Functional Polymorphism in the *CAV1* T29107A Gene and Its Association with Prostate Cancer Risk among Japanese Men

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Abstract. *Aim: To evaluate the relationship between the Caveolin-1 (CAV1) T29107A (rs7804372) polymorphism and the risk of prostate cancer among Japanese populations, and the associations between CAV1 polymorphisms and clinicopathological characteristics, including Gleason grade and prostate-specific antigen (PSA) grade. Materials and Methods: We recruited 134 patients with prostate cancer and 86 healthy controls matched for age and smoking status. The CAV1 T29107A polymorphism status was determined by polymerase chain reaction and restriction fragment-length polymorphism analysis. Results: Genotype distributions (p=0.0045) and allelic frequencies (p=0.0018) differed between prostate cancer and control groups in terms of the CAV1 T29107A polymorphism (Pearson's χ^2 test). Logistic regression analysis of case and control outcomes showed an odds ratio of 0.35 (95% Condifence interval=0.13-0.91, p=0.033) between the TT and AA polymorphisms, indicating a reduced risk of prostate cancer to be associated with the AA polymorphism. Subset analysis revealed no significant associations between this polymorphism and clinicopathological characteristics of prostate cancer. Conclusion: The results of this study demonstrated a relationship between the CAV1 T29107A variant and risk of prostate cancer. This polymorphism thus, merits further investigation as a potential genomic marker for the early detection of prostate cancer. Our results support the hypothesis that the CAV1 T29107A (rs7804372) polymorphism may influence susceptibility to prostate cancer; however, prostate cancer progression was not associated with this polymorphism in a Japanese population.*

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Prostate cancer is one of the most common types of cancer and the sixth leading cause of cancer-related death among Japanese men (1). In most cases, death from prostate cancer results from metastatic disease. Understanding the mechanisms underlying the progression of prostate cancer will facilitate the development of biomarkers and novel therapeutic strategies to control this devastating malignancy. Caveolin-1, encoded by *CAV1*, is a major structural component of caveolae, which are specialized plasma membrane invaginations involved in multiple cellular processes such as molecular transport, cell adhesion and signal transduction (2). Although *CAV1* may suppress tumorigenesis under some conditions (3), it is associated with and contributes to malignant progression through various mechanisms (4, 5).

The role of *CAV1* in cancer cells remains controversial. It is down-regulated in tumors such as human ovarian carcinoma (6) and head and neck squamous cell carcinoma (SCC) (7), suggesting a possible tumor suppressor role. Consistent with this, the human *CAV1* gene maps to the suspected tumor locus at 7q31.1, which is deleted in many types of human cancers (8). Conversely, however, *CAV1* overexpression is associated with more aggressive behavior, increased recurrence rate and poorer prognosis in prostatic cancer (9) and hepatocellular carcinoma (10). These apparent discrepancies mean that it is still unclear whether up- or down-regulation of *CAV1* contributes to a biological advantage in tumorigenesis.

Emerging evidence of a role for *CAV1* in carcinogenesis prompted us to investigate the relationship between different alleles of this gene and prostate cancer. We, therefore, aimed to determine the genotypic frequency of the *CAV1* T29107A polymorphism and its association with prostate cancer susceptibility. We also analyzed the relationship between *CAV1* polymorphisms and clinicopathological characteristics such as Gleason grade and Prostate specific antigen (PSA) grade. To the best of our knowledge, this is the first study to evaluate the contribution of *CAV1* polymorphisms to prostate oncology in a Japanese population.

Materials and Methods

Study participants. The study population consisted of a total of 220 Japanese men, including 134 histologically-confirmed cases of prostate cancer and 86 healthy age-, ethnicity- and smoking status-matched controls. The patients with prostate cancer were treated at the Department of Urology, Miyazaki Medical University Hospital and its related hospitals between August 2011 and October 2012. Tumor grade was evaluated in these samples using the Gleason scoring system. Controls were selected randomly from healthy individuals with no history of cancer. All participants were informed of the details, procedures and objectives of this study. During the study period, critical information such as age and smoking status were collected from the participants using a standardized questionnaire. This study was approved by the Ethics Committee of Miyazaki Medical University and related hospitals.

Assessment of smoking status. Participants were asked about their smoking status and were classified as "smokers" or "non-smokers". Information on demographics, smoking history, family history of cancer and medical history were collected during the interview. Any individual who had never smoked or had smoked only a few packs of cigarettes during his lifetime was defined as a non-smoker. Any individual who had smoked cigarettes for more than 20 years was defined as a smoker. Both cases and controls were subjected to similar protocols/questionnaires by the same interviewer.

