Significant Association of Caveolin-1 Single Nucleotide Polymorphisms with Childhood Leukemia in Taiwan

CHUNG-HSING WANG[1,2,*], YU-LIANG LAI[1,*], WEN-SHIN CHANG[1,2,*], KANG-HSI WU[1], HSIEN-YUAN LANE[2], CHANG-FANG CHIU[1], FUU-JEN TSAI[3], CHENG-CHIEH LIN[5] and DA-TIAN BAU[1,2,4]

[1]Terry Fox Cancer Research Laboratory and [3]Department of Medical Genetics, China Medical University Hospital, Taichung, Taiwan, R.O.C.; [2]Graduate Institutes of Clinical Medical Science and [4]Basic Medical Science, China Medical University, Taichung, Taiwan, R.O.C.; [5]Department of Healthcare Administration, College of Health Science, Asia University, Taichung, Taiwan, R.O.C.

Abstract. *Background: A growing body of evidence indicates that caveolin-1 (CAV1) may influence the development of human cancer. However, the exact role of CAV1 in childhood leukemia is still controversial. We investigated six novel polymorphic variants of CAV1, namely C521A (rs1997623), G14713A (rs3807987), G21985A (rs12672038), T28608A (rs3757733), T29107A (rs7804372), and G32124A (rs3807992), and analyzed the association of each specific genotype with susceptibility to childhood leukemia. Materials and Methods: In total, 266 patients with childhood leukemia and 266 age-matched healthy controls, recruited from two major medical centers in Taiwan, were genotyped investigating the association of these polymorphisms with childhood leukemia. Results: We found that there were significant differences between childhood leukemia and control groups in the distributions of their genotypes ($p=4.1\times10^{-8}$ and 0.0167) and allelic frequencies ($p=4.9\times10^{-10}$ and 3.7×10^{-3}) in the CAV1 G14713A and T29107A polymorphisms, respectively. As for the haplotype analysis, those who had GG/AT or GG/AA at CAV1 G14713A/T29107A had a reduced risk of childhood leukemia compared to those with GG/TT, while those with any other combinations were at increased risk. Conclusion: The A allele of CAV1 G14713A is risky, while the A allele of CAV1 T29107A is protective for the development of childhood leukemia and these may be novel useful genomic markers for the early detection of childhood leukemia.*

Childhood leukemia is the most common type of childhood cancer over the world, accounting for approximately one-third of childhood malignancies and poses a severe issue for every society. The etiology and genomic contributing factors of leukemia are still largely unknown. In recent years, investigators have become interested in caveolae and in defining how these lipid domains participate in the pathogenesis of human cancer and what their possible utility may be for its detection and treatment (1). Caveolae are vesicular invaginations of the plasma membrane, and are believed to play a critical role in transcytosis, communication between cell surface membrane receptors and intracellular signaling protein cascades, such as apoptosis and tumorigenesis (2, 3).

A growing body of evidence indicates that caveolin-1 (*CAV1*) influences the development of human cancer. However, the exact functional role of *CAV1* in leukemogenesis is still controversial. In 2010, *CAV1* was found to be overexpressed in adult T-cell leukemia cells (4). In certain cell types, antisense inhibition of *CAV1* expression is sufficient to induce oncogenic transformation (5). Targeted down-regulation of *CAV1* activates mitogen-activated protein kinases (MAPK) and stimulates anchorage-independent growth of NIH-3T3 cells (5). Loss of *CAV1* is required to accelerate tumorigenesis and metastasis; PyMT/*CAV1*$^{(-/-)}$ mice exhibited accelerated onset of mammary tumors and lung metastasis (6). *CAV1* is highly expressed in the normal ovary but markedly down-regulated in human grade 3 serous ovarian carcinoma (7). In addition to ovarian carcinoma, *CAV1* is also down-regulated in human tumors derived from the breast and colon, while controversy exits that it is up-regulated in tumor samples from the kidney, prostate, and stomach (7). *CAV1* expression is lost in human mammary carcinoma cell lines (5). Expression of *CAV1* in a highly metastatic carcinoma-derived cell line suppressed lung

*These Authors contributed equally to the study.

