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Association of Macrophage Capping Protein (CAPG) Arg335His Polymorphism and Cancer Susceptibility in the Elderly Japanese

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Abstract

Background: Macrophage capping protein (CAPG), an actin filament end-capping protein, plays an important role in regulation of cellular motility and structural rearrangement within cells and has been implicated with development of various types of cancer. Recent study demonstrated that a *CAPG* variant was associated with a rare fallopian tube tumor, albeit with a small sample size. The present study aimed to determine the association of *CAPG* variants with cancer susceptibility.

Methods: Four non-synonymous single nucleotide variations (NSVs), rs2229668 (p.V41I), rs117284777 (p.K227R), rs200233412 (p.A229T) and rs6886 (p.R335H), in *CAPG* were retrieved from genotyping, by an exome-chip, in 2,317 consecutive autopsy cases (1,284 men and 1,033 women, mean age 80.7 years), in which the presence or absence of cancer was verified pathologically. The association of *CAPG* variants with presence of cancer and with different types of cancer was determined. Interaction with smoking was also determined.

Results: There were 1,446 cancer-bearing and 897 cancer-free subjects. Among four SNVs, only p.R335H (c.1004C>T) was associated with the presence of cancer (adjusted OR=1.49, 95% CI=1.23-1.81, P=5.08 × 10^{-5}). The association was found in men (adjusted OR=1.64, 95% CI=1.26-2.14, P=2.25 × 10^{-4}), but not in women. Investigation with different types of cancer revealed that gastric cancer showed a positive association (adjusted OR=1.61, 95% CI=1.16-2.24, P=0.005) in men. The effect size of *CAPG* variants showed no difference between smokers and non-smokers.

Conclusions: Our study suggests that a non-synonymous SNV of *CAPG*, p.R335H, affects cancer susceptibility in men without interaction with smoking habit and that the SNV is associated with gastric cancer in men.

Keywords: Macrophage capping protein (CAPG); Pathology; Cancer susceptibility; Non-synonymous variants; Single nucleotide variants (SNVs)

Introduction

Cancer is the major cause of death in the pasting decades worldwide [1]. In Japan, malignancy has been the first leading cause of death since 1980 [2]. Massive technological advances in modern oncology have enabled the identification of genetic aberrations associated with malignancies and led to tremendous progress in the understanding of the genetic underpinnings of cancer at its molecular core. Indeed, despite increases in evidence suggesting that a number of candidate genes and proteins were associated with cancer, limitations still exist in fully understanding the oncogenesis and related unsolved questions.

Macrophage capping protein (CAPG), also known as capping protein (actin filament) or gelsolin-like, is a relatively small actin filament end-capping protein (38.5 kDa) of gelsolin superfamily. CAPG localizes in both nucleus and cytoplasm of the cell [3]. Its function in the cytoplasm is involved in capping the ends of actin filaments and controlling cell motility and phagocytosis, while its nuclear function seems to be still ambiguous [4]. Dysregulation of actin-based motility is a prominent factor in cell transformation and is probably associated with carcinogenesis. Actually, CAPG expression was up-regulated in a variety of cancer types, particularly in invasive and metastatic cancers such as breast cancer [4], gastric cancer [5], lung cancer [6], pancreatic cancer [7], colorectal cancer [8], oral squamous cell carcinoma [9], and ovarian cancer [10]. These observations suggest a common role of CAPG in cancer development. In addition, recent advances in proteomics approach have highlighted a role of CAPG as a potential biomarker for both breast [11] and ovarian cancer [12]. Several mechanisms underlying the regulation of CAPG expression have been proposed including the activation of AP-1 transcription factor complex [13], hypoxia-inducible factor 1 (HIF1) [14], and tyrosine kinases [15].

The *CAPG* gene, 15.6 kb in size, contains 10 exons and 9 introns and is located at the 2p11.2 [16]. Although previous studies have identified the role of *CAPG* in cell differentiation, membrane ruffing, phagocytosis and cell motility [17], the mechanism of *CAPG* in cancer development has not been precisely determined yet, and there are still controversial reports that expressions of *CAPG* in tumor cell are decreased in certain tumors [18-20].

As mentioned above, the causal role for *CAPG* in tumorigenesis has been extensively explored. In addition, recent study with a small sample size demonstrated a positive association of a *CAPG* variant with a rare fallopian tube tumor [21]. Along with the above evidence, we hypothesized that *CAPG* might be crucial for the development and progression of malignancy. Thus, the purpose of the present study is to clarify whether *CAPG* polymorphisms affect cancer susceptibility in elderly Japanese population using an autopsy cases.

