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Original Article

Polymorphic variants of FGFR-4 associated with clinical characteristics in urothelial cell carcinoma

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Abstract: Background: Fibroblast growth factor receptor-4 (FGFR-4) polymorphic variants have an important role on the development of various cancers. However, the association between FGFR-4 polymorphic variants and the risk of urothelial cell carcinoma (UCC) has not been determined. In this study, we studied the associations of FGFR-4 polymorphic variants with UCC susceptibility and its clinicopathological features. Materials and methods: Four SNPs in FGFR-4 were analyzed among 558 participants comprising 279 controls and 279 patients with UCC by performing a real-time genotype PCR assay. Results: Our results showed that UCC patients who carried at least one A genotype at rs1966265 exhibited a higher risk of invasive tumor stage compared with those carrying the wild-type genotype ($P < 0.05$). Patients with UCC who carried at least one G genotype (AG and GG) at rs2011077 also exhibited a higher risk of invasive tumor stage. Conclusion: Our findings suggest that polymorphic variants in FGFR-4 rs1966265 and rs2011077 may be associated with the risk of invasive tumor stage in Taiwanese patients with UCC. This is the first study to determine the association between FGFR-4 polymorphic variants and UCC tumor stage progression.

Keywords: Polymorphic variants, fibroblast growth factor receptor 4, urothelial cell carcinoma

Introduction

Urothelial cell carcinoma (UCC) is the most common malignancy of the urinary tract. In Taiwan, UCC is the ninth leading malignancy among men and the 16th leading malignancy among women. The most widely known risk factors for UCC are tobacco consumption and exposure to aromatic amines [1-3]. Increasingly more evidence regarding the impact of genetic factors in the risk of UCC has been published [4-6].

Fibroblast growth factors (FGFs) are effective regulators of cell proliferation, and cell differentiation. The function are critical in normal development, tissue maintenance angiogenesis, embryonic development, and wound repair [7]. At least 20 FGF members exist, designated FGF-1 through FGF-20, but acidic FGF and basic FGF are names commonly used for FGF-1 and FGF-2, and keratinocyte growth factor (KGF) is the name generally used for FGF-7. FGFs represent a large family of secreted molecules [8]. The FGF receptor (FGFR) family comprises 4 family members, is a subsequent formation of various complexes to initiate downstream signal transduction [9-11]. Aberrant FGFR signaling is mainly contributed to several mechanisms involving genetic variants, gene amplification and chromosomal translocation [12-14].

Fibroblast growth factor receptor-4 (FGFR-4) overexpression is commonly detected in numerous types of human cancers, for example breast cancers, ovarian cancer, bladder cancer, lung cancer, and gastric cancers [15]. Moreover, previous studies have reported that for FGFR-4, the G to A polymorphic variants in rs1966265 (Ile10Val), and the C to T polymorphic variants

Table 1. The distributions of demographical characteristics in 279 patients with UCC

Variable	Patients (N = 279)
Age (yrs)	Mean ± S.D.
	68.75 ± 12.06
Gender	n (%)
Male	182 (65.2%)
Female	97 (34.8%)
Tobacco consumption	
No	203 (72.8%)
Yes	76 (27.2%)
Stage	
Superficial tumor (pTa-pT1)	170 (60.9%)
Invasive tumor (pT2-pT4)	109 (39.1%)
Tumor T status	
T0	76 (27.2%)
T1-T4	203 (72.8%)
Lymph node status	
N0	251 (90.0%)
N1+N2	28 (10.0%)
Metastasis	
M0	275 (98.6%)
M1	4 (1.4%)
Histopathologic grading	
Low grade	40 (14.3%)
High grade	239 (85.7%)

in rs351855 (Gly388Arg) may alters protein expression [16-18]. Additionally, these polymorphic variants have a pathophysiological impact on tumor development in prostate or breast cancers [19, 20]. However, no report has been published on the relationship between FGFR-4 polymorphic variants and UCC risks. Thus, this study explored the associations among these 4 polymorphic variants of FGFR-4 and the risk of UCC, and evaluated the impact of these polymorphic variants on the clinicopathological features of UCC.

