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Research Paper

Variations in the *AURKA* Gene: Biomarkers for the Development and Progression of Hepatocellular Carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is a liver malignancy and a major cause of cancer mortality worldwide. AURKA (aurora kinase A) is a mitotic serine/threonine kinase that functions as an oncogene and plays a critical role in hepatocarcinogenesis. We report on the association between 4 single nucleotide polymorphisms (SNPs) of the *AURKA* gene (rs1047972, rs2273535, rs2064836, and rs6024836) and HCC susceptibility as well as clinical outcomes in 312 patients with HCC and in 624 cancer-free controls. We found that carriers of the TT allele of the variant rs1047972 were at greater risk of HCC compared with wild-type (CC) carriers. Moreover, carriers of at least one A allele in rs2273535 were less likely to progress to stage III/IV disease, develop large tumors or be classified into Child-Pugh class B or C. Individuals with at least one G allele at *AURKA* SNP rs2064863 were at lower risk of developing large tumors or progressing to Child-Pugh grade B or C. Our results indicate that genetic variations in the *AURKA* gene may serve as an important predictor of early-stage HCC and be a reliable biomarker for the development of HCC.

Key words: *AURKA* polymorphisms; Hepatocellular carcinoma; Single nucleotide polymorphism; Susceptibility.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer among men worldwide and the ninth in women, and a major cause of cancer-related mortality [1]. HCC is associated with a low 5-year survival rate and an increasing mortality rate [2, 3]. In Taiwan, HCC is the second major cause of cancer-associated deaths [4, 5].

Genetic variation plays a key role in HCC susceptibility and development of the disease. The majority of people who are exposed to the well-known infectious, lifestyle or environmental risk factors (i.e., hepatitis B or C virus infection, alcohol abuse or nonalcoholic fatty liver disease caused by obesity, type 2 diabetes and insulin resistance) do not develop HCC, which suggests that individual susceptibility modulates the tumor process [4]. Genotype distribution frequency data can be used to map single nucleotide polymorphism (SNP) diversity

in a population and to examine the risk and development of specific diseases [6]. Emerging reports indicate an association between SNPs in certain genes and the susceptibility and clinicopathological status of HCC. For instance, individuals carrying specific interleukin-18 (*IL-18*) or high-mobility group box protein 1 (*HMGB1*) SNPs are at higher risk of HCC than wild-type carriers [7, 8].

AURKA, also known as aurora kinase A, is a mitotic serine/threonine kinase that plays a critical role in centrosome duplication and separation, spindle assembly, maturation, chromosomal alignment, spindle assembly checkpoint, and cytokinesis [9]. Increased expression of AURKA may cause to chromosomal instability and transformation as well as centrosome amplification in mammalian cells [10]. AURKA overexpression has been observed in many human tumors [11-13], particularly in HCC [14]. It has also been reported that AURKA promotes the oncogenic effects of c-Myc, which is frequently amplified and overexpressed in many human cancers including HCC [15]. Genetic polymorphisms of *AURKA* have been indicated in several different cancer types (oral cancers, breast and ovarian cancers) [13, 16, 17]. It has been suggested that carriers of the *AURKA* 31Phe allele are less susceptible to hepatitis B virus (HBV)-related HCC when compared with noncarriers [18]. Scant research has examined the association between *AURKA* SNPs, HCC risk and prognosis. We therefore conducted a case-control study to evaluate the role of four *AURKA* SNPs on HCC susceptibility and clinicopathological features in a cohort of Chinese Han individuals.

Materials and Methods

Participants

We enrolled 312 patients (cases) presenting with HCC to Chung Shan Medical University Hospital, Taiwan, between 2007 and 2015. A total of 624 anonymised healthy controls (HCs) were randomly selected from the Taiwan Biobank Project. All study participants were of Chinese Han ethnicity. HCC patients were staged according to the 2002 American Joint Committee on Cancer (AJCC) TNM staging system, which incorporates tumor morphology, number of lymph nodes affected, and metastases [19]. Before entering the study, each participant provided informed written consent and completed a structured questionnaire about sociodemographic status, cigarette and alcohol use. Liver cirrhosis was diagnosed by biopsy, appropriate sagittal CT or MRI scans, or biochemical evidence of liver parenchymal damage with endoscopic esophageal or gastric varices. The study was approved by the Institutional Review Board of Chung Shan Medical University Hospital prior to commencement.

