 11 SNPs, four in the *HOTTIP* and *MALAT1* genes were associated with HCC risk, and they all increased HCC risk (*HOTTIP*: rs17501292, rs2067087, rs17427960; *MALAT1*: rs4102217; Table 1, Supplementary Table 3). Among them, two SNPs (*HOTTIP*: rs17501292; *MALAT1*: rs4102217) showed significant in a dominant model and the other two

showed in a recessive model. *HOTTIP* rs17501292 and *MALAT1* rs4102217 were associated with an increased risk of HCC (*P* = 0.017 and 0.028, OR = 1.54 and 1.32, respectively) in a dominant model. In addition, *HOTTIP* rs2067087 and rs17427960 variant genotypes also showed associations with an increased risk of HCC (*P* = 0.035 and 0.028, OR = 1.35 and 1.39, respectively) in a recessive model. Stratified analysis based on gender, age, smoking, and drinking was performed to analyze the association between each SNP and HCC risk. The results are shown in Supplementary Table 4 and suggest these variables have potential predictive value for specific subgroup populations in HCC risk.

The association of haplotype in four lncRNA genes with HCC risk

We chose to exclude haplotypes with a frequency of less than 0.03 from the analysis. We found only one haplotype in the *HOTTIP* gene that was associated with HCC risk. Compared with other haplotypes, patients with the C-G-T-A haplotype of *HOTTIP* rs3807598-rs17501292-rs2067087-rs17427960 showed a 1.91-fold increased risk of HCC (*P* = 0.006, 95%CI: 1.20-3.05; Table 2).

Two-way SNP-SNP interaction models for lncRNA polymorphisms

For the data mining of two-way SNP-SNP interactions, we analyzed all possible pair combinations between all of these 11 SNPs and found that the pairwise interaction of *HOTTIP* rs17501292-*MALAT1* rs619586 was significant (*P*_{interaction} = 0.028, OR = 0.30, 95%CI: 0.10-0.88; Table 3).

We further analyzed the epistatic effect of *HOTTIP* rs17501292 and *MALAT1* rs619586 and found in the

Table 2 Association of haplotype of lncRNA gene and hepatocellular cancer risk (*n*)

Haplotype	Control (%)	Case (%)	OR (95%CI)	P value
<i>HOTTIP</i> ¹				
CGCA	33.54 (2.4)	407.00 (4.5)	1.91 (1.20-3.05)	0.006
CTGC	663.39 (47.3)	389.97 (43.4)	0.85 (0.71-1.01)	0.066
GTCA	604.75 (43.1)	401.77 (44.7)	1.08 (0.91-1.28)	0.406
<i>CCAT2</i> ²				
AAG	623.60 (39.8)	434.27 (42.7)	1.13 (0.96-1.33)	0.136
AAT	937.40 (59.8)	577.73 (56.9)	0.89 (0.75-1.04)	0.136
<i>MALAT1</i> ³				
CTCA	217.99 (13.8)	167.00 (16.3)	1.22 (0.08-1.52)	0.080
GCCA	934.81 (59.3)	599.74 (58.6)	0.97 (0.82-1.14)	0.718
GTCA	296.19 (18.8)	1720 (16.6)	0.86 (0.70-1.06)	0.160
GTGG	85.00 (5.4)	58.94 (5.8)	1.07 (0.76-1.51)	0.689

Haplotype for ¹*HOTTIP* rs3807598-rs17501292-rs2067087-rs17427960; ²*CCAT2* rs3843549-rs138947056-rs6983267; ³*MALAT1* rs4102217-rs591291-rs11227209-rs619586.