Materials and methods

Subjects and specimen collection

279 patients (182 men and 97 women, with a mean age of 68.75 years) were recruited in 2010-213 at Taichung Veterans General Hospital (TVGH) in Taichung, Taiwan. All 279 patients have pathology proved as urothelial cell carcinoma of bladder or upper urinary tract. The control group was enrolled from the physical examination during the hospital. The approval was obtained from the Institutional Review Board of TVGH, and informed written consent to patients was obtained from each person before commencement of this study.

FGFR-4 polymorphic variants genotyping

Genomic DNA was extracted using AxyPrep Blood Genomic DNA Miniprep Kit (Axygen Biosciences, Union City, CA, USA). The FGFR-4 rs351855, rs1966265, rs7708357 and rs2011077 polymorphic variants were assessed by using the TaqMan assay with an ABI StepOnePlus™ Real-Time PCR System as previously described [21].

Statistical analysis

The AOR and 95% CIs of the association between genotype frequencies and risk or clinicopathological features were estimated using multiple logistic regression models, after controlling for age, gender and tobacco. Differences between the 2 groups were significant if p values were < 0.05. We analyzed all data with SPSS software (version 17.0, SPSS Inc., Chicago, IL, USA).

Results

The distributions of demographics of 279 patients with UCC are shown in **Table 1**. Compared with the control group, no significant differences were found in age (68.8 ± 12.1 vs 67.9 ± 10.8 y, P = 0.375), sex, and tobacco consumption. The frequencies of FGFR-4 genes were all in the Hardy-Weinberg equilibrium among the control group. The distribution of FGFR-4 genotypes is shown in **Table 2**. The most frequent alleles were heterozygous G/A, C/T, and A/G for rs1966265, rs351855, and rs2011077, respectively, and homozygous G/G for rs7708357. After adjusting for age, sex, and tobacco consumption, no difference in genotype frequencies for rs1966265, rs351855, rs2011077, and rs7708357 of the FGFR-4 gene was observed between the case and control groups (**Table 2**).

The distribution of the pathological status and FGFR-4 genotypes in patients with UCC were estimated to clarify the role of FGFR-4 polymorphic variants in the pathological clinical status of patients with UCC. Pathological status

Table 2. Distribution frequency of FGFR-4 genotypes in 279 controls and 279 UCC patients

Variable	Controls (N = 279) n (%)	Patients (N = 279) n (%)	OR (95% CI)	AOR (95% CI)
rs1966265				
GG	73 (26.2%)	75 (26.9%)	1.00	1.00
GA	143 (51.2%)	140 (50.2%)	0.953 (0.640-1.418)	0.893 (0.568-1.404)
AA	63 (22.6%)	64 (22.9%)	0.989 (0.615-1.589)	0.766 (0.443-1.324)
GA+AA	206 (73.8%)	204 (73.1%)	0.964 (0.662-1.404)	0.853 (0.555-1.309)
rs351855				
CC (Gly/Gly)	76 (27.2%)	84 (30.1%)	1.00	1.00
CT (Gly/Arg)	149 (53.4%)	136 (48.7%)	0.826 (0.560-1.217)	0.789 (0.508-1.226)
TT (Arg/Arg)	54 (19.4%)	59 (21.2%)	0.989 (0.610-1.601)	0.773 (0.455-1.342)
CT+TT	203 (72.8%)	195 (69.9%)	0.869 (0.602-1.255)	0.784 (0.516-1.192)
rs2011077				
AA	72 (25.8%)	76 (27.2%)	1.00	1.00
AG	143 (51.3%)	139 (49.9%)	0.921 (0.619-1.371)	0.868 (0.552-1.364)
GG	64 (22.9%)	64 (22.9%)	0.947 (0.590-1.521)	0.727 (0.421-1.256)
AG+GG	207 (74.2%)	203 (72.8%)	0.929 (0.638-1.353)	0.823 (0.536-1.263)
rs7708357				
GG	269 (96.4%)	272 (97.5%)	1.00	1.00
GA	10 (3.6%)	7 (2.5%)	0.692 (0.260-1.845)	0.749 (0.246-2.282)
AA	0 (0%)	0 (0%)	---	---
GA+AA	10 (3.6%)	7 (2.5%)	0.692 (0.260-1.845)	0.749 (0.246-2.282)