Determination of genotypes

Total genomic DNA was isolated from whole blood specimens using QIAamp DNA blood mini kits (Qiagen, Valencia, CA), as per the manufacturer's instructions. This DNA was dissolved in TE buffer (10 mM Tris pH 7.8, 1 mM EDTA] and stored at −20°C until it was subjected to quantitative polymerase chain reaction (PCR) analysis. Four *AURKA* SNPs (rs1047972, rs2273535, rs2064836, and rs6024836) with minor allele frequencies >5% in the HapMap population were selected. Moreover, these SNPs have previously been found to associate with the development of cancer [13, 20, 21]. The *AURKA* SNPs were examined by the commercially available TaqMan SNP genotyping assay (Applied Biosystems, Warrington, UK), according to the manufacturer's protocols [22, 23].

Statistical analysis

The genotype distribution of each SNP was analyzed for Hardy–Weinberg equilibrium and confirmed by Chi-square analysis. Demographic characteristics were compared between patients and controls using the Mann–Whitney U-test and Fisher's exact test. Associations between genotypes, HCC risk and clinicopathological characteristics were estimated using adjusted odds ratios (AORs) and 95% confidence intervals (CIs) obtained from age- and gender-adjusted multiple logistic regression models. A p value of <0.05 was considered statistically significant. Data were analyzed using SAS statistical software (Version 9.1, 2005; SAS Institute Inc., Cary, NC).

Results

Demographic characteristics did not differ significantly between the 312 patients with HCC and 624 cancer-free healthy controls (HCs) (Table 1). Significantly fewer ($p < 0.001$) controls compared with patients reported that they consumed alcohol, but cigarette smoking status did not differ between the two groups ($p = 0.604$) (Table 1). Compared with controls, significantly higher proportions of HCC patients were positive for HBsAg (11.1% vs 43.9%; $p < 0.001$) and anti-HCV antibodies (4.5% vs 47.4%; $p < 0.001$) (Table 1). 213 patients (68.3%) had stage I/II HCC and 99 (31.75%) had stage III/IV disease (Table 1).

The distribution of the *AURKA* genotypes between the HCC patients and HCs is shown in Table 2. In the HCs, all genotypic frequencies were in Hardy-Weinberg equilibrium ($p > 0.05$). In both

patients and controls, most of those with the rs1047972 SNP were homozygous for the C/C genotype, most of those with the rs2273535 SNP were homozygous for the T/T genotype, most of those with the rs2064836 SNP were homozygous for T/T, and most of those with the rs6024836 SNP were homozygous for A/A (Table 2). After adjusting for potential confounders, subjects with T/T homozygotes of the *AURKA* rs1047972 polymorphism had a 2.678-fold (95% CI: 1.012-7.092; $p < 0.05$) higher risk of developing HCC compared to those with C/C homozygotes. However, no significant differences in the incidences of HCC patients with the rs2273535, rs2064836, and rs6024836 polymorphisms compared to HCs.

Table 1. Demographic characteristics of 624 healthy controls and 312 patients with HCC.

Variable	Controls (N=624)	Patients (N=312)	*p* value
Age (yrs)	Mean ± S.D.	Mean ± S.D.	
	59.53 ± 7.53	60.41 ± 9.44	$p = 0.155$
Gender			
Male	452 (72.4%)	226 (72.4%)	
Female	172 (27.6%)	86 (27.6%)	$p = 1.000$
Cigarette smoking			
No	379 (60.7%)	184 (59.0%)	
Yes	245 (39.3%)	128 (41.0%)	$p = 0.604$
Alcohol drinking			
No	537 (86.1%)	194 (62.2%)	
Yes	87 (13.9%)	118 (37.8%)	$p < 0.001$*
HBsAg			
Negative	555 (88.9%)	175 (56.1%)	
Positive	69 (11.1%)	137 (43.9%)	$p < 0.001$*
Anti-HCV			
Negative	596 (95.5%)	164 (52.6%)	
Positive	28 (4.5%)	148 (47.4%)	$p < 0.001$*
Stage			
I+II		213 (68.3%)	
III+IV		99 (31.7%)	
Tumor T status			
T1+T2		215 (68.9%)	
T3+T4		97 (31.1%)	
Lymph node status			
N0		302 (96.8%)	
N1+N2+N3		10 (3.2%)	
Metastasis			
M0		297 (95.2%)	
M1		15 (4.8%)	
Child-Pugh grade			
A		242 (77.6%)	
B or C		70 (22.4%)	
Liver cirrhosis			
Negative		52 (16.7%)	
Positive		260 (83.3%)	

Mann-Whitney U test or Fisher's exact test was used between healthy controls and patients with HCC. * p value < 0.05 as statistically significant.