CAV1 genotyping. Genomic DNA was extracted from peripheral blood leukocytes using a DNA Extractor WB kit (Wako Pure Chemical Industries, Ltd. Osaka, Japan.), according to the manufacturer`s instructions, and eluted with 100 μl (TE) buffer (Nacalaitesque, Tokyo, Japan.). *CAV1* T29107A genotypes were determined using polymerase chain reaction (PCR)-based restriction fragment-length polymorphism assay, as described previously (11, 12). The following primers were used: *CAV1* T29107A, forward, 5'-GCCTGAATTGCAATCCTGTG-3'; reverse, 5'-ACGGTGTGAA CACGGACATT-3'. Reactions were performed using KAPA Taq PCR Kits (Nippon Genetics, Tokyo, Japan) in a thermal cycler (TaKaRa PCR Thermal Cycler Dice; Takara, Tokyo, Japan). PCR conditions consisted of one cycle at 94˚C for 5 min, 35 cycles at 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 overnight with Sau3AI restriction enzyme (TaKaRa) for *CAV1* T29107A. The fragments were separated in a 2% agarose gel. The TT genotype (wild-type) yielded two distinct digestion products (172 and 164 bp), the TA genotype yielded three distinct digestion products (336, 172 and 164 bp), and the AA genotype yielded one digestion product (336 bp) (Figure 1).

Statistical analysis. Statistical analysis was performed using the R i386 2.15.1 software package (Wirtschaftsuniversität Wien, Vienna University of Economics and Business, Vienna, Austria). The significance of differences in *CAV1* T29107A genotypes among cases and controls were determined by Pearson's χ^2 tests. Probability values <0.05 were regarded as statistically significant. Odds ratios (ORs) and 95% confidence intervals (CIs) for prostate cancer were calculated by multivariate logistic regression analysis after adjusting for several confounding variables such as age and smoking status.

Results

The backgrounds of the cases and controls are summarized in Table I. The mean ages of the cases and controls were 68.3±7.4 (range=61-75) years and 66.9±8.3 (range=59-75) years, respectively. There were no significant differences between prostate cancer cases and controls in terms of mean age distribution (p=0.21, not significant (NS)) and relative frequencies of smokers and non-smokers (p=0.24, NS).

CAV1 T29107A genotypic and allelic frequencies are indicated in Table II. The genotype and allele frequencies were in Hardy-Weinberg equilibrium. The genotypic distributions (p=0.0045) and allelic frequencies (p=0.0018) differed significantly between prostate cancer and control groups in terms of the *CAV1* T29107A polymorphisms. The frequency of T-allele carriers was higher in case than in control samples. Logistic regression analysis of outcomes (adjusted for age at diagnosis and smoking status) showed that the AA genotype was associated with decreased susceptibility to prostate cancer (OR=0.35, 95% CI=0.13-0.91, p=0.033). Subset analysis to investigate possible associations between *CAV1* polymorphisms and clinicopathological characteristics such as the Gleason grade and PSA grade revealed no significant associations.

CAV1 genotype and risk associated with Gleason grade. *CAV1* genotypes were further analyzed for risk associated with less-aggressive or highly-aggressive disease, based on Gleason grade. Patients were then categorized into three groups based on this combined score (Gleason score≤6=low-grade; Gleason score 7=intermediate-grade; Gleason score≥8=high-grade). The results demonstrated no significant associations between genotype and Gleason grade (Table III).

CAV1 genotype and risk associated with PSA grade. Patients were categorized into three groups based on PSA values (PSA <10.0 ng/ml=low-grade; 10.0 PSA ≤10–<20.0 ng/ml= intermediate-grade; PSA ≥20.0 ng/ml=high-grade). No significant associations were found between *CAV1* polymorphisms and PSA grade in patients with prostate cancer (Table III).

