Significant Association of Caveolin-1 (*CAV1*) Genotypes with Upper Urothelial Tract Cancer

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Abstract. *Aim: Upper urothelial tract cancer is unusually of high incidence in Taiwan and it is valuable to study the specificity of this disease in Taiwan and compare the corresponding findings with those of Western countries. In the literature, it has been reported that single nucleotide variation of caveolin-1 gene (CAV1) plays an important role in risk of several types of cancer, such as hepatoma, leukemia, nasopharyngeal carcinoma, oral, breast, bladder and prostate cancer, but we are not aware of any reports on upper urothelial tract cancer. The aim of this study was to evaluate the association of six polymorphic genotypes of CAV1 with upper urothelial tract cancer within a Taiwanese population. Materials and Methods: A total of 218 patients with upper urothelial tract cancer and 580 healthy controls in central Taiwan were genotyped by polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP) for six CAV1 polymorphic genotypes, C521A (rs1997623), G14713A (rs3807987), G21985A (rs12672038), T28608A (rs3757733), T29107A (rs7804372), and G32124A (rs3807992), and their association with upper urothelial tract cancer susceptibility was examined. Results: The distribution of genotypes of CAV1 rs3807987 and rs7804372 were significantly different between cancer patient and control groups (p=0.0188 and 0.0090, respectively), while those for CAV1 rs1997623, rs12672038, rs3757733 and rs3807992 were not significant (p>0.05). The haplotype analysis of the two polymorphic genotypes showed that compared with the GG/AT, and GG/AA haplotypes of CAV1 rs3807987/rs7804372, those carrying GG/TT, AG/TT and AA/TT variants have a significantly increased risk of upper urothelial tract cancer (odds ratio=1.61, 1.50 and 2.67, 95% confidence interval=1.05-2.47, 1.18-1.90, and 1.37-5.18, respectively). On the contrary, other haplotype variants conferred non-significant elevated risk. Conclusion: Our results suggest that individual and combined CAV1 rs3807987/rs7804372 genotypes are involved in predisposition to upper urothelial tract cancer in the Taiwanese population.*

Upper urothelial tract cancer (UUTC) is relatively rare in the West, where a ratio of 3:1:51 is reported for the incidence of urothelial cancer of the renal pelvis, ureter and bladder, respectively (1). However, it is reportedly elevated to a ratio of 1:2.08:6.72 in Taiwan (2). Thus it would be valuable to perform a genomic study of UUTC from Taiwan and then compare the corresponding findings in Western populations. From the epidemiological viewpoint, the elevated incidence of UUTC may be associated with arsenic exposure, smoking, analgesic abuse, occupational carcinogens, hypertension, long-standing urinary obstructions, infection and Balkan nephropathy (3-8). A recent study has provided evidence that genetic polymorphisms may also predispose to the development of UUTC (9).

Previous reports have suggested the gene for caveolin-1 (*CAV1*) may function as a tumor suppressor (10-13). Firstly, *CAV1* mRNA and protein levels are down-regulated in various cancer cell lines, including in oncogene-transformed

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Key Words: CAV1, polymorphism, genotype, upper urothelial track cancer.

NIH 3T3 cells, in many human and mouse breast cancer cell lines, in primary human mammary gland tumors, and in breast cancer transgenic mouse cells (10-12). Secondly, *CAV1* re-expression in breast cancer cell lines inhibits anchorage-dependent growth in soft agar and reduces their invasive potential (11, 13). Finally, *CAV1* expression also reduces the migratory and invasive potential of MTLn3 cells, by preventing epidermal growth factor (EGF)-induced lamellipodia formation, reducing cell migration (14). In human cells, *CAV1* is the major structural and functional protein component of caveolae, which play an important role in many signaling pathways, molecular transport, and cellular proliferation and differentiation. Before 2006, the genomic association of *CAV1* with different types of cancer was not well-studied and the analyses mostly focused on genetic mutations but not polymorphisms. For instance in 2006, a study reported that mutations of *CAV1* were associated with breast cancer risk (15). The evidence showed that genomic variation of *CAV1* played a role in carcinogenesis, and led us to study whether different alleles of *CAV1* are associated with UUTC, which as far as we are aware of has never been studied. Thus, the aims of the current study were to determine the genotypic frequency of six single nucleotide polymorphisms (SNPs) of *CAV1* at rs1997623, rs3807987, rs12672038, rs3757733, rs7804372, and rs3807992, and their contribution to UUTC susceptibility in Taiwan.