Next, we compared the distributions of the clinical aspects and *AURKA* genotypes in HCC patients. Compared with patients with the T/T genotype, those with at least one polymorphic allele at the rs2273535 SNP (A/T or A/A genotype) were less prone to developing stage III/IV disease ($p = 0.033$), large tumors ($p = 0.033$) and Child-Pugh B or C grade ($p = 0.033$), but were more likely to develop liver cirrhosis ($p = 0.045$) (Table 3). Moreover, carriers of the G/T+G/G genotype of rs2064863 had a lower risk than T/T carriers of developing large tumors ($p = 0.047$) and Child-Pugh grade B or C ($p = 0.033$), but were more likely to have HCV infection ($p = 0.039$) (Table 4).

Table 2. Genotyping and allele frequency of *AURKA* single nucleotide polymorphisms (SNPs) in HCC patients and healthy controls.

Variable	Controls (N=624 (%)	Patients (N=312 (%)	OR (95% CI)[a]
rs1047972			
CC	485 (77.7%)	235 (75.3%)	1.000 (reference)
TC	131 (21.0%)	67 (21.5%)	1.094 (0.751-1.594)
TT	8 (1.3%)	10 (3.2%)	2.678 (1.012-7.092)[b]
TC+TT	139 (22.3%)	77 (24.7%)	1.203 (0.841-1.720)
rs2273535			
TT	310 (49.7%)	152 (48.7%)	1.000 (reference)
AT	257 (41.2%)	124 (39.8%)	1.004 (0.716-1.407)
AA	57 (9.1%)	36 (11.5%)	1.263 (0.768-2.078)
AT+AA	314 (50.3)	160 (51.3%)	1.061 (0.775-1.451)
rs2064863			
TT	444 (71.1%)	217 (69.6%)	1.000 (reference)
GT	162 (26.0%)	88 (28.2%)	1.143 (0.804-1.624)
GG	18 (2.9%)	7 (2.2%)	0.600 (0.221-1.628)
GT+GG	180 (28.9%)	95 (30.4%)	1.073 (0.764-1.506)
rs6024836			
AA	284 (45.5%)	147 (47.1%)	1.000 (reference)
AG	268 (43.0%)	130 (41.7%)	1.052 (0.755-1.466)
GG	72 (11.5%)	35 (11.2%)	0.949 (0.569-1.582)
AG+GG	340 (54.5%)	165 (52.9%)	1.029 (0.752-1.407)

[a] adjusted for the effects of age and gender.
[b] $p = 0.047$.

When we investigated associations between *AURKA* gene polymorphisms and serum levels of alpha-fetoprotein (AFP), aspartate transaminase (AST) and alanine transaminase (ALT) in HCC patients [24], we found significantly lower AFP levels in those carrying the rs1047972 T/C or T/T genotypes ($p = 0.037$; Table 5).

Discussion

AURKA, a centrosome-associated serine/threonine kinase, has demonstrated higher expression in various human cancers including colorectal cancer, breast cancer, head and neck squamous cell carcinoma, as well as HCC [11-13, 25]. It is postulated that this increase in expression might result in high chromosome instability in cancer and encourage susceptibility to malignant transformation [26], processes that may arise from the acquisition of the chromosome 20q amplicon, which promotes the adenoma to carcinoma progression [27]. In addition,

overexpression of AURKA has been found to enhance tumor proliferation, differentiation, and metastasis [28-30]. AURKA also promotes cancer metastasis and cancer stem cells in HCC [31]. Inhibition of AURKA promotes autophagy and cell cycle arrest, and induces chemosensitivity in HCC [32]. These results suggest that knockdown AURKA might be a valuable therapeutic strategy for HCC. However, we dose not recruited the survival results of HCC patients. Future research could evaluate the association of AURKA polymorphisms with survival of HCC patients. In addition, it would be advisable to collect data on a larger number of patients for analysis of the functions of AURKA polymorphisms in HCC.