Discussion

Several investigations have demonstrated a critical role for *CAV1* in many types of tumors (13, 14), but few studies have reported on the relationship between *CAV1* and the genetic predisposition to cancer. In 2004, inactivation of *CAV1* by mutation or reduced expression was found to be involved in the pathogenesis of oral cancer (15). In that study, the sequences of exons 1 and 3 of *CAV1* were investigated in 74 oral squamous cell carcinomas and 15 oral cancer cell lines, and the CAV1 expression was also examined. Only five

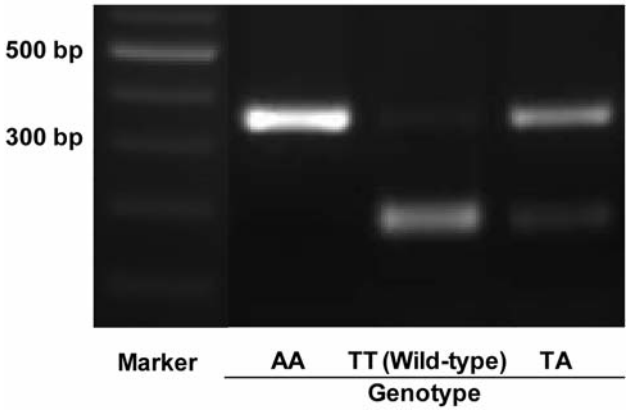

Figure 1. *Polymerase chain reaction (PCR)-based restriction analysis of the T29107A rs7804372 polymorphisms of the Caveolin-1 (CAV1) gene by 2% agarose gel electrophoresis. M: 100 bp DNA size marker.*

Table I. *Participants' backgrounds.*

	Cases	Controls	*p*-Value
Age, years mean±SD	68.3±7.4	66.9±8.3	0.21 (NS)
Smoking status	n (%)		0.24 (NS)
Non smoker	64 (47.8)	48 (55.8)	
Smoker	70 (52.2)	38 (44.2)	
PSA (ng/ml) mean±SD	22.8±18.2	2.5±0.9	<0.001*
PSA grade	n (%)		
Low<10	46 (34%)		
Intermediated≤10-<20.0	28 (21%)		
High≥20	60 (45%)		
Gleason grade	n (%)		
Low≤6	29 (22%)		
Intermediated=7	42 (31%)		
High≥8	63 (47%)		
Total	134	86	

NS: Not significant, PSA: prostate specific antigen. *Based on Students *t*-test.

CAV1 mutations (one missense and four silent mutations) were identified in those cases, all of which occurred in exon 3 (16). In contrast, sequencing of exon and promoter regions have failed to reveal any *CAV1* variants that might be directly involved in cancer risk. We selected intronic single-nucleotide polymorphisms (SNPs) from the NCBI database and evaluated the role of *CAV1* polymorphisms in prostate cancer risk in a Japanese population. *CAV1* is thought to act as a suppressor of tumor growth and metastasis in human breast and colon cancer (17, 18). However, *CAV1* function may differ among organs, and *CAV1* could, thus, exert opposite functions resulting in promotion or suppression of tumor progression, respectively.

For example, *CAV1* expression increased in tumor samples from the kidney, prostate and stomach, and re-expression has been found in some advanced adenocarcinomas (16). Elevated *CAV1* expression is associated with progression in some adenocarcinomas, such as prostate carcinoma (19), and in adult T-cell leukemia (20). Interestingly, activated *CAV1* expression was associated with higher grades of prostate cancer, although few significant relationships have been identified between *CAV1* expression and tumor multiplicity, recurrence and progression, or overall survival (21).

Li *et al*. showed that *CAV1* was secreted by mouse and human prostate cancer cell lines, and that secreted *CAV1* promoted cancer cell survival and clonal growth *in vitro* (22, 23). They further showed that tumor cell-secreted CAV1 promoted pro-angiogenic activities in prostate cancer through the Phosphainositol-3-kinase (PI3K) -Protein Kinase B (AKT)-endothelial nitric oxide synthase (eNOS) signaling module (24). With regard to the underlying mechanisms responsible for *CAV1*-mediated oncogenic activities, they showed that *CAV1* maintained activated AKT in prostate cancer cells through binding to and inhibiting the serine/threonine protein phosphatases PP1 and PP2A (25). Thus, engagement of CAV1 as a tumor metastasis promoter depends on the specific cellular context and, at the molecular level, by the signaling molecules interacting with and the signaling pathways affected and regulated by *CAV1*. We hypothesize that altered CAV1 expression may result in failure of homeostatic maintenance, leading to an increased frequency of prostate cancer.