Materials and Methods

Study subjects

The study group comprised 2,317 consecutive autopsy cases, which were collected at the Tokyo Metropolitan Geriatric Hospital between 1995 and 2012 (1,284 men and 1,033 women; the mean age at the time of death was 80.6 ± 8.8 years, range 46-104 years; Table 1). All subjects were registered in the Database of Japanese SNPs for Geriatric Research (JG-SNP) [22]. The autopsy was performed on approximately 29% of patients who died at the hospital. Cancer-bearing subjects include those with any type of cancer, including occult cancer, found on autopsy. The presence or absence of a disease was pathologically diagnosed by pathologists who were blinded to genotyping data. Smoking history was retrospectively retrieved from medical records, and cases were categorized into smokers (current/ex-smokers) and non-smokers. Participants (n=26) with family relationships were excluded from this study.

Genotyping and quality control

Genomic DNA was extracted from the renal cortex using a standard procedure [23]. SNVs in the exomes were analyzed by Illumina® Infinium HumanExome BeadChip array version 1.1 (Illumina Inc, San Diego, CA, USA) containing 242,901 loci. The genome scanning was conducted by iScan in accordance with protocols from Illumina® at the Center for Molecular Biology and Genetics, Life Science Research Center, Mie University, Tsu, Mie, Japan. Variant quality control involved checking genotype calling rate of all samples using Genotyping Module (version 1.9) of GenomeStudio data analysis software. Initial genotype clustering was conducted by the default Illumina® cluster file (HumanExome-12vl-l_A.egt) and manifest file (HumanExome-12v 1-1_A.bmp) by GenTrain2 clustering algorithm. Variants showing success rate less than 0.99 in either cases or controls, minor allele frequency less than 0.05 in both cases and controls, or deviation from Hardy-Weinberg equilibrium (HWE) were excluded from the analysis. A total of 2,317 subjects were tested in the association analysis. The pathological assessment and genotyping were performed in different institutions in a double-blind fashion to minimize bias.

Statistical analysis

In the exome array, twelve probes were available for non-synonymous variants in the *CAPG* gene. Since eight of them were excluded from the analysis because they were monomorphic in our samples, the remaining four SNVs were analyzed: rs2229668 (C41I), rs117284777 (K227R), rs200233412 (A229T) and rs6886 (R335H). All SNVs were confirmed for obeying the Hardy-Weinberg equilibrium using a χ^2 test. Multiple logistic regression analyses under a dominant model were performed to determine the association between cancer and SNVs, and were then adjusted for age and gender using SPSS version 19.0 (IBM Corp., Chicago IL), compared with subjects with or without any cancer at autopsy inspection. We adopted Bonferroni's correction by the testing number of four SNVs and significance was accepted at P<0.0125. The power calculation of the included SNPs was carried out using OSSE, an Online Sample Size Estimator in the following: http://osse.bii.a-star.edu.sg/index.php. Linkage disequilibrium among SNVs was assessed using Haploview software [24].

Ethical statements

The study was approved by the ethical committees of the Tokyo Medical and Dental University (approval No. 2009-19-4) and Tokyo Metropolitan Geriatric Hospital (approval No. 230405). Written informed consent was obtained from a family member of all participants involved in this study before autopsy.

Results

Characteristics of the subjects

A summary of demographics of the subjects is shown in Table 1. Among a total of 2,317 subjects, 889 controls had no cancer and 1,428 cases carried at least one cancer after pathological inspection. Thus, 38.4% was cancer-free and 61.6% was cancer-bearing. Traditional risk factors including aging, male sex and cigarette smoking were found to be significantly associated with the presence of cancer (P<0.0125). When stratified by age, no significant association was found between the presence of cancer with participants younger than 80 years of age or those aged 80 and older. The majority of subjects who had a history of smoking were men (80.3%). Figure 1 presents our pathological investigation including up to 37 types of cancer, including lung cancer, gastrointestinal cancer, prostatic cancer, gynecologic tumor, brain tumor, hematopoietic malignancy, and other tumors. Three most common cancers among population were lung cancer (11.7%), gastric cancer (11.2%), and colorectal cancer (9.5%).