Table 3. Odds ratios (ORs) and 95% confidence intervals (CIs) of clinical status and *AURKA* rs2273535 genotype frequencies in 312 HCC patients.

Variable	Genotypic frequencies			
	TT (N=152)	AT+AA (N=160)	OR (95% CI)	*p* value
Clinical Stage				
Stage I/II	95 (62.5%)	118 (73.7%)	1.00	***P*=0.033***
Stage III/IV	57 (37.5%)	42 (26.3%)	0.593 (0.367-0.960)	
Tumor size				
≤ T2	96 (63.2%)	119 (74.4%)	1.00	***P*=0.033***
> T2	56 (36.8%)	41 (25.6%)	0.591 (0.364-0.959)	
Lymph node metastasis				
No	146 (96.1%)	156 (97.5%)	1.00	*P*=0.472
Yes	6 (3.9%)	4 (2.5%)	0.624 (0.173-2.256)	
Distant metastasis				
No	144 (94.7%)	153 (95.6%)	1.00	*P*=0.714
Yes	8 (5.3%)	7 (4.4%)	0.824 (0.291-2.329)	
Vascular invasion				
No	124 (81.6%)	134 (83.8%)	1.00	*P*=0.613
Yes	28 (18.4%)	26 (16.2%)	0.859 (0.478-1.546)	
Child-Pugh grade				
A	110 (72.4%)	132 (82.5%)	1.00	***P*=0.033***
B or C	42 (27.6%)	28 (17.5%)	0.556 (0.323-0.954)	
HBsAg				
Negative	79 (52.0%)	96 (60.0%)	1.00	*P*=0.496
Positive	73 (48.0%)	64 (40.0%)	0.898 (0.659-1.224)	
Anti-HCV				
Negative	86 (56.6%)	78 (48.8%)	1.00	*P*=0.099
Positive	66 (43.4%)	82 (51.2%)	1.320 (0.949-1.836)	
Liver cirrhosis				
Negative	32 (21.1%)	20 (12.5%)	1.00	***P*=0.045***
Positive	120 (78.9%)	140 (87.5%)	1.867 (1.015-3.434)	

The ORs with analyzed by their 95% CIs were estimated by logistic regression models.

> T2: multiple tumor more than 5 cm or tumor involving a major branch of the portal or hepatic vein(s)

* *p* value < 0.05 as statistically significant.

Since HCC is one of the most common and lethal tumors worldwide, preventing its occurrence and lowering its mortality rate is an important challenge. Infection with HBV or HCV, a history of liver cirrhosis, family history of HCC, and alcohol consumption are the dominant etiological factors for HCC in Taiwan [33]. In this study, there is no difference between the ratios of cigarette smokers/nonsmokers in controls (60.7:39.3) and HCC patients (59:41), whereas a higher proportion of HCC patients consumed alcohol (37.8%) compared with controls (13.9%). This suggests that alcohol consumption is a risk factor for HCC development. Chronic alcohol consumption promotes hepatobiliary tumors by increasing microRNA-122-controlled HIF-1α activity and stemness [34]. In a pig model, moderate alcohol consumption changed autophagy- and apoptosis-regulated pathways [35]. Exposure alcohol frequently changed genes at fragile sites, and promoted AURKA functioning. An increasing body of evidence shows that alcohol consumption is a risk factor for HCC [36, 37]. Our data is consistent with this finding, as those HCC patients who consumed alcohol were at higher risk of worsening disease.

Table 4. Odds ratio (OR) and 95% confidence interval (CI) of clinical status and *AURKA* rs2064863 genotypic frequencies in 312 HCC patients.