Table 3 The two-way interaction of *HOTTIP* rs17501292-*MALAT1* rs619586 polymorphisms in the risk of hepatocellular cancer

Variables	<i>MALAT1</i> rs619586	
	AA	AG + GG
	HCC vs CON (<i>n</i> = 335 vs 572)	
<i>HOTTIP</i> rs17501292		
TT		
Case/control	372/617	78/107
OR (95%CI)	1	1.21(0.88-1.66)
TG + GG		
Case/control	61/55	6/15
OR (95%CI)	1.84 (1.25-2.71)	0.66 (0.26-1.73)
	<i>P</i> _{interaction} = 0.028, OR (95%CI) = 0.30 (0.10-0.88)	

HCC: Hepatocellular cancer; CON: Control.

subset with *MALAT1* rs619586 AA wild type and *HOTTIP* rs17501292 SNP an increased risk of HCC under a dominant model (*P* = 0.002, OR = 1.85); however, in the subset with the *HOTTIP* rs17501292 TG+GG genotype, the *MALAT1* rs619586 SNP decreased the risk of HCC under a dominant model (*P* = 0.050, OR = 0.36; Supplementary Table 5).

The association of lncRNA SNPs with HCC cancer prognosis

We analyzed the association of all 11 SNPs with the overall survival of HCC patients but found no significant association in either univariate or multivariate Cox proportional hazard analysis (Supplementary Table 6). In the stratified analysis, those with the *HOTTIP* rs3807598 variant genotype were shown to have a significantly longer survival time in the HBV-negative subgroup (*P* = 0.049, HR = 0.12, 95%CI = 0.02-0.99), and *MALAT1* rs591291 showed an association with a significantly better prognosis in the female and HBV-negative subgroups (*P* = 0.022, HR = 0.37, 95%CI = 0.16-0.87; *P* = 0.042, HR = 0.25, 95%CI = 0.07-0.95, respectively; Table 4, Supplementary Table 7).

eQTL analysis

We used eQTL analysis to investigate the effect of the SNPs identified to be associated with HCC risk on lncRNA expression. In neither the cancerous group nor the noncancerous group was a significant difference observed for the effect of the positive SNPs on lncRNA expression levels (Table 5). Among them, only the heterozygote genotype of intronic rs17427960 of the *HOTTIP* gene was associated with higher lncRNA-*HOTTIP* expression, with borderline significance (CA vs CC: *P* = 0.063; Table 5). Next, we searched public databases for the SNPs for which positive results were obtained in the eQTL analysis (rs17501292, rs2067087, rs17427960, rs4102217). The results from the GTExPortal showed that rs4102217 is a functional SNP in 34 different tissues, such as pancreas and stomach (Supplementary Table 8), and that rs17501292 is a functional SNP in tibial artery tissue; however, no eQTL data for rs2067087 and rs17427960 were found in the public databases. In addition, in Haploreg, it was shown that these SNPs are associated with several kinds of regulatory motifs if the SNP bases altered (Supplementary Figure 1).

DISCUSSION

In this study, we preliminarily screened all of the tagSNPs covering three onco-lncRNAs, *HOTTIP*, *CCAT2*, and *MALAT1*, for associations with HCC risk and prognosis. We identified four promising risk-associated SNPs, one haplotype, and a two-way pairwise interaction combination associated with HCC risk. We also found that patients carrying the *HOTTIP* rs3807598 and *MALAT1* rs591291 variant genotypes had a longer survival time in the HBV-negative subgroup. Further molecular experiments were also conducted to investigate whether the tagSNPs could affect the expression of the corresponding lncRNAs. Our study provides an experimental basis for seeking predictive biomarkers for the risk and prognosis of HCC.

Table 4 Univariate proportional hazard analysis stratified by host characteristics for the association of *lncRNA* polymorphisms and hepatocellular cancer *n* (%)