Genotyping results of *CAPG* polymorphisms

Among 242,901 markers on the exome array, 12 markers were identified in the CAPG region. Eight of them were monomorphic in our samples, thus four of the following SNVs were examined in our study: rs2229668 (p.V41I), rs117284777 (p.K227R), rs200233412 (p.A229T), and rs6886 (p.R335H). The success rates for genotype call in four nsSNVs were 100% for p.V41I, p.K227R, and p.R335H and 99.96% for p.A229T. The allele frequencies of p.K227R and p.A229T were low,

Characteristics	All subjects	Cancer-free	Cancer-bearing	P value [b]
	(n=2,317)	(n=889)	(n=1,428)	
Age at death (years) [a]	80.7 ± 8.9	81.4 ± 9.2	80.2 ± 8.6	0.001
≥ 80 years, n (%)	1,292	521 (40.3)	771 (59.7)	0.03
< 80 years, n (%)	1,025	368 (35.9)	657 (64.1)	
Male, n (%)	1,284	427 (33.3)	857 (66.7)	1.67×10^{-8}
Female, n (%)	1,033	462 (44.7)	571 (55.3)	
Smoking, n (%)	1,109	375 (33.8)	734 (66.2)	7.04×10^{-5}

[a] The data represent mean ± SD (standard deviation), [b] P values were calculated by Student's t-test or χ^2 test

Table 1: Characteristics of the study population.

2.9% and 0.4%, respectively. The MAF of p.V41I, and p.R335H were 6.5% and 47.0%, respectively. The observed genotypic frequencies of the latter two SNVs were consistent with Hardy-Weinberg equilibrium ($P \geq 0.05$). The genotyping results for the four selected SNVs are shown in Table 2.

Association of *CAPG* polymorphisms with overall cancer susceptibility

The association between *CAPG* variants and presence of cancer are shown in Table 3. Our association analysis revealed that only p.R335H (c.1004C>T, forward strand) was significantly associated with presence of cancer, assuming a dominant model, (adjusted OR=1.49, 95% CI=1.23-1.81, P=5.08×10^{-5}). Carriers of the minor allele (T allele) in *CAPG* variants have 49% increased odds of having cancer susceptibility compare to non-carriers.

Subgroup analysis revealed a gender difference that the significant association was found in men (adjusted OR=1.64, 95% CI=1.26-2.14, P=2.25×10^{-4}), but not in women (adjusted OR=1.32, 95% CI=0.99-1.75, P=0.058). In addition, we examined the association of p.R335H with smoking habit. The significant associations were found in both groups (adjusted OR=1.48, 95% CI=1.13-1.94, P=0.004 in smokers, and adjusted OR=1.49, 95% CI=1.13-1.97, P=0.005 in non-smokers). There was no difference in genotype effect between the two.

Association of *CAPG* polymorphisms with specific cancer susceptibility

We further investigated the association of p.R335H (c.1004C>T) with presence or absence of cancer in various types of cancer (Table 4). Only gastric cancer showed a positive association (adjusted OR=1.61, 95% CI=1.16-2.24, P=0.005). No significant association was observed
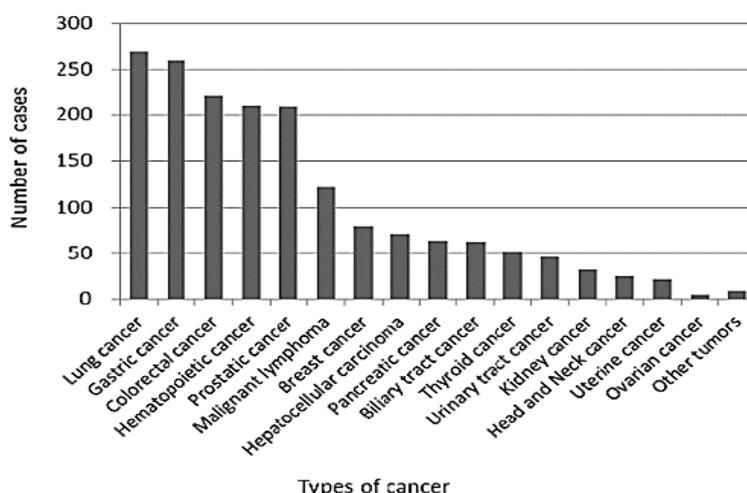

Figure 1: Distribution of cancer cases in 2,317 subjects. In the present study, top five cancers were lung cancer, gastric cancer, colorectal cancer, hematopoietic cancer, and prostatic cancer.