Correspondence to: Da-Tian Bau, Terry Fox Cancer Research Lab, China Medical University Hospital, 2 Yuh-Der Road, Taichung, 404 Taiwan, R.O.C. Tel: +886 422052121 Ext.1523, e-mail: datian@mail.cmuh.org.tw/artbau2@gmail.com

Key Words: Caveolin-1, single nucleotide polymorphism, childhood leukemia.

Table I. *The primer sequences, polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP) conditions for Caveolin-1 gene polymorphisms.*

Polymorphisms (locations)	Primer sequences	Restriction enzyme	SNP sequence	DNA fragment size (bp)
C521A (rs1997623)	F: 5'-GTGTCCGCTTCTGC TATCTG-3'	*Avr* II	C	485 bp
	R: 5'-GCCAAGATGCAGAAGGAG TT-3'		T	315+170 bp
G14713A (rs3807987)	F: 5'-CCTTCCAGTAAGCAAGCTGT-3'	*Bfa* I	A	268 bp
	R: 5'-CCTCTCAATCTTGCCATAGT-3'		G	202+66 bp
G21985A (rs12672038)	F: 5'-GGTGTCAGCAAGGCTATGCT-3'	*Hae* III	A	251+43 bp
	R: 5'-CCAGACACTCAGAATGTGAC-3'		G	153+98+43 bp
T28608A (rs3757733)	F: 5'-GCTCAACCTCATCTGAGGCA-3'	*Tsp*509 I	T	298 bp
	R: 5'-GGCCTATTGTTGAGTGGATG-3'		A	198+100 bp
T29107A (rs7804372)	F: 5'-GCCTGAATTGCAATCCTGTG-3'	*Sau*3AI	A	336 bp
	R: 5'-ACGGTGTGAACACGGACATT-3'		T	172+164 bp
G32124A (rs3807992)	F: 5'-GGTGTCTTGCAGTTGAATG-3'	*Nla* III	A	213+142+67 bp
	R: 5'-ACGGAGCTACTCAGTGCCAA-3'		T	142+118+95+67 bp

*F and R indicate forward and reverse primers, respectively.

metastasis *in vivo* and reduced cancer invasion *in vitro* (6). Decreased invasion of *CAV1*-expressing cells was accompanied by reduction in matrix metalloproteinase-9 (MMP9) and MMP2 secretion and gelatinolytic activity, and reduced extracellular signal-regulated kinases (ERK)1/2 signaling in response to growth factors (6). In addition to lung cancer cell lines, *CAV1* re-expression in human breast cancer and in colon carcinoma cell lines also inhibited tumor cell growth (8).

To the extent of our knowledge, there is no study of the role of *CAV1* genotypes in childhood leukemia. The emerging evidence pointing to the role of *CAV1* in carcinogenesis led us to study whether different alleles of this gene are associated with leukemogenesis. Thus, the aims of the current study were to determine the genotypic frequency of six single nucleotide polymorphisms (SNPs) of the *CAV1* gene at C521A (rs1997623), G14713A (rs3807987), G21985A (rs12672038), T28608A (rs3757733), T29107A (rs7804372), and G32124A (rs3807992), and their association with susceptibility to childhood leukemia. To the best of our knowledge, this is the first study carried out aiming to evaluate the contribution of *CAV1* polymorphisms in childhood leukemia.

Materials and Methods

Study population and sample collection. Two hundred and sixty-six patients diagnosed with childhood leukemia (*i.e.* the population under 18 years old) were recruited from the Pediatric Departments at the China Medical University Hospital and National Taiwan University Hospital, Taiwan, Republic of China in 2005-2009. A non-cancer healthy person was matched by gender and age after initial random sampling from the Health Examination Cohort of the two hospitals for each patient. Patients and controls completed a self-administered questionnaire and provided their peripheral blood samples.