Materials and Methods

Study population and sample collection. A total of 218 patients with UUTC were recruited at the China Medical University and Kaohsiung Medical University medical centers, all of whom were diagnosed by a pathological examination of specimens obtained by biopsy or surgical resection. The clinical and histopathological information were collected from patient charts and pathology reports. The information was reviewed, and the data were entered into the database. The tumor stage was assigned according to the TNM staging system (16), and the pathological grade was determined according to the World Health Organization criteria (17). Five hundred and eighty healthy individuals, who had been matched with the patients by age, admitted to the same hospital for a health checkup and who had no previous diagnosis of neoplastic urological disease or other malignancy were enrolled as controls. All the participants enrolled provided an informed consent and Human Research Committees of participating hospitals approved this study (KMU-IRB-950195).

Genotyping conditions. Genomic DNA was prepared from peripheral blood leucocytes using a QIAamp Blood Mini Kit (Blossom, Taipei, Taiwan, ROC) and further processed according to our previous reports (18-24). Briefly, the following primers were used for *CAV1* genotyping: rs1997623: 5'-GTGTCCGCTTCTGCTATCTG-3' and 5'-GCCAAGATGCAGAAGGAGTT-3'; rs3807987: 5'-CCTTCCAGTA AGCAAGCTGT-3' and 5'-CCTCTCAATCTTGCCATAGT-3'; rs12672038: 5'-GGTGTCAGCAAGGCTATGCT-3' and 5'-CCAG ACACTCAGAATGTGAC-3'; rs3757733: 5'-GCTCAACCTCATC TGAGGCA-3' and 5'-GGCCTATTGTTGAGTGGATG-3'; rs7804372: 5'-GCCTGAATTGCAATCCTGTG-3' and 5'-ACGGTG TGAACACGGACATT-3'; and rs3807992: 5'-GGTGTCTTGCAGT TGAATG-3' and 5'-ACGGAGCTACTCAGTGCCAA-3'. The following cycling conditions were used: one cycle at 94˚C for 5 min; 35 cycles of 94˚C for 30 s, 55˚C for 30 s, and 72˚C for 30 s; and a final extension at 72˚C for 10 min. The PCR products were studied after digestion with *Avr*II, *Bfa*I, *Hae*III, *Tsp509*I, *Sau3A*I and *Nla*III, restriction enzymes for *CAV1* rs1997623 (cut from 485 bp C type into 170+315 bp T type), rs3807987 (cut from 268 bp A type into 66+202 bp G type), rs12672038 (cut from 251+43 bp A type into 153+98+43 bp G type), rs3757733 (cut from 298 bp T type into 100+198 bp A type), rs7804372 (cut from 336 bp A type into 172+164 bp T type), and rs3807992 (cut from 213+142+67 bp A type into 142+118+95+67 bp T type), respectively.

Statistical analyses. Two hundred and eighteen cases and 580 controls were analyzed in the presented Tables. To ensure that the controls used were representative of the general population and to exclude the possibility of genotyping error, the deviation of the genotype frequencies of *CAV1* single nucleotide polymorphism in the controls from those expected under the Hardy–Weinberg equilibrium was assessed using the goodness-of-fit test. Pearson's chi-square test or Fisher's exact test (when the expected number in any cell was less than five) was used to compare the distribution of the *CAV1* genotypes between cases and controls. Cancer risk associated with the genotypes was estimated as odds ratio (ORs) and 95% confidence intervals (CIs) using unconditional logistic regression. All statistical tests were performed using SPSS for Windows (version 14.0; SPSS Inc., Chicago, IL, USA) on two-sided probabilities. The correlation between categorical variables was calculated for statistical significance using Pearson's chi-square test and the threshold for significance was $p \leq 0.05$.

Results

The frequency distributions of baseline clinical characteristics for the 218 patients with UUTC and 580 healthy controls are presented in Table I. Epidemiologically, there was no difference in the frequency distribution between gender ($p=0.4256$) and age ($p=0.8518$) so the population was well-matched (Table I). From the clinical and pathological viewpoints, tumors distributed in renal pelvic, ureter and multiple sites were 38.5%, 34.9% and 26.6%, respectively. About 60% of tumors were high grade, and 77.1% were of stages lower than pT3 (Table I).