SNP ID	Amino acid mutation	MM	Mm	Mm
		(n)	(n)	(n)
rs2229668	V41I	2,030	274	13
rs117284777	K227R	2,186	130	1
rs200233412	A229T	2,298	18	0
rs6886	R335H	654	1,152	511

M, major allele; m, minor allele; MAF, minor allele frequency; JPT, Japanese in Tokyo; N/A, not available

Table 2: Genotype frequencies of the four selected SNVs in the CAPG gene (n=2,317).

CAPG (rs6886)	Cancer-free (n=889)				Cancer-bearing (n=1,428)				P value of χ² test	Adjusted OR [a] (95% CI)	P value
	CC n (%)	CT n (%)	TT n (%)	MAF	CC n (%)	CT n (%)	TT n (%)	MAF			
All Subjects (n=2,317)	297 (33.4)	414 (46.6)	178 (20.0)	0.43	357 (25.0)	737 (51.6)	334 (23.4)	0.49	6.32×10^{-5}	1.49 [b] (1.23-1.81)	5.08×10^{-3}
Male (n=1,284)	146 (34.2)	198 (46.4)	83 (19.4)	0.43	209 (24.4)	443 (51.7)	205 (23.9)	0.50	0.001	1.64 [c] (1.26-2.14)	2.25×10^{-4}
Female (n=1,033)	151 (32.7)	216 (46.8)	95 (20.6)	0.44	148 (25.9)	294 (51.4)	129 (22.6)	0.48	0.058	1.32 [c] (0.99-1.75)	0.058
Current/ex- smokers (n=1,109)	132 (35.2)	173 (46.1)	70 (18.7)	0.42	192 (26.2)	364 (49.6)	178 (24.3)	0.49	0.004	1.48 [d] (1.13-1.94)	0.004
Nonsmokers (n=1,018)	139 (32.4)	197 (45.9)	93 (21.7)	0.45	143 (24.3)	321 (54.5)	125 (212.)	0.49	0.009	1.49 [d] (1.13-1.97)	0.005

[a] OR, odds ratio; CI, confidence interval, [b] Adjusted for age, gender and smoking, [c] Adjusted for age and smoking, [d] Adjusted for age and gender

Table 3: Genotype frequencies of p.R335H (c.1004C>T) polymorphism and association of the variant with presence of cancer using logistic regression analysis assuming a dominant model, classified by gender and smoking habits.

CAPG (rs6886)	Without Gastric Cancer (n=2,058)				With Gastric Cancer (n=259)				P value of χ^2 test	Adjusted OR [a] (95% CI)	P value
	CC n (%)	CT n (%)	TT n (%)	MAF	CC n (%)	CT n (%)	TT n (%)	MAF			
All Subjects (n=2,317)	600 (29.1)	1,018 (49.4)	440 (21.5)	0.46	54 (20.9)	133 (51.3)	72 (27.8)	0.53	0.007	1.61 [b] (1.16-2.24)	0.005
Male (n=1,284)	319 (28.9)	550 (49.9)	233 (21.2)	0.46	36 (19.8)	91 (50.0)	55 (30.2)	0.55	0.006	1.73 [c] (1.16-2.59)	0.008
Female (n=1,033)	281 (29.4)	468 (48.9)	207 (21.7)	0.46	18 (23.4)	42 (54.5)	17 (22.1)	0.49	0.505	1.38 [c] (0.78-2.44)	0.264
Current/ ex-smokers (n=1,108)	293 (30.6)	460 (48.1)	204 (21.3)	0.45	31 (20.5)	76 (50.3)	44 (29.1)	0.54	0.016	1.64 [d] (1.08-2.50)	0.021
Non-smokers (n=1,015)	262 (28.4)	469 (50.9)	191 (20.7)	0.46	19 (20.4)	48 (51.6)	26 (28.0)	0.54	0.133	1.56 [d] (0.92-2.64)	0.098

[a] OR, odds ratio; CI, confidence interval, [b] Adjusted for age, gender and smoking, [c] Adjusted for age and smoking, [d] Adjusted for age and gender

Table 4: Genotype frequencies of p.R335M (c.1004C>T) polymorphism and association of the variant with gastric cancer using logistic regression.

between the variant and other cancers. The positive association between p.R335H (c.1004C>T) and gastric cancer were found only in men, but not in women (adjusted OR=1.73, 95% CI=1.16-2.59, P=0.008, and adjusted OR=1.38, 95% CI=0.78-2.44, P=0.264, respectively). Smokers with the minor allele were more susceptible to gastric cancer than smokers without the minor allele (adjusted OR=1.64, 95% CI=1.08-2.50, P=0.021). Comparing gastric cancer cases and cancer-free controls by logistic regression analysis, the results were also in the same direction as the above comparison (data not shown).