Genotyping assays. Genomic DNA was prepared from peripheral blood leucocytes using a QIAamp Blood Mini Kit (Blossom, Taipei, Taiwan) and further processed according to our previous articles (9-19). The polymerase chain reaction (PCR) cycling conditions were: 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. Pairs of PCR primer sequences and restriction enzyme for each DNA product are all listed in Table I.

Statistical analyses. Only cases with both the complete clinical data and successful genotypic data (case/control=266/266) were selected for analyzing. 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* SNPs 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. Data were recognized as significant when the statistical *p*-value was less than 0.05.

Results

The frequencies of the genotypes for *CAV1* C521A (rs1997623), G14713A (rs3807987), G21985A (rs12672038), T28608A (rs3757733), T29107A (rs7804372), and G32124A (rs3807992) for controls and childhood leukemia patients are shown in Table II. Genotypic distributions of the polymorphisms of *CAV1* G14713A and T29107A were significantly different between childhood leukemia and control groups ($p=4.1\times10^{-8}$ and 0.0167, respectively), while those for *CAV1* C521A, G21985A, T28608A and G32124A were not significant ($p>0.05$) (Table II). To sum up, the polymorphisms of *CAV1* G14713A and T29107A are associated with childhood leukemia risk and may be useful biomarkers for childhood leukemia early detection. The people carrying A allele of *CAV1* G14713A and T allele of *CAV1* T29107A in their genome seemed to be of higher risk of childhood leukemia in the Taiwanese population. The representative

Table II. *Distribution of Caveolin-1 genotypes among childhood leukemia and control groups.*

Genotype	Controls	%	Patients	%	*p*-Value[a]
C521A rs1997623					1.0000
CC	259	97.4%	260	97.7%	
AC	7	2.6%	6	2.3%	
AA	0	0.0%	0	0.0%	
G14713A rs3807987					**4.1×10^{-8}**
GG	176	65.3%	110	38.4%	
AG	67	25.6%	106	42.7%	
AA	23	9.1%	50	18.9%	
G21985A rs12672038					0.8964
GG	161	60.5%	157	59.0%	
AG	85	32.0%	90	33.8%	
AA	20	7.5%	19	7.2%	
T28608A rs3757733					0.9226
TT	158	59.4%	154	57.9%	
AT	86	32.3%	88	33.1%	
AA	22	8.3%	24	9.0%	
T29107A rs7804372					**0.0167**
TT	140	52.6%	167	62.8%	
AT	99	37.2%	86	32.3%	
AA	27	10.2%	13	4.9%	
G32124A rs3807992					0.9297
GG	130	48.9%	126	47.4%	
AG	106	39.8%	108	40.6%	
AA	30	11.3%	32	12.0%	

[a]Based on chi-square test.

Table III. *Distribution of alleles for Caveolin-1 gene among the childhood leukemia and control groups.*

Allele	Controls	%	Patients	%	*p*-Value[a]
C521A rs1997623					1.0000
Allele C	525	98.7%	526	98.9%	
Allele A	7	1.3%	6	1.1%	
G14713A rs3807987					**4.9×10^{-10}**
Allele G	419	78.8%	326	61.3%	
Allele A	113	21.2%	206	38.7%	
G21985A rs12672038					0.8290
Allele G	407	76.5%	404	75.9%	
Allele A	125	23.5%	128	24.1%	
T28608A rs3757733					0.6710
Allele T	402	75.6%	396	74.4%	
Allele A	130	24.4%	136	25.6%	
T29107A rs7804372					**3.7×10^{-3}**
Allele T	379	71.2%	420	78.9%	
Allele A	153	28.8%	112	21.1%	
G32124A rs3807992					0.6928
Allele G	366	68.8%	360	67.7%	
Allele A	166	31.2%	172	32.3%	

[a]Based on chi-square test.

PCR-based restriction analyses for the *CAV1* G14713A and T29107A polymorphisms are shown in Figure 1.