Gene	SNP	Stratified	Stratified factors	Genotype	HCC	Death	MST (M)	P value	Hazard ratio (95%CI)		
HOTTIP	rs3807598	HBV	Positive	CC	n = 136 30 (22.06)	12	90.0	0.391	1 (reference)		
				CG	73 (53.68)	23	90.1 ^b		0.74 (0.37-1.48)		
				GG	33 (24.26)	11	64.1 ^b		0.680	0.84 (0.37-1.91)	
			Negative	CC	n = 31 10 (32.26)	7	21.0	0.374	1 (reference)		
				CG	13 (41.94)	4	41.8 ^b		0.60 (0.16-1.97)		
				GG	8 (25.80)	1	70.3 ^b		0.049	0.12 (0.02-0.99)	
		MALAT1	rs591291	Gender	Male	CC	n = 285 n = 286 98 (34.27)	39	48.0	0.865	1 (reference)
						TC	146 (51.05)	56	56.0		0.97 (0.64-1.45)
						TT	42 (14.68)	19	47.0		0.678
					Female	CC	n = 64 22 (34.38)	13	32.0	0.022	1 (reference)
						TC	37 (57.81)	9	56.0		0.37 (0.16-0.87)
						TT	5 (7.81)	0	NA		0.286
HBV	Positive			CC	n = 139 54 (38.85)	18	69.0	0.816	1 (reference)		
				TC	69 (49.64)	21	92.1 ^b		0.93 (0.49-1.74)		
				TT	16 (11.51)	7	90.0		0.965	0.98 (0.41-2.35)	
	Negative			CC	n = 31 8 (25.81)	5	6.0	0.042	1 (reference)		
				TC	16 (51.61)	4	27.0		0.25 (0.07-0.95)		
				TT	7 (22.58)	3	21.0		0.215	0.40 (0.09-1.71)	

HR: Hazard rate; MST: Median survival time (months); NA: Not available.

Table 5 Differences of *lncRNA* gene mRNA levels in different genotypes in hepatocellular cancer and non-cancer tissues

Variable	Non-cancer tissues				Cancer tissues			
	<i>n</i>	ΔCt (Mean ± SD)	Normalized 2-ΔΔCt	P ¹ value	<i>n</i>	ΔCt (Mean ± SD)	Normalized 2-ΔΔCt	P ¹ value
The effect of <i>HOTTIP</i> rs17501292 genotypes to <i>HOTTIP</i> mRNA expression								
TT	10	12.32 ± 4.06	1 (0.60, 16.68)	Ref.	25	11.84 ± 3.87	1.39 (0.10, 20.39)	Ref.
TG	1	NA	NA	NA	2	15.30 ± 1.65	NA	0.735
GG	0	NA	NA	NA	0	NA	NA	NA
The effect of <i>HOTTIP</i> rs2067087 genotypes to <i>HOTTIP</i> mRNA expression								
GG	2	8.64 ± 2.06	1 (0.24, 4.17)	Ref.	5	11.66 ± 1.43	1 (0.37, 2.69)	Ref.
GC	5	12.25 ± 4.17	0.13 (0.01, 1.23)	0.253	13	11.85 ± 3.53	0.88 (0.08, 10.13)	0.101
CC	4	13.70 ± 3.86	0.03 (0.00, 0.86)	0.453	8	12.23 ± 5.42	0.67 (0.02, 28.84)	0.444
The effect of <i>HOTTIP</i> rs17427960 genotypes to <i>HOTTIP</i> mRNA expression								
CC	2	8.64 ± 2.06	1 (0.24, 4.17)	Ref.	6	12.47 ± 2.34	1 (0.20, 5.06)	Ref.
CA	5	11.55 ± 3.21	0.13 (0.01, 1.15)	0.254	13	11.88 ± 3.72	2.13 (0.04, 125.37)	0.063
AA	3	13.56 ± 4.71	0.03 (0.00, 0.86)	0.465	6	11.38 ± 5.88	1.51 (0.11, 19.84)	0.348
The effect of <i>MALAT1</i> rs4102217 genotypes to <i>MALAT1</i> mRNA expression								
GG	52	-2.25 ± 4.40	1 (0.05, 21.11)	Ref.	51	-0.98 ± 4.88	1 (0.03, 29.45)	Ref.
GC	16	-3.76 ± 3.60	2.85 (0.23, 34.54)	0.404	16	-2.79 ± 4.55	3.51 (0.15, 82.14)	0.742
CC	NA	NA	NA	NA	1	NA	NA	NA