Table 3. Distribution frequency of the clinical status and *FGFR-4* rs1966265 genotype frequencies in 279 patients with UCC

Variable	FGFR-4 (rs1966265)			
	GG (%) (*N* = 75)	GA+AA (%) (*N* = 204)	*p* value	*p* value
Stage				
Superficial tumor (pTa-pT1)	53 (70.7%)	117 (57.4%)	1.00	
Invasive tumor (pT2-pT4)	22 (29.3%)	87 (42.6%)	1.791 (1.014-3.165)	P = 0.029*
Tumor T status				
T0	19 (25.3%)	57 (27.9%)	1.00	
T1-T4	56 (74.7%)	147 (72.1%)	0.875 (0.478-1.600)	P = 0.393
Lymph node status				
N0	71 (94.7%)	180 (88.2%)	1.00	
N1+N2	4 (5.3%)	24 (11.8%)	2.367 (0.793-7.064)	P = 0.082
Metastasis				
M0	74 (98.7%)	201 (98.5%)	1.00	
M1	1 (1.3%)	3 (1.5%)	1.104 (0.113-10.785)	P = 0.707
Histopathologic grading				
Low grade	9 (12.0%)	31 (15.2%)	1.00	
High grade	66 (88.0%)	173 (84.8%)	0.761 (0.344-1.684)	P = 0.321

*p value < 0.05 as statistically significant.

assessments included the stage, tumor size and lymph node statuses, as well as metastasis and histopathologic grading. No significant differences were observed between other FGFR-4 genotypic frequencies and tumor and lymph node statuses or metastasis and histopathologic grading (**Tables 3** and **4**). However, for FGFR-4 rs1966265, patients with the het-

Table 4. Distribution frequency of the clinical status and *FGFR-4* rs2011077 genotype frequencies in 279 patients with UCC

Variable	FGFR-4 (rs2011077)			
	AA (%) (*N* = 76)	AG+GG (%) (*N* = 203)	*p* value	*p* value
Stage				
Superficial tumor (pTa-pT1)	54 (71.1%)	116 (57.1%)	1.00	
Invasive tumor (pT2-pT4)	22 (28.9%)	87 (42.9%)	1.841 (1.043-3.250)	P = 0.023*
Tumor T status				
T0	19 (25.0%)	57 (28.1%)	1.00	
T1-T4	57 (75.0%)	146 (71.9%)	0.854 (0.467-1.560)	P = 0.362
Lymph node status				
N0	72 (94.7%)	179 (88.2%)	1.00	
N1+N2	4 (5.3%)	24 (11.8%)	2.413 (0.809-7.202)	P = 0.076
Metastasis				
M0	75 (98.7%)	200 (98.5%)	1.00	
M1	1 (1.3%)	3 (1.5%)	1.125 (0.115-10.984)	P = 0.701
Histopathologic grading				
Low grade	9 (11.8%)	31 (15.3%)	1.00	
High grade	67 (88.2%)	172 (84.7%)	0.745 (0.337-1.649)	P = 0.302

*p value < 0.05 as statistically significant.