The frequencies of the alleles for the *CAV1* C521A, G14713A, G21985A, T28608A, T29107A, and G32124A between controls and patients with childhood leukemia are shown in Table III. The two SNPs of *CAV1* found to be associated with childhood leukemia risk are shown in Table II, G14713A and T29107A, are also found to be associated with differential childhood leukemia susceptibility in the analysis of their allelic frequency analysis ($p=4.9\times10^{-10}$ and 3.7×10^{-3}, respectively). As for the other four SNPs, the distributions of their allelic frequencies are not significantly different in controls and patients (Table III). The conclusion deduced from Table II and III is that *CAV1* G14713A and T29107A seem to be markers for childhood leukemia.

Considering potential interactions between these significant SNPs of the *CAV1* gene and susceptibility to childhood leukemia, the risk of childhood leukemia related to haplotype of *CAV1* G14713A and T29107A were further analyzed (Table IV). Both odds ratios (ORs) adjusted for individual age and gender and chi-square *p*-value were calculated to evaluate the contribution for each haplotype to childhood leukemia. Compared with the major GG/TT haplotype of *CAV1* G14713A/T29107A combination, the GG/AT and GG/AA group has a lightly lower risk of childhood leukemia (OR=0.68, 95% confidence interval, CI=0.43-1.12, $p=0.1117$). Other combinations of AG/TT (OR=2.61, 95% CI=1.60-4.27, $p=0.0004$) AG/AT or AG/AA (OR=2.92, 95% CI=1.79-4.91, $p=0.0886$), AA/TT (OR=2.26, 95% CI=1.22-4.17, $p=0.0006$), and AA/AT or AA/AA (OR=2.34, 95% CI=1.06-5.27, $p=0.0459$), all have increased childhood leukemia risk compared to the GG/TT haplotype (Table IV).

Discussion

To our knowledge, there has been no investigation regarding the polymorphisms of *CAV1*, whose products play an important role in membrane signaling, in childhood leukemia. According to our results, the G14713A and T29107A polymorphisms of the *CAV1* gene were found to be associated with childhood leukemia (Tables II and III). In our hypothesis, the variant polymorphisms of intronic G14713A and T29107A on *CAV1* may alter the normal expression and/or the protein function of *CAV1* by alternative splicing and regulation of mRNA stability. It has been reported that hematological cells express *CAV1* in certain states of cell activation (20) and in adult T-cell leukemia, *CAV1* was found to be overexpressed (4).

A wealth of evidence suggests a role for *CAV1* as a suppressor of tumor growth and metastasis in ovarian, breast and colon human carcinomas (5-8). However, the function of *CAV1* might be entirely different in different tissues. *CAV1* could exert opposing functions, resulting in tumor progression promotion rather than inhibition. *CAV1* expression is increased in tumor samples from the kidney, prostate, stomach with respect to the normal tissues, and re-expression is found in