Variable	Genotypic frequencies			
	TT (N=217)	GT+GG (N=95)	OR (95% CI)	*p* value
Clinical Stage				
Stage I/II	141 (65.0%)	72 (75.8%)	1.00	*P*=0.061
Stage III/IV	76 (35.0%)	23 (24.2%)	0.593 (0.343-1.023)	
Tumor size				
≤ T2	142 (65.4%)	73 (76.8%)	1.00	***P*=0.047***
> T2	75 (34.6%)	22 (23.2%)	0.571 (0.328-0.992)	
Lymph node metastasis				
No	209 (96.3%)	93 (97.9%)	1.00	*P*=0.471
Yes	8 (3.7%)	2 (2.1%)	0.562 (0.117-2.697)	
Distant metastasis				
No	205 (94.5%)	92 (96.8%)	1.00	*P*=0.374
Yes	12 (5.5%)	3 (3.2%)	0.557 (0.154-2.021)	
Vascular invasion				
No	176 (81.1%)	82 (86.3%)	1.00	*P*=0.265
Yes	41 (18.9%)	13 (13.7%)	0.681 (0.346-1.339)	
Child-Pugh grade				
A	161 (74.2%)	81 (85.3%)	1.00	***P*=0.033***
B or C	56 (25.8%)	14 (14.7%)	0.497 (0.261-0.946)	
HBsAg				
Negative	117 (53.9%)	58 (61.1%)	1.00	*P*=0.193
Positive	100 (46.1%)	37 (38.9%)	0.793 (0.559-1.125)	
Anti-HCV				
Negative	119 (54.8%)	45 (47.4%)	1.00	***P*=0.039***
Positive	98 (45.2%)	50 (52.6%)	1.441 (1.019-2.038)	
Liver cirrhosis				
Negative	38 (17.5%)	14 (14.7%)	1.00	*P*=0.546
Positive	179 (82.5%)	81 (85.3%)	1.228 (0.631-2.392)	

The ORs with analyzed by their 95% CIs were estimated by logistic regression models.

> T2: multiple tumor more than 5 cm or tumor involving a major branch of the portal or hepatic vein(s)

* *p* value < 0.05 as statistically significant.

The risk of breast cancer is high in individuals with the *AURKA* rs2273535 polymorphism [38], while the *AURKA* 91A (rs2273535) polymorphism is associated with a high risk of oral cancer [39]. In Caucasians, the *AURKA* rs1047972 polymorphism is associated with a decreased risk of breast cancer [40]. In this study, we did not find that the *AURKA* rs2273535 polymorphism was associated with HCC risk. However, our data does indicate that the *AURKA* rs1047972 polymorphism increases the risk of developing HCC. These findings suggest that different *AURKA* polymorphisms play different roles in cancer development.

Table 5. Association of *AURKA* genotype frequencies with laboratory findings in liver tests from HCC patients.

Characteristic	α-Fetoprotein [a] (ng/mL)	AST (IU/L)	ALT (IU/L)	AST/ALT ratio
rs1047972				
CC	1226.8 ± 365.6	58.61 ± 5.88	54.82 ± 5.48	1.23 ± 0.03
TC+TT	396.8 ± 153.0	47.51 ± 3.91	49.10 ± 4.84	1.19 ± 0.04
p value	**0.037***	0.116	0.434	0.470
rs2273535				
TT	1480.6 ± 523.4	63.39 ± 8.66	57.91 ± 8.00	1.23 ± 0.03
AT+AA	601.2 ± 230.3	48.89 ± 3.41	49.20 ± 3.63	1.21 ± 0.05
p value	0.125	0.120	0.322	0.654
rs2064863				
TT	1144.4 ± 369.3	57.82 ± 6.18	54.39 ± 5.77	1.22 ± 0.02
GT+GG	772.8 ± 380.2	51.79 ± 5.12	51.36 ± 5.25	1.21 ± 0.07
p value	0.483	0.453	0.698	0.889
rs6024836				
AA	1365.9 ± 493.4	65.00 ± 9.21	59.93 ± 8.49	1.26 ± 0.05
AG+GG	753.0 ± 314.7	48.41 ± 3.35	48.01 ± 3.57	1.19 ± 0.02
p value	0.295	0.091	0.196	0.193

Mann-Whitney U test was used between two groups.

[a] Mean ± S.E.

* *p* value < 0.05 as statistically significant.