Table II. *Distribution of Caveolin-1 (CAV1) polymorphism among patients with prostate cancer and controls.*

Genotype (T29107A; rs7804372)	Cases, n (%)	Controls, n (%)	Total
TT	60 (44.8)	25 (29.1)	85
TA	63 (47.0)	42 (48.9)	105
AA	11 (8.2)	19 (22.1)	30
Total	134	86	220

p=0.0045*

*Based on Pearson's χ^2 test

A recent study of eleven *CAV1* SNPs only identified one (rs9920, chr7: 115987328) as being associated with prostate cancer risk among Caucasians, while rs7804372 (chr7: 116194228) was associated with prostate cancer risk in Taiwanese. The present study evaluated the association between the latter SNP and prostate cancer risk in Japanese men. We investigated the potential associations between *CAV1* polymorphisms and the risk and progression of prostate

Table III. *Association between Caveolin-1 (CAV1) polymorphism and clinicopathological characteristics, including Gleason grade and PSA grade.*

Genotype	Low ≤6	Gleason score intermediate 7	High ≥8	OR (95% CI) between Gleason ≤6 and 7	*p*-Value	OR (95% CI) between Gleason ≤6 and ≥8	*p*-Value
TT	14	17	29	Reference		Reference	
TA	14	19	30	1.05 (0.37-2.94)	0.93	1.08 (0.43±2.72)	0.87
AA	1	6	4	3.69 (0.47-77.85)	0.27	2.08 (0.26-43.4)	0.54
TA±AA	15	25	34	1.20 (0.43-3.30)	0.72	1.14 (0.46-2.83)	0.77
	Low <10	PSA (ng/ml) grade intermediate ≤10-<20.0	High ≥20	OR (95% CI) between low and intermediate	*p*-Value	OR (95% CI) between low and high	*p*-Value
TT	21	12	27	Reference		Reference	
TA	20	15	28	1.30 (0.47-3.63)	0.61	1.33 (0.57-3.14)	0.52
AA	5	1	5	0.40 (0.02-3.01)	0.43	0.93 (0.22-3.90)	0.92
TA±AA	25	16	33	1.13 (0.42-3.09)	0.81	1.13 (0.42-3.09)	0.6

OR: Odds ratio adjusted for age, alcohol, smoking status; CI: confidence interval, PSA: prostate specific antigen.

cancer. Our results indicate that prostate cancer susceptibility and risk are influenced by genetic polymorphisms of the *CAV1* gene; in particular, the AA genotype or presence of the A allele of the *CAV1* T29107A gene reduced the risk of prostate cancer. However, further analysis revealed no significant associations between this polymorphism and clinicopathological characteristics associated with prostate cancer progression. This apparent discrepancy could be attributable to the small number of cases (n=134) in the study, and further studies with larger sample sizes are, thus, needed to clarify the relationship between this polymorphism and clinicopathological characteristics in prostate cancer.

No molecular basis for the initiation of *CAV1* expression in prostate cancer has been established. Previous studies determined that the *CAV1* gene promoter has multiple CpG sites, and alterations in gene methylation status have been shown in prostate cancer (26, 27). However, patterns of *CAV1* gene methylation have, thus far, failed to provide a convincing argument for the up-regulation of *CAV1* in prostate cancer. In general, *CAV1* has been associated with the stimulatory effects of steroid receptors, including the androgen receptor, suggesting a possible starting point for further mechanistic studies (28). The results of the current study, however, support the hypothesis that the *CAV1* T29107A polymorphism is associated with transcriptional control. A search of *CAV1* motifs revealed that the polymorphic site included the binding site for pre-B-cell leukemia homeobox-1 (PBX1), which belongs to the homeobox family of transcription factors. PBX1 binds to the promoter and is known to regulate transcription. The relationship between PBX1 and splicing has not yet been established.

This is the first study to demonstrate an association between a *CAV1* gene polymorphism and risk of prostate cancer in Japanese men. However, this was a pilot study, and further studies in larger cohorts are required to confirm the results.

In summary, this study provided evidence for a relationship between the *CAV1* T29107A variant and risk of prostate cancer. This polymorphism therefore merits further study as a potential genomic marker for the early detection of prostate cancer. Moreover, these results suggest that the *CAV1* T29107A polymorphism plays an important role in prostate cancer susceptibility in the Japanese population. To our knowledge, this is the first such study to be conducted in a Japanese population, and demonstrated that individuals carrying the A allele of T29107A appear to be at a lower risk of developing prostate cancer. Further studies considering the effects of environmental exposure to specific carcinogens must also be investigated in larger studies to further elucidate the role of *CAV1* polymorphisms in prostate tumorigenesis.

Conflicts of Interest

The Authors indicate that no potential conflicts of interest exist.

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