¹The statistical analysis for the effect of genotype to phenotype was used two-independent sample *t*-test, and for the combination of genotype to phenotype was used ANOVA analysis. NA: Not available.

lncRNAs function as ceRNAs to compete with mRNAs for access to miRNAs, which could regulate the expression of coding genes^[5]. Most studies on lncRNA expression have focused on H19 and HOTAIR as well as other lncRNAs such as PRNCR1, *HOTTIP*, *CCAT1*, *CCAT2*, and *MALAT1*. *HOTTIP*, *CCAT2*, and *MALAT1* are all onco-lncRNAs, which have similar biological functions in promoting cell proliferation and invasion^[23-29]. They can also promote HCC metastasis and epithelial-mesenchymal

transition^[30-33]. The *HOTTIP* gene is located in 7p15.2 and has three exons, the *CCAT2* gene is located in 8q24.21 and has one exon, and the *MALAT1* gene is located in 11q13.1 and has two exons. The most common SNPs reported for these genes are *HOTTIP* rs3807598, *CCAT2* rs6983267, and *MALAT1* rs619586. The first of these was found to be predictive of hematological toxicity in a three-way interaction pattern^[34], and the latter two were indicated to be associated with platinum-based

chemotherapy response in lung cancer^[11]. In this study, we found that SNPs in two exons (rs17501292 and rs2067087) and one intron (rs17427960) of the *HOTTIP* gene as well as an SNP in the promoter (rs4102217) of the *MALAT1* gene were associated with HCC risk; these variant alleles increased HCC risk in the range from 1.18- to 1.55-fold. These four SNPs are reported here for the first time to be associated with cancer risk. Concerning the commonly studied *HOTTIP* rs3807598 and *MALAT1* rs619586 SNPs, no significant associations with HCC risk were found in this study, which is consistent with the findings in a report by Liu^[35]. In addition, we found that none of the *CCAT2* SNPs was associated with HCC risk. Following the identification of the possible significant SNPs, we further analyzed the relationship between the *HOTTIP* C-G-C-A haplotype of rs3807598-rs17501292-rs2067087-rs17427960 and HCC risk. The results showed an increase in HCC risk of 1.91-fold in those with this haplotype, and the OR value was greater than that for each SNP alone. Taking these findings together, it is newly indicated that the *HOTTIP* SNPs rs17501292, rs2067087, and rs17427960 and the *MALAT1* SNP rs4102217 have potential to be biomarkers for HCC risk.

Combined interaction analysis for multiple SNPs from different genes is more sensitive and powerful than one-dimensional SNP analysis^[36]. For individual SNPs at single loci that were previously shown to have no or a weak effect on disease risk, an epistatic effect may appear when they are analyzed in combination^[37]. One of the most significant findings in this study was the SNP-SNP interaction identified for the *HOTTIP* rs17501292-*MALAT1* rs619586 polymorphisms, which was confirmed by the epistatic effect analysis. In the main-effect analysis, *HOTTIP* rs17501292 had a weak effect, and *MALAT1* rs619586 had no effect on the risk of HCC. However, the pairwise analysis of these two in combination showed that they had an interactive effect on HCC risk. Subsequently, we analyzed the epistatic effect of these two SNPs and found that *MALAT1* rs619586 was associated with a decreased risk of HCC only in the presence of the *HOTTIP* rs17501292 TG+GG genotype. A similar epistatic effect between coding genes was also found in our previous study^[38]. Further investigations are needed to verify our findings and the mechanism involved in the epistatic phenomenon.