This study found that HCC patients with the *AURKA* rs2273535 polymorphism had a lower risk of developing stage III/IV disease, large tumors, and Child-Pugh grade B or C. Similarly, the *AURKA* rs2064863 polymorphism was also associated with a lower risk of developing large tumors and Child-Pugh grade B or C. It is established that overexpression of the *AURKA* gene is implicated in the development of colorectal adenoma to colorectal cancer [26]. In addition, *AURKA* upregulation promotes high chromosome instability in cancerous tissue and induces increased susceptibility to tumor transformation [26]. However, more research is required to determine whether an association exists among advanced-stage disease, *AURKA* expression levels, and *AURKA* genotype, and clarification is needed in regard to the effects of the *AURKA* genotype on HCC risk.

In conclusion, the current study suggests a potentially clinically significant finding showing that several variants of the *AURKA* gene are associated with the clinical status and susceptibility of HCC. We found that individuals carrying the T/T allele of the *AURKA* SNP rs1047972 were at higher risk of HCC than wild-type (C/C) carriers. Genetic variations in the gene encoding *AURKA* may be a significant predictor of early HCC occurrence and a reliable biomarker for disease progression.

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Competing Interests

The authors have declared that no competing interest exists.

References

[1] Siegel R, Naishadham D and Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013; 63: 11-30.
[2] Blechacz B and Mishra L. Hepatocellular carcinoma biology. Recent results in cancer research. Fortschritte der Krebsforschung. Progres dans les recherches sur le cancer 2013; 190: 1-20.
[3] Ezzikouri S, Benjelloun S and Pineau P. Human genetic variation and the risk of hepatocellular carcinoma development. Hepatol Int 2013; 7: 820-831.
[4] Bosch FX, Ribes J, Cleries R and Diaz M. Epidemiology of hepatocellular carcinoma. Clinics in liver disease 2005; 9(v): 191-211.
[5] Wu CY, Huang HM and Cho DY. An acute bleeding metastatic spinal tumor from HCC causes an acute onset of cauda equina syndrome. Biomedicine (Taipei) 2015; 5: 18.
[6] Shastry BS. SNP alleles in human disease and evolution. J Hum Genet 2002; 47: 561-566.
[7] Lau HK, Hsieh MJ, Yang SF, Wang HL, Kuo WH, Lee HL and Yeh CB. Association between Interleukin-18 Polymorphisms and Hepatocellular Carcinoma Occurrence and Clinical Progression. Int J Med Sci 2016; 13: 556-561.
[8] Wang B, Yeh CB, Lein MY, Su CM, Yang SF, Liu YF and Tang CH. Effects of HMGB1 Polymorphisms on the Susceptibility and Progression of Hepatocellular Carcinoma. Int J Med Sci 2016; 13: 304-309.
[9] Vader G and Lens SM. The Aurora kinase family in cell division and cancer. Biochim Biophys Acta 2008; 1786: 60-72.
[10] Zhou H, Kuang J, Zhong L, Kuo WL, Gray JW, Sahin A, Brinkley BR and Sen S. Tumour amplified kinase STK15/BTAK induces centrosome amplification, aneuploidy and transformation. Nat Genet 1998; 20: 189-193.
[11] Treekitkarnmongkol W, Katayama H, Kai K, Sasai K, Jones JC, Wang J, Shen L, Sahin AA, Gagea M, Ueno NT, Creighton CJ and Sen S. Aurora kinase-A overexpression in mouse mammary epithelium induces mammary adenocarcinomas harboring genetic alterations shared with human breast cancer. Carcinogenesis 2016; 37: 1180-1189.
[12] Wang C, Yan Q, Hu M, Qin D and Feng Z. Effect of AURKA Gene Expression Knockdown on Angiogenesis and Tumorigenesis of Human Ovarian Cancer Cell Lines. Target Oncol 2016; 11: 771-781.
[13] Chou CH, Chou YE, Chuang CY, Yang SF and Lin CW. Combined effect of genetic polymorphisms of AURKA and environmental factors on oral cancer development in Taiwan. PLoS One 2017; 12: e0171583.
[14] Simon EP, Freije CA, Farber BA, Lalazar G, Darcy DG, Honeyman JN, Chiaroni-Clarke R, Dill BD, Molina H, Bhanot UK, La Quaglia MP, Rosenberg BR and Simon SM. Transcriptomic characterization of fibrolamellar hepatocellular carcinoma. Proc Natl Acad Sci U S A 2015; 112: E5916-5925.
[15] Lu L, Han H, Tian Y, Li W, Zhang J, Feng M and Li Y. Aurora kinase A mediates c-Myc's oncogenic effects in hepatocellular carcinoma. Mol Carcinog 2015; 54: 1467-1479.
[16] Ruan Y, Song AP, Wang H, Xie YT, Han JY, Sajdik C, Tian XX and Fang WG. Genetic polymorphisms in AURKA and BRCA1 are associated with breast cancer susceptibility in a Chinese Han population. J Pathol 2011; 225: 535-543.
[17] Zheng L, Song A, Ruan Y, Chen L, Liu D, Li X, Guo H, Han J, Li Y, Tian X and Fang W. Genetic polymorphisms in AURKA, BRCA1, CCNE1 and CDK2 are associated with ovarian cancer susceptibility among Chinese Han women. Cancer Epidemiol 2013; 37: 639-646.
[18] Bao Z, Lu L, Liu X, Guo B, Zhai Y, Li Y, Wang Y, Xie B, Ren Q, Cao P, Han Y, Jia W, Chen M, Liang X, Wang X, Zeng YX, He F, Zhang H, Cui Y and Zhou G. Association between the functional polymorphism Ile31Phe in the AURKA