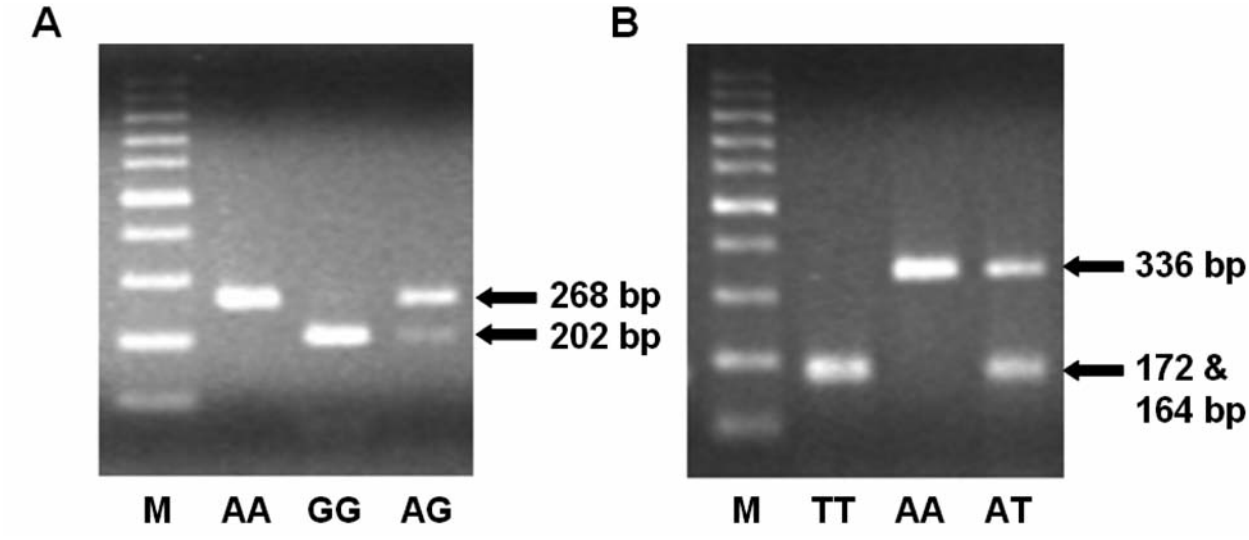

Figure 1. *Polymerase chain reaction (PCR)-based restriction analysis of the G14713A (A) and T29107A (B) polymorphisms of the Caveolin-1 gene, shown on 3% agarose electrophoresis. M: 100 bp DNA size marker; A: AA: indivisible homozygote, AG: heterozygote, and GG: divisible homozygote. B: AA: Indivisible homozygote, AT: heterozygote, and TT: divisible homozygote.*

Table IV. *Frequencies of combined Caveolin-1 G14713A/T29107A haplotypes among the childhood leukemia and control groups.*

G14713A/T29107A haplotype	Control	%	Patients	%	Adjusted odds ratio (95% CI)[a]	*p*-Value[b]
All	266	100.0	266	100.0		
GG/TT	93	35.0	69	25.9	1.00 (Reference)	
GG/AT or GG/AA	83	31.2	41	15.4	0.68 (0.43-1.12)	0.1117
AG/TT	35	13.2	67	25.2	**2.61 (1.60-4.27)**	**0.0004**
AG/AT or AG/AA	32	12.0	39	14.7	**2.92 (1.79-4.91)**	0.0886
AA/TT	12	4.5	31	11.7	**2.26 (1.22-4.17)**	**0.0006**
AA/AT or AA/AA	11	4.1	19	7.1	**2.34 (1.06-5.27)**	**0.0459**

95% CI, 95% Confidence interval. [a]Date were calculated by unconditioned logistic regression and adjusted for age and gender. [b]Based on Fisher's exact test.

some advanced adenocarcinomas (7). Elevated expression of *CAV1* is associated with progression in the prostate, colon, breast, lung carcinoma (7), and adult T-cell leukemia (4). Remarkably, induced re-expression of *CAV1* in less invasive caveolin-negative lung cancer cell lines enhanced their invasive capability (21). We postulated that induced *CAV1* expression may alter the interactions between cell and extracellular matrix by lipid raft internalization of adhesion molecules, such as catenin and cadherin, and subsequently facilitate tumor metastasis (22). *CAV1* protects prostate cancer cells from c-myelocytomatosis oncogene (c-MYC)-induced apoptosis (23). Thus, engagement of *CAV1* as a tumor metastasis promoter or tumor metastasis suppressor is strongly determined by the specific cellular context, and, at the molecular level, by the signaling molecules interacting with *CAV1* and by the signaling pathways affected and regulated by *CAV1*. We hypothesize that altered *CAV1* expression may somehow lead to failure of homeostatic maintenance, resulting in an increased frequency of childhood leukemogenesis.

In this study, we screened six SNPs of the *CAV1* gene and investigated their genotypic associations with childhood leukemia susceptibility. We found that two novel SNPs, G14713A and T29107A of the *CAV1* gene, were associated with childhood leukemia. However, the effects of these SNPs of the *CAV1* gene need further studies, such as immunohistochemistry or western blotting, in leukemogenesis of different stages (in bone marrow, metastatic sites and peripheral blood), to reveal the role of each section or even each nucleotide in the subtle regulation of the transcriptional, translational, and post-translational expression of the *CAV1* gene in different body compartments. Therefore, these two SNPs, together with other SNPs, may be found to play a role in childhood leukemia progression in their joint effects. In addition, an enlarged population size and genomic-environmental combinatorial

studies could provide with more comprehensive and realistic data regarding the progression of childhood leukemia.