Discussion

The present study provided the evidence that there was a significant association between p.R335H on the *CAPG* gene and cancer susceptibility. The T allele for p.R335H (c.1004C>T) was associated with higher risk of malignancy. Among individual cancer types, only gastric cancer showed a sign of significant association with the SNV. Smoking habit may limitedly affect *CAPG* variants on gastric cancer susceptibility in men.

Recent evidence that *CAPG* p.R335H was associated with risk of fallopian tube carcinoma in a small case-control study promoted us to examine the effect of the SNV of *CAPG* on various cancers using large-sized autopsy cases [21]. Most previous reports demonstrated a positive association between cancer and CAPG protein expression [5-10, 25-29]. Although it has been reported that *CAPG* SVPs was associated with carotid atherosclerosis [30], to our best knowledge, this is the first report which examined an association of malignant tumor with *CAPG* polymorphism in detail.

We sought the possibility whether other SNPs closely linked with p.R335H (rs6886) might be the true causative factors and explored 76 kb regions nearby rs6886 using Haploview. However, no other SNVs which explain the causality were found. Thus, although not proven, it is speculated that this non-synonymous SNV may be the causative variation.

The present study showed significant association between presence of cancer and gastric cancer with p.R335H. In order to predict the biological significance of p.R335H variant, we tried to apply some analytic software. Firstly, we applied PolyPhen-2, SIFT and SWISS-MODEL to predict the potential functional and/or structural changes of the SNV p.R335H (c.1004C>T) [31,32], but none of the above programs showed positive sign. Through evolutionary analysis of coding SNPs by PANTHER software, p.R335H has a significant deleterious effect on protein function [33]. Next, we used NetPhosK, PHOSIDA and PhosphoSite, and identified potential phosphorylation sites for protein

kinase C (PKC) on Ser337 of CAPG [34-36]. In addition, PhosSNP revealed that p.R335H induces alteration of a certain kind of protein kinase for flanking phosphorylation site [37]. Thus, it is possible that p.R335H variant leads dysfunction of CAPG protein.

PKC is involved in many biological processes via phosphorylation of target proteins including, cell cycle regulation, cell adhesion, DNA synthesis and transcription, cell motility, apoptosis, drug resistance, and cell growth and differentiation [38]. In principle, basic amino acids (R or K) at the position -2 and/or -3 amino-terminal to the phosphorylated sites (S or T) are critical for PKC substrate recognition [38]. Regarding the location of Arg335 allele, which is located in the surface of loop, this makes Arg335 allele is likely to be phosphorylated by PKC compare to His335 allele. Indeed, Glaser and colleagues described that CAPG protein (p.R335H) with histidine variant diminished the phosphorylation level of adjacent Ser337 by PKC [21]. Interestingly, a recent analysis of somatic mutations in tumors using TCGA database suggests that mutations in phosphosite flanking region are found in 89% of tumors [39].

The results of *CAPG* SNVs appear applicable in personalized medicine. For example, it is possible that periodical screening can detect cancer at early stage in those who have cancer susceptibility. In addition, early detection of cancer may be able to reduce mortality and contribute to maintain a quality of life.

The present study has some limitation. Subjects who died of cancer at early age might be excluded among our study, predisposing to survival bias. However, the young age group generally indicates low death rate and is expected to have difficulty in collecting autopsy examples. Association of cancer with *CAPG* SNVs in the younger group should be examined using different kind of cohort. In addition, permission of autopsy might be influenced by various reasons. Thus, unavoidable deviation may exist in our cohort. The power analysis of our study was 0.79 assuming the current sample size and detection of OR ≥ 1.49 at the significance level of P<0.05.

In conclusion, we found a missense variation of p.R335H (c.1004C>T) in *CAPG* to be significantly associated with risk for cancer occurrence in general and gastric cancer in elderly Japanese population. Validation studies using larger sample size and different cohort are required to confirm concise effects of polymorphism on *CAPG* gene.

Acknowledgements

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