Table 5. The estimated haplotype frequencies of four examined polymorphic variants in *FGFR-4* gene and the corresponding risk for UCC

Variable				Controls (N = 558) n (%)	Patients (N = 558) n (%)	OR (95% CI)	*p* value
rs1966265 G/A	rs351855 T/A	rs2011077 A/G	rs7708357 G/T				
G	C	A	G	279 (50.0%)	286 (51.3%)	Reference	
A	T	G	G	247 (44.2%)	248 (44.3%)	0.979 (0.769-1.247)	0.866
A	C	G	G	16 (2.9%)	12 (2.2%)	0.732 (0.340-1.575)	0.423
Others#				16 (2.9%)	12 (2.2%)	0.732 (0.340-1.575)	0.423

#Others: ATGA: 7 cases; GTAG: 6 cases; GCAA: 5 cases; ACGA: 5 cases; GTGG: 3 cases; ACAG: 2 cases.

erozygous G/A or A/A genotype exhibited a high risk of UCC with invasive tumor stage ($P < 0.05$) compared with those with the homozygous G/G genotype, as shown in **Table 3**. In addition, patients with the heterozygous A/G or G/G genotype also exhibited a high risk of UCC with invasive tumor stage ($P < 0.05$) compared with those with the homozygous A/A genotype for FGFR-4 rs2011077 (**Table 4**). No significant differences were observed between FGFR-4 rs351855 and rs7708357 genotypic and invasive tumor clinical status. The relationship of FGFR-4 haplotypes with the risk of developing UCC was also evaluated. The frequency distributions of three common FGFR-4 rs1966265, rs351855, rs2011077, and rs7708357 haplotypes are shown in **Table 5**, with the most frequent haplotype in the controls (GCAG) being chosen as the reference. We found that all these common FGFR-4 haplotypes exhibit no significant associations with increased susceptibility to UCC (**Table 5**).

Discussion

This is the first study to determine a significant association between FGFR-4 polymorphic variants and UCC risk. The results showed that patients carrying the G/A or A/A genotype of the FGFR-4 rs1966265 polymorphic variant exhibited a significantly increased risk of UCC invasive tumor stage. Compared with the A/A genotype of the FGFR-4 rs2011077, the A/G + G/G genotype also exhibited a higher risk of UCC invasive tumor stage.

FGFRs consist of 4 closely related genes (FGFR1-4) associated with the development

of several types of human cancers, for example breast cancers, ovarian cancer, bladder cancer, lung cancer, and gastric cancers [22, 23]. Bang et al reported that the FGFR-4 rs351855 polymorphic variant was associated with metastasis in prostate and breast cancer patients [24]. Moreover, Sugiyama et al., also reported the FGFR-4-R388 allele could increase tumor invasion by decreasing MT1-MMP degradation, thus exerts to poor cancer prognosis [25]. Aberrant expression and polymorphic variant of fibroblast growth factor receptor 4 (FGFR-4) has been linked to tumor progression and anticancer drug resistance. Knockdown of FGFR-4-R388 or MT1-MMP through RNA interference blocked tumor cell invasion and growth in collagen. This was coupled with impaired phosphorylation of FGFR substrate 2 and Src, upregulation of E-cadherin, and suppression of cadherin-11 and N-cadherin [26]. However, few studies have reported the expression of FGFR-4 and its associated polymorphic variants with UCC. However, no significant differences were observed between FGFR-4 rs351855 genotypic and invasive tumor clinical status in our study.

We observed that polymorphic variants in FGFR-4 rs1966265 and FGFR-4 rs2011077 were associated with a high risk of invasive tumor stage in patients with UCC. FGFR-4 polymorphic variant rs1966265 exhibited an association with both respiratory distress and bronchopulmonary dysplasia [16]. FGFR-4 G alleles of the rs2011077 polymorphic variant have a significant impact on the development of prostate cancer and benign prostate hyperplasia [17]. Although the rs2011077 polymorphic variant is located in the intron, it may affect mRNA splicing or transcription activity. It is suggested that the rs2011077 SNP may increase the activity or expression of FGFR-4 at the UCC progressive stage. These findings may explain the relationship between the G alleles of the rs2011077 of FGFR-4 and the increased invasive tumor status of UCC observed in the present study. However, the mechanism by which this SNP modulates the tumor development of UCC should be further investigated in future studies.

In conclusion, our results show that an association between FGFR-4 rs1966265 and rs2011077 was detected with a high risk of invasive tumor in patients with UCC. These findings indicate a novel genetic predisposition to urothelial cell tumorigenesis.

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Disclosure of conflict of interest

None.

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