In conclusion, to our knowledge this is the first report to provide evidence for *CAV1* G14713A and T29107A polymorphisms, but not C521A, G21985A, T28608A, or G32124A, being associated with higher susceptibility to childhood leukemia. In addition, the G allele of *CAV1* G14713A and A allele of *CAV1* T29107A might become potential biomarkers for early detection, prediction and integrative cancer therapy of childhood leukemia.

Acknowledgements

This study was supported by research grants from the China Medical University and Hospital (CMU-101-122) and the Terry Fox Cancer Research Foundation. The assistance from Tsai-Ping Ho in clinical data collection, and from Liang-Yi Lin, Yi-Ting Chang, Hong-Xue Ji in genotyping were highly appreciated by the Authors.

References

1 Lloyd PG. and Hardin CD: Caveolae in cancer: two sides of the same coin? Focus on "Hydrogen peroxide inhibits non-small cell lung cancer cell anoikis through the inhibition of caveolin-1 degradation". Am J Physiol Cell Physiol *300*: 232-234, 2011.

2 Juhasz M, Chen J, Tulassay Z, Malfertheiner P and Ebert MP: Expression of caveolin-1 in gastrointestinal and extraintestinal cancers. J Cancer Res Clin Oncol *129*: 493-497, 2003.

3 Zou H, Volonte D, and Galbiati F: Interaction of caveolin-1 with Ku70 inhibits Bax-mediated apoptosis. PLoS One *7*: e39379, 2012.

4 Sawada S, Ishikawa C, Tanji H, Nakachi S, Senba M, Okudaira T, Uchihara JN, Taira N, Ohshiro K, Yamada Y, Tanaka Y, Uezato H, Ohshima K, Sasai K, Burgering BM, Duc Dodon M, Fujii M, Sunakawa H and Mori N: Overexpression of caveolin-1 in adult T-cell leukemia. Blood *115*: 2220-2230, 2010.

5 Engelman JA, Zhang XL, Razani B, Pestell RG and Lisanti MP: p42/44 MAP kinase-dependent and -independent signaling pathways regulate caveolin-1 gene expression. Activation of RAS-MAP kinase and protein kinase A signaling cascades transcriptionally down-regulates caveolin-1 promoter activity. J Biol Chem *274*: 32333-32341, 1999.

6 Williams TM, Medina F, Badano I, Hazan RB, Hutchinson J, Muller WJ, Chopra NG, Scherer PE, Pestell RG and Lisanti MP: Caveolin-1 gene disruption promotes mammary tumorigenesis and dramatically enhances lung metastasis *in vivo*. Role of *CAV-1* in cell invasiveness and matrix metalloproteinase (MMP-2/9) secretion. J Biol Chem *279*: 51630-51646, 2004.

7 Wiechen K, Diatchenko L, Agoulnik A, Scharff KM, Schober H, Arlt K, Zhumabayeva B, Siebert PD, Dietel M, Schafer R and Sers C: Caveolin-1 is down-regulated in human ovarian carcinoma and acts as a candidate tumor suppressor gene. Am J Pathol *159*: 1635-1643, 2001.

8 Lee SW, Reimer CL, Oh P, Campbell DB and Schnitzer JE: Tumor cell growth inhibition by caveolin re-expression in human breast cancer cells. Oncogene *16*: 1391-1397, 1998.

9 Bau DT, Tseng HC, Wang CH, Chiu CF, Hua CH, Wu CN, Liang SY, Wang CL, Tsai CW and Tsai MH: Oral cancer and genetic polymorphism of DNA double strand-break gene *Ku70* in Taiwan. Oral Oncol *44*: 1047-1051, 2008.

10 Chang CH, Chiu CF, Liang SY, Wu HC, Chang CL, Tsai CW, Wang HC, Lee HZ and Bau DT: Significant association of Ku80 single nucleotide polymorphisms with bladder cancer susceptibility in Taiwan. Anticancer Res *29*: 1275-1279, 2009.