In the prognostic analysis, we found no significant association of the studied SNPs with the overall survival of HCC patients. However, in the stratified analysis based on gender, we found that *MALAT1* rs591291 was associated with significantly better prognosis in the female subgroup. When stratified by HBV infection status, we found that patients carrying *HOTTIP* rs3807598 and *MALAT1* rs591291 variant genotypes had longer survival times. As some biomarkers are specific for certain subgroups and have potential to be used for the diagnosis or individualized therapy of specific subgroups^[39], the above-mentioned polymorphisms could have value in predicting HCC prognosis for certain subgroups.

eQTL is an analysis in which the combination of mRNA expression and genotype data is applied to determine which variants are correlated with the transcription levels of genes^[40]. We analyzed the SNPs potentially associated with HCC risk in our own data and then reanalyzed them in two public databases for the eQTL analysis. *HOTTIP* rs17501292 and rs2067087 are both located in exon 2 of this gene, while rs17427960 is in intron 2. In contrast, rs4102217 is located at -1255 bp of the *MALAT1* gene, within the promoter region. Among these four SNPs, we found that only the heterozygous genotype of intronic rs17427960 of the *HOTTIP* gene was associated with a higher lncRNA-*HOTTIP* expression level, with borderline significance. The public databases offered some supportive evidence for this from findings in other tissues, suggesting that rs4102217 in the *MALAT1* promoter is a functional SNP in 34 different tissues, such as pancreas and stomach, and that exonic rs17501292 of *HOTTIP* is a functional SNP in tibial artery tissue. In addition, some regulatory motifs, which were predicted by the bioinformatical software listed in Supplementary Figure 1, are transcription factors like PAX-4 and AP1. Thus, it is reasonable to assume that these SNPs could regulate certain motifs, leading to higher expression of oncogenic lncRNA and thus an elevation of HCC risk. However, further functional research is required to confirm this.

In summary, we found that the SNPs rs17501292, rs2067087, and rs17427960 in the *HOTTIP* gene, rs4102217 in the *MALAT1* gene, and a haplotype of *HOTTIP* increased the risk of HCC. In addition the SNPs *HOTTIP* rs3807598 and *MALAT1* rs591291 were associated with longer survival time in the HBV-negative subgroup.

ARTICLE HIGHLIGHTS

Research background

Genetic polymorphisms could be biomarkers for cancer risk and prognosis. Recent years, it was found that coding genes and non-coding genes had single nucleotide polymorphisms (SNPs). lncRNAs had important roles in the tumor incidence, progression, and prognosis. Thus, lncRNA polymorphisms had potential to be biomarkers for cancer precaution and prognostic prediction.

Research motivation

The aim of this study is to screen out the effective biomarkers for the hepatocellular cancer (HCC) risk and prognosis. The selected polymorphisms would have potential for the prediction of cancer risk and prognosis.

Research objectives

Five hundred and twenty-one patients of HCC and frequency matched 817 controls were studied for the cancer risk study. Among them, 351 patients for which the information was all available were recruited for the prognosis study. Then, 68 HCC specimens and corresponding samples from the noncancerous region were detected for the expression level study.

Research methods

For the risk and prognosis study, the samples were detected by the genomic DNA extracted and allele-specific PCR with KASPar reagents. The single nucleotide polymorphisms were selected by the Haploview software. The expression level study isolated the RNA isolated and then converted it to cDNA.

The SYBR based real-time PCR were adopted for the lncRNA expression.

Research results

We found the *HOTTIP* rs17501292, rs2067087, and rs17427960 SNPs increased HCC risk by 1.55-, 1.20-, and 1.18-fold under an allelic model, and the *MALAT1* rs4102217 SNP increased HCC risk by 1.32-fold under a dominant model. In addition, the two-way interaction of *HOTTIP* rs17501292 and *MALAT1* rs619586 polymorphisms decreased HCC risk and exhibited epistatic effects. In the survival analysis, the *HOTTIP* rs3807598 variant genotype showed significantly longer survival time in the hepatitis B virus (HBV)-negative subgroup, and *MALAT1* rs591291 showed an association with significantly better prognosis in the female and HBV-negative group. In this study, no significant effect in eQTL analysis was observed.

Research conclusions

Some specific *HOTTIP* and *MALAT1* SNPs have the potential to be biomarkers for HCC risk and prognosis.

Research perspectives

Screening SNPs could be valuable for the identification of biomarkers for HCC risk and prognosis. It could also be used for patient care, as there would be a cohort of patients who would benefit from screening using these positive SNPs.

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