The frequencies of the genotypes for *CAV1* rs1997623, rs3807987, rs12672038, rs3757733, rs7804372, and rs3807992 among the cancer patients and healthy controls are summarized and analyzed in Table II. Among the six polymorphic genotypes investigated, two, rs3807987 and rs7804372, were found to be differentially distributed between cancer and control groups (Table II). The frequency of A-carrying genotypes of *CAV1* rs3807897 and of T-carrying genotypes of *CAV1* rs7804372 was significantly higher among than healthy controls (Table II). As for

Table I. *Frequency distributions of baseline clinical characteristics among patients with upper urothelial tract cancer and healthy controls.*

Characteristic	Cases (n=218) n (%)	Control (n=580) n (%)	*p*-Value
Gender			
Male	114 (52.3)	323 (55.7)	
Female	104 (47.7)	257 (44.3)	0.4256
Mean age, years	65.4±4.7	62.9±3.9	0.8518
Location			
Renal pelvis	84 (38.5)		
Ureter	76 (34.9)		
Multiple tumors	58 (26.6)		
Grade			
Low	86 (39.4)		
High	132 (60.6)		
Stage			
I and II	168 (77.1)		
III and IV	50 (22.9)		

rs1997623, rs12672038, rs3757733 and rs3807992, there was no difference in the distribution of genotypes between patients and controls (Table II).

In addition, we performed allelic frequency analysis of the alleles for *CAV1* rs1997623, rs3807987, rs12672038, rs3757733, rs7804372, and rs3807992 among cancer patients and healthy controls (Table III). The two SNPs of *CAV1* rs3807987 and rs7804372 were found to be associated with UUTC susceptibility, with a higher frequency of A allele of rs3807987 and T allele of rs7804372 for the cancer group (Table III; p=0.0040 and 0.0022, respectively). As for the other four *CAV1* genotypic sites, their allelic frequencies were not significantly different in controls and patients (Table III).

Considering the possible interactions between these two *CAV1* genotypes for UUTC susceptibility, the haplotypic distributions of *CAV1* rs3807987 and rs7804372 were further analyzed (Table IV). We have set the genotypes with lower risk as being the wild-type genotypes for the haplotypic combination. Under this criterion, the GG genotype for *CAV1* rs3807987 and AT or AA for *CAV1* rs7804372 were selected. Compared with the GG/AT or GG/AA haplotype of *CAV1* rs3807987/rs7804372, the GG/TT, AG/TT and AA/TT groups have a significantly higher risk of UUTC (crude OR=1.61, 1.50, and 2.67, respectively) (Table IV). After adjusting for age and gender, these significantly adjusted odds values do not appear to differ substantially from the unadjusted odds, which suggests age and gender may not synergistically enhance the effects of genotype on UUTC risk (Table IV). The other two combinations, AG/AT or AG/AA and AA/AT or AA/AA, did not significantly alter cancer risk compared to the wild-type haplotypes before or after adjusting for age and gender (Table IV).

Table II. *Distribution of caveolin-1 (CAV1) genotypes among patients with upper urothelial tract cancer and controls.*

Genotype	Cases		Controls		*p*-Value
	n	%	n	%	
rs1997623					0.4560
CC	207	95.0%	560	96.6%	
AC	9	4.1%	18	3.1%	
AA	2	0.9%	2	0.3%	
rs3807987					0.0188*
GG	118	54.1%	377	65.0%	
AG	72	33.0%	146	25.2%	
AA	28	12.8%	57	9.8%	
rs12672038					0.7447
GG	125	57.3%	349	60.2%	
AG	75	34.4%	189	32.6%	
AA	18	8.3%	42	7.2%	
rs3757733					0.9661
TT	128	58.7%	345	59.5%	
AT	72	33.0%	190	32.8%	
AA	18	8.3%	45	7.7%	
rs7804372					0.0090*
TT	140	64.2%	303	52.2%	
AT	65	29.8%	224	38.6%	
AA	13	6.0%	53	9.2%	
rs3807992					0.6689
GG	111	50.9%	286	49.3%	
AG	88	40.4%	231	39.8%	
AA	19	8.7%	63	10.9%	

*Significantly different between case and control groups, p<0.05.

Table III. *Distribution of caveolin-1 (CAV1) alleles among patients with upper urothelial tract cancer and controls.*

Allele	Cases		Controls		*p*-Value
	n	%	n	%	
rs1997623					0.1872
Allele C	423	97.0%	1138	98.1%	
Allele A	13	3.0%	22	1.9%	
rs3807987					0.0040*
Allele G	308	70.6%	900	77.6%	
Allele A	128	29.4%	260	22.4%	
rs12672038					0.4229
Allele G	325	74.5%	887	76.5%	
Allele A	111	25.5%	273	23.5%	
rs3757733					0.7929
Allele T	328	75.2%	880	75.9%	
Allele A	108	24.8%	280	24.1%	
rs7804372					0.0022*
Allele T	345	79.1%	830	71.6%	
Allele A	91	20.9%	330	28.4%	
rs3807992					0.4671
Allele G	310	71.1%	803	69.2%	
Allele A	126	28.9%	357	30.8%	

*Significantly different between case and control groups, p<0.05.