gene and susceptibility of hepatocellular carcinoma in chronic hepatitis B virus carriers. Oncotarget 2017;
[19] Vauthey JN, Lauwers GY, Esnaola NF, Do KA, Belghiti J, Mirza N, Curley SA, Ellis LM, Regimbeau JM, Rashid A, Cleary KR and Nagorney DM. Simplified staging for hepatocellular carcinoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2002; 20: 1527-1536.
[20] Bao Z, Lu L, Liu X, Guo B, Zhai Y, Li Y, Wang Y, Xie B, Ren Q, Cao P, Han Y, Jia W, Chen M, Liang X, Wang X, Zeng YX, He F, Zhang H, Cui Y and Zhou G. Association between the functional polymorphism Ile31Phe in the AURKA gene and susceptibility of hepatocellular carcinoma in chronic hepatitis B virus carriers. Oncotarget 2017; 8: 54904-54912.
[21] Mesic A, Rogar M, Hudler P, Juvan R and Komel R. Association of the AURKA and AURKC gene polymorphisms with an increased risk of gastric cancer. IUBMB Life 2016; 68: 634-644.
[22] Lin YJ, Ho TJ, Lin TH, Hsu WY, Huang SM, Liao CC, Lai CH, Liu X, Tsang H, Lai CC and Tsai FJ. P-coumaric acid regulates exon 12 splicing of the ATP7B gene by modulating hnRNP A1 protein expressions. Biomedicine (Taipei) 2015; 5: 10.
[23] Li TC, Li CI, Liao LN, Liu CS, Yang CW, Lin CH, Hsiao JH, Hsiao CY, Lin WY, Wu FY and Lin CC. Associations of EDNRA and EDN1 polymorphisms with carotid intima media thickness through interactions with gender, regular exercise, and obesity in subjects in Taiwan: Taichung Community Health Study (TCHS). Biomedicine (Taipei) 2015; 5: 8.
[24] Simpson HN and McGuire BM. Screening and detection of hepatocellular carcinoma. Clinics in liver disease 2015; 19: 295-307.
[25] Goos JA, Coupe VM, Diosdado B, Delis-Van Diemen PM, Karga C, Belien JA, Carvalho B, van den Tol MP, Verheul HM, Geldof AA, Meijer GA, Hoekstra OS, Fijneman RJ and DeCoDe PETg. Aurora kinase A (AURKA) expression in colorectal cancer liver metastasis is associated with poor prognosis. Br J Cancer 2013; 109: 2445-2452.
[26] Chuang TP, Wang JY, Jao SW, Wu CC, Chen JH, Hsiao KH, Lin CY, Chen SH, Su SY, Chen YJ, Chen YT, Wu DC and Li LH. Over-expression of AURKA, SKA3 and DSN1 contributes to colorectal adenoma to carcinoma progression. Oncotarget 2016; 7: 45803-45818.
[27] Sillars-Hardebol AH, Carvalho B, Tijssen M, Belien JA, de Wit M, Delis-van Diemen PM, Ponten F, van de Wiel MA, Fijneman RJ and Meijer GA. TPX2 and AURKA promote 20q amplicon-driven colorectal adenoma to carcinoma progression. Gut 2012; 61: 1568-1575.
[28] Dar AA, Belkhiri A and El-Rifai W. The aurora kinase A regulates GSK-3beta in gastric cancer cells. Oncogene 2009; 28: 866-875.
[29] Xu LZ, Long ZJ, Peng F, Liu Y, Xu J, Wang C, Jiang L, Guo T, Kamran M, Li SS, Wang CL, Wang HJ, Zhao YF, Wan XY and Liu Q. Aurora kinase a suppresses metabolic stress-induced autophagic cell death by activating mTOR signaling in breast cancer cells. Oncotarget 2014; 5: 7498-7511.
