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 rs206486 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, rs206486, 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    | 0.155   |
| Gender         |                 |                 |         |
| Male           | 452 (72.4%)     | 226 (72.4%)     |         |
| Female         | 172 (27.6%)     | 86 (27.6%)      | 1.000   |
| Cigarette smoking |             |                 |         |
| No             | 379 (60.7%)     | 184 (59.0%)     | 0.604   |
| Yes            | 245 (39.3%)     | 128 (41.0%)     |         |
| Alcohol drinking |             |                 |         |
| No             | 537 (86.1%)     | 194 (62.2%)     | <0.001* |
| Yes            | 87 (13.9%)      | 118 (37.8%)     |         |
| HBsAg Negative | 555 (88.9%)     | 175 (56.1%)     | <0.001* |
| Positive       | 69 (11.1%)      | 137 (43.9%)     |         |
| Anti-HCV Negative |         | 164 (52.6%)    | <0.001* |
| Positive       | 28 (4.5%)       | 148 (47.4%)     |         |
| Stage          |                 |                 |         |
| I+II           | 213 (68.3%)     | 100 (32.3%)     |         |
| III+IV         | 99 (31.7%)      | 100 (32.3%)     |         |
| Tumor T status |                 |                 |         |
| T1+T2          | 215 (68.9%)     | 100 (32.3%)     |         |
| T3+T4          | 97 (31.1%)      | 100 (32.3%)     |         |
| Lymph node status |             |                 |         |
| N0             | 302 (96.8%)     | 100 (32.3%)     |         |
| N1+N2+N3       | 10 (3.2%)       | 100 (32.3%)     |         |
| Metastasis     |                 |                 |         |
| M0             | 297 (95.2%)     | 100 (32.3%)     |         |
| M1             | 15 (4.8%)       | 100 (32.3%)     |         |
| Child-Pugh grade |             |                 |         |
| A              | 242 (77.6%)     | 100 (32.3%)     |         |
| B or C         | 70 (22.4%)      | 100 (32.3%)     |         |
| Liver cirrhosis |             |                 |         |
| Negative       | 52 (16.7%)      | 100 (32.3%)     |         |
| Positive       | 260 (83.3%)     | 100 (32.3%)     |         |

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)* |
|----------------|----------------------|----------------------|--------------|
| rs1047972      |                      |                      |              |
| CC             | 485 (77.7%)          | 235 (75.3%)          | 1.00 (ref)   |
| 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)* |
| rs2273535      |                      |                      |              |
| TT             | 310 (49.7%)          | 152 (48.7%)          | 1.00 (ref)   |
| 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      |                      |                      |              |
| TT             | 444 (71.1%)          | 217 (69.6%)          | 1.000 (ref)   |
| 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      |                      |                      |              |
| TT             | 444 (71.1%)          | 217 (69.6%)          | 1.000 (ref)   |
| 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) |

a adjusted for the effects of age and gender.

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 | p value |
|-------------------------------|-----------------------|---------|
|                              | TT (N=152) | AT+AA (N=160) | OR (95% CI) |
| 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 to alcohol frequently changes 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 genotype frequencies in 312 HCC patients.

| Variable                      | Genotypic frequencies | p value |
|-------------------------------|-----------------------|---------|
|                              | TT (N=217) | GT+GG (N=95) | OR (95% CI) |
| 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%) | 0.595 (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]. However, our data does indicate that the AURKA rs2273535 polymorphism was associated with HCC risk. These findings suggest that different AURKA polymorphisms play different roles in cancer development.

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.

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

| Characteristic | α-Fetoprotein (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         |
| rs024836      |                       |            |            |               |
| 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. *p value < 0.05 as statistically significant.

The authors have declared that no competing interest exists.

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