11 Chang CH, Chiu CF, Wang HC, Wu HC, Tsai RY, Tsai CW, Wang RF, Wang CH, Tsou YA and Bau DT: Significant association of *ERCC6* single nucleotide polymorphisms with bladder cancer susceptibility in Taiwan. Anticancer Res *29*: 5121-5124, 2009.

12 Chang CH, Wang RF, Tsai RY, Wu HC, Wang CH, Tsai CW, Chang CL, Tsou YA, Liu CS and Bau DT: Significant association of *XPD* codon 312 single nucleotide polymorphism with bladder cancer susceptibility in Taiwan. Anticancer Res *29*: 3903-3907, 2009.

13 Chiu CF, Tsai MH, Tseng HC, Wang CL, Tsai FJ, Lin CC and Bau DT: A novel single nucleotide polymorphism in *ERCC6* gene is associated with oral cancer susceptibility in Taiwanese patients. Oral Oncol *44*: 582-586, 2008.

14 Chiu CF, Tsai MH, Tseng HC, Wang CL, Wang CH, Wu CN, Lin CC and Bau DT: A novel single nucleotide polymorphism in *XRCC4* gene is associated with oral cancer susceptibility in Taiwanese patients. Oral Oncol *44*: 898-902, 2008.

15 Chiu CF, Wang CH, Wang CL, Lin CC, Hsu NY, Weng JR and Bau DT: A novel single nucleotide polymorphism in *XRCC4* gene is associated with gastric cancer susceptibility in Taiwan. Ann Surg Oncol *15*: 514-518, 2008.

16 Hsu CF, Tseng HC, Chiu CF, Liang SY, Tsai CW, Tsai MH and Bau DT: Association between DNA double-strand break gene *Ku80* polymorphisms and oral cancer susceptibility. Oral Oncol *45*: 789-793, 2009.

17 Wang HC, Chiu CF, Tsai RY, Kuo YS, Chen HS, Wang RF, Tsai CW, Chang CH, Lin CC and Bau DT: Association of genetic polymorphisms of *EXO1* gene with risk of breast cancer in Taiwan. Anticancer Res *29*: 3897-3901, 2009.

18 Wang HC, Liu CS, Chiu CF, Chiang SY, Wang CH, Wang RF, Lin CC, Tsai RY and Bau DT: Significant association of DNA repair gene *Ku80* genotypes with breast cancer susceptibility in Taiwan. Anticancer Res *29*: 5251-5254, 2009.

19 Yang MD, Hsu YM, Kuo YS, Chen HS, Chang CL, Wu CN, Chang CH, Liao YM, Wang HC, Wang MF and Bau DT: Significant association of Ku80 single nucleotide polymorphisms with colorectal cancer susceptibility in Central Taiwan. Anticancer Res *29*: 2239-2242, 2009.

20 Hatanaka M, Maeda T, Ikemoto T, Mori H, Seya T and Shimizu A: Expression of caveolin-1 in human T-cell leukemia cell lines. Biochem Biophys Res Commun *253*: 382-387, 1998.

21 Ho CC, Huang PH, Huang HY, Chen YH, Yang PC and Hsu SM: Up-regulated caveolin-1 accentuates the metastasis capability of lung adenocarcinoma by inducing filopodia formation. Am J Pathol *161*: 1647-1656, 2002.

22 del Pozo MA, Balasubramanian N, Alderson NB, Kiosses WB, Grande-Garcia A, Anderson RG and Schwartz MA: Phospho-caveolin-1 mediates integrin-regulated membrane domain internalization. Nat Cell Biol *7*: 901-908, 2005.

23 Timme TL, Goltsov A, Tahir S, Li L, Wang J, Ren C, Johnston RN and Thompson TC: Caveolin-1 is regulated by c-MYC and suppresses c-MYC-induced apoptosis. Oncogene *19*: 3256-3265, 2000.

Received February 26, 2013
Revised March 16, 2013
Accepted March 18, 2013