Table IV. *Distribution of CAV1 G14713A/T29107A haplotypes among patients with upper urothelial tract cancer and controls.*

G14713A/T29107A haplotype	Cases		Controls		Odds ratio (95% CI)	Adjusted odds ratio (95% CI)[a]	*p*-Value[ab]
	n	%	n	%			
GG/AT or GG/AA	43	19.7%	181	31.2%	1.00 (Reference)	1.00 (Reference)	
GG/TT	75	34.4%	196	33.8%	1.61 (1.05-2.47)	1.68 (1.11-2.80)	0.0034
AG/AT or AG/AA	26	11.9%	69	11.9%	1.59 (0.91-2.78)	1.52 (0.89-2.94)	0.1364
AG/TT	46	21.1%	77	13.3%	1.50 (1.18-1.90)	1.54 (1.24-2.38)	0.0003
AA/AT or AA/AA	9	4.1%	27	4.7%	1.40 (0.62-3.20)	1.38 (0.59-3.24)	0.4999
AA/TT	19	8.7%	30	5.1%	2.67 (1.37-5.18)	2.80 (1.76-6.93)	0.0047

95% CI, 95% Confidence interval; [a]adjusted for age and gender; [b]based on Fisher's exact two-tailed test.

Discussion

Urothelial carcinoma is the second most common cancer, and usually arises from the urothelium with transitional cell differentiation, including that of the renal pelvis, ureter and bladder. In literature, there were a few articles investigating the contribution of individual genomic variations to bladder cancer (25-29), while few to UUTC (9). The single nucleotide variations of *CAV1* may determine their differential expression of CAV1 and personal susceptibility to cancer. Supporting data comes from various types of cancer, including oral cancer (20), breast cancer (15, 22), colorectal cancer (30, 31), prostate cancer (24, 32, 33), bladder cancer (19), glaucoma (34, 35), nasopharyngeal carcinoma (23), and hepatocellular carcinoma (21). However, there is no report about UUTC. In the present study, the genotypes of *CAV1* of UUTC patients together with 580 controls (Table I) were examined. The results showed that the A allele of rs3807987 and T allele of rs7804372 were associated with higher risk for UUTC and the haplotype analysis suggested that individuals with GG/TT, AG/TT or AA/TT haplotype at rs3807987/rs7804372 were at higher risk of UUTC (Table IV). We have strengthened the sample size from 56 cases and 436 controls in our previous study (36) to 218 cases and 580 controls (Table I). The enlarged sample size and the same trend of significant genotype distribution after age adjustment highlighted the value, accuracy and reliability of the overall findings (Table IV).

Epidemiologically, the highest incidence of bladder cancer has been found in areas where black-foot disease is endemic (37), and chronic drinking of arsenic-contaminated deep-well water (38) were associated with high bladder cancer prevalence in Taiwan. However, the differences and similarity in causes between bladder cancer and UUTC are not yet well-understood. The chronic abuse of toxic traditional Chinese medicine was a serious threat to public health and may be associated with a high kidney-washing rate together with UUTC or bladder cancer in Taiwan (39, 40). In the future, alterations of CAV1 mRNA and protein expression levels in UUTC and their relationship to *CAV1* genotypes among patients with UUTC, and the intracellular mechanism related to carcinogenesis could be investigated after classifying fresh UUTC tissue samples by their *CAV1* genotypes.

In conclusion, to our knowledge, this is the first study showing the *CAV1* genotype to be associated with UUTC risk. The A allele of *CAV1* rs3807987 and T allele of *CAV1* rs7804372 might become potential biomarkers for the early screening and risk prediction of UUTC.

Acknowledgements

We thank all the colleagues at the China Medical University and Kaohsiung Medical University medical centers for their technical assistance. We also appreciate the continuous contribution of our team-mates Yi-Ting Chang, Hong-Xue Ji and Chieh-Lun Hsiao. This study was supported by research grants from the Terry Fox Cancer Research Foundation.

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Received August 5, 2013
Revised September 30, 2013
Accepted October 1, 2013