[30] Jia L, Lee HS, Wu CF, Kundu J, Park SG, Kim RN, Wang LH, Erkin OC, Choi JS, Chae SW, Yang HB, Choi YL and Shin YK. SMAD4 suppresses AURKA-induced metastatic phenotypes via degradation of AURKA in a TGFbeta-independent manner. Mol Cancer Res 2014; 12: 1779-1795.
[31] Chen C, Song G, Xiang J, Zhang H, Zhao S and Zhan Y. AURKA promotes cancer metastasis by regulating epithelial-mesenchymal transition and cancer stem cell properties in hepatocellular carcinoma. Biochem Biophys Res Commun 2017; 486: 514-520.
[32] Zhu Q, Yu X, Zhou ZW, Zhou C, Chen XW and Zhou SF. Inhibition of Aurora A Kinase by Alisertib Induces Autophagy and Cell Cycle Arrest and Increases Chemosensitivity in Human Hepatocellular Carcinoma HepG2 Cells. Curr Cancer Drug Targets 2017; 17: 386-401.
[33] Chen TH, Chen CJ, Yen MF, Lu SN, Sun CA, Huang GT, Yang PM, Lee HS and Duffy SW. Ultrasound screening and risk factors for death from hepatocellular carcinoma in a high risk group in Taiwan. Int J Cancer 2002; 98: 257-261.
[34] Ambade A, Satishchandran A and Szabo G. Alcoholic hepatitis accelerates early hepatobiliary cancer by increasing stemness and miR-122-mediated HIF-1alpha activation. Sci Rep 2016; 6: 21340.
[35] Potz BA, Lawandy IJ, Clements RT and Sellke FW. Alcohol modulates autophagy and apoptosis in pig liver tissue. J Surg Res 2016; 203: 154-162.
[36] Yang MD, Hsu CM, Chang WS, Yueh TC, Lai YL, Chuang CL, Wang SC, Jeng LB, Ji HX, Hsiao CL, Wu CN, Tsai CW, Chung JG and Bau DT. Tumor Necrosis Factor-alpha Genotypes Are Associated with Hepatocellular Carcinoma Risk in Taiwanese Males, Smokers and Alcohol Drinkers. Anticancer research 2015; 35: 5417-5423.
[37] Urata Y, Yamasaki T, Saeki I, Iwai S, Kitahara M, Sawai Y, Tanaka K, Aoki T, Iwadou S, Fujita N, Nakayama Y, Maeshiro T, Takami T and Sakaida I. Clinical characteristics and prognosis of non-B non-C hepatocellular carcinoma patients with modest alcohol consumption. Hepatology research : the official journal of the Japan Society of Hepatology 2015;
[38] Guo XG, Zheng L, Feng WB and Xia Y. The AURKA gene rs2273535 polymorphism contributes to breast carcinoma risk - meta-analysis of eleven studies. Asian Pac J Cancer Prev 2014; 15: 6709-6714.
[39] Lee CP, Chiang SL, Lee CH, Tsai YS, Wang ZH, Hua CH, Chen YC, Tsai EM and Ko YC. AURKA Phe31Ile polymorphism interacted with use of alcohol, betel quid, and cigarettes at multiplicative risk of oral cancer occurrence. Clin Oral Investig 2015; 19: 1825-1832.
[40] Dai ZJ, Kang HF, Wang XJ, Shao YP, Lin S, Zhao Y, Ren HT, Min WL, Wang M and Liu XX. Association between genetic polymorphisms in AURKA (rs2273535 and rs1047972) and breast cancer risk: a meta-analysis involving 37,221 subjects. Cancer Cell Int 2014; 14: 91.