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A Novel *Caveolin-1* Biomarker for Clinical Outcome of Sarcopenia

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Abstract. *Sarcopenia, defined by the European Working Group on Sarcopenia in Older People as leading to significantly decreased muscle mass and function, contributes to increased risk of adverse health outcomes among older people. Caveolin-1 (CAV1) is a main structural protein playing a regulatory role in signaling pathways and muscle normality. However, the role of CAV1 in the development of sarcopenia is largely unknown. In this study, we aimed to investigate the contribution of CAV1 genotype to sarcopenia in a Taiwanese population. We enrolled 175 patients with sarcopenia (56 pre-sarcopenia, 63 sarcopenia and 56 severe sarcopenia) and 327 age- and gender-matched controls in this community-based case control study. The associations of six single nucleotide polymorphisms of the CAV1 gene at C521A (rs1997623), G14713A (rs3807987), G21985A (12672038), T28608A (rs3757733), T29107A (rs7804372), and G32124A (rs3807992) with sarcopenia risk were evaluated. After grouping the sarcopenia patients together, the results showed that there was a significant differential distribution among the cases and controls in their CAV1 G14713A genotype (p=0.0235), and those carrying the AG and AA genotypes had 1.65- and 1.78-fold higher odds ratios for sarcopenia compared to those with the GG genotype (95% confidence interval=1.09-2.49 and 0.96-3.31, respectively). Furthermore, the carriers with CAV1 G14713A AG or AA genotype had a higher risk for sarcopenia and severe sarcopenia, but not pre-sarcopenia, compared to those with the GG genotype. Our findings suggest that Cav1 may play a critical role in the etiology of sarcopenia, and the A allele of Cav1 G14713A may serve as an early marker for detection of sarcopenia and severe sarcopenia.*

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In human, skeletal muscle mass and strength decreases progressively with aging by 6% per decade after the age of 45 years (1, 2). This rate may accelerate to 1-2% annually beyond 50 years of age (3-5) As we get older and older, this rapid loss of muscle mass may contribute to increased risk of adverse health outcomes, including physical disability, functional dependency, and increased morbidity and mortality (6-9). Therefore, from 1997, sarcopenia was included as an important geriatric syndrome (10-13). The European Working Group on Sarcopenia in Older People (EWGSOP) established consensus diagnostic criteria for sarcopenia in 2009 (11), and the International Working Group on Sarcopenia also published a consensus definition in 2011 (12). With the efforts of these two groups, the diagnostic criteria of sarcopenia have been defined by the consensus of the presence of both decreased muscle mass and low muscle function (either muscle strength or physical performance). Universally, the estimated prevalence of sarcopenia varies from 5% to 13% among individuals aged between 60 and 70 years, and from 11% to 50% among those aged over 80 years (6, 14-17). In Taiwan, it is more threatening as Taiwan is well-known for having the fastest-aging population in the world, and sarcopenia was found to be present in 14.4% of a Taiwanese population aged 65 years and older (18).

There are three major caveolin proteins, CAV1 to -3, which serve as scaffolding proteins. Evidence gathered from knockout animal models have indicated that caveolins play a role in diabetes, cancer, cardiovascular diseases, atherosclerosis, pulmonary fibrosis and a variety of degenerative muscular

Table I. *Distribution of selected characteristics among sarcopenia patients and controls.*

Characteristics	Control (N=327)	Pre-sarcopenia (N=56)	Sarcopenia (N=63)	Severe sarcopenia (N=56)	*p*-Value[a]
Mean age,years (SD)	71.88 (4.93)	73.14 (5.97)	76.59 (6.5)	79.8 (6.41)	0.8164
Gender					
Male	173 (52.91%)	30 (53.57%)	32 (50.79%)	30 (53.57%)	1.0000
Female	154 (47.09%)	26 (46.43%)	31 (49.21%)	26 (46.43%)	
BMI, kg/m^2					
<18.5	2 (0.61%)	9 (16.07%)	11 (17.46%)	10 (17.86%)	Reference
18.5 to <24	130 (39.76%)	39 (69.64%)	40 (63.49%)	32 (57.14%)	0.0001*
24.0 to <27	129 (39.45%)	8 (14.29%)	10 (15.87%)	9 (16.07%)	0.0001*
≥27	66 (20.18%)	0 (0%)	2 (3.18%)	5 (8.93%)	0.0001*

[a]Based on chi-square test. BMI <18.5 groups were set as reference groups. *Statistically significant.

dystrophies (19). Among the caveolin proteins, CAV1 is a protein of 178 amino acids, originally identified as a tumor suppressor in 1989 (20). In 2007, Parker and his colleagues found that *CAV-1* mutations may lead to muscle dystrophy and locomotion defects (21). However, whether genetic variation can determine the complex balance of muscle formation and metabolism during the aging process is not understood.

The aims of the present study were to: (i) determine the genotype of *CAV1* among patients with sarcopenia, applying the EWGSOP criteria for defining low muscle mass; and (ii) compare the genotypes of *CAV1* of patients with sarcopenia with those of age- and gender-matched healthy controls to find biomarkers for sarcopenia in a metropolitan elderly population in Taiwan.

Materials and Methods

Study population. The population of interest included all those aged 65 years or older who were registered in June 2009 as residents of the eight administrative neighborhoods (region named as "Li" in Chinese) of North District, Taichung City, Taiwan. Taichung City had a population of over 1 million and a population density of 6,249/km^2 in 2009. The North District is one of its eight districts, which comprised 36 administrative neighborhoods. The age and gender distributions of the residents for the eight administrative neighborhoods are similar to those of the population of both Taichung City and Taiwan generally. Originally, a total of 3,997 older citizens registered by the Bureau of Households in these eight administrative neighborhoods were invited to participate in the study. Through household visits, we excluded 1,247 individuals because of death, institutionalization, having moved out of the area, and errors of the registry. Among the remaining 2,750, 1,347 were willing to participate, but 475 refused to undertake the dual-energy X-ray absorptiometry (DXA) examination. After excluding another 107 who had provided incomplete information on marital status, education and disease history, 765 individuals were finally included in the data analysis. Those age- and gender-matched citizens were selected as controls in the same population without any symptom of pre-sarcopenia, sarcopenia or severe sarcopenia. The basic characteristics of patients and controls are given in Table I. The study was approved by the Institutional Review Board of our hospital and all participants gave their written informed consent.

Skeletal muscle index. We used DXA (Lunar DPX; General Electric, Madison, WI, USA) to determine lean soft tissue mass. DXA is recommended by the EWGSOP (11) as the main method for measuring skeletal muscle mass. Using manual DXA analysis software (Lunar enCORE; General Electric), the lean soft tissue mass in the arms, legs, trunk, and the entire body was determined, and body composition analyzed. The skeletal muscle index (SMI) was calculated by dividing limb muscle mass (kilograms) by the square of height (meters). Low muscle mass was defined as having an SMI of two standard deviations (SD) or more below the gender-specific means of young adults. Because of the lack of a norm of SMI for young adults among the local population, we used the reference value recorded by Sanada and colleagues (22), which was derived from 529 Japanese young adults. The cutoff points for low muscle mass were 6.87 and 5.46 kg/m^2 for men and women, respectively.

Muscle strength and function. Low physical performance was defined by poor performance (slowest quintile) in a 15-foot walk time test, on the basis of subgroups of gender and standing height (23). The patients were asked to walk as fast as possible, and the time taken for the 15-foot walk was recorded. Grip strength was measured by a dynamometer, and the lowest quintile based on subgroups of gender and body mass index (23) was defined as low muscle strength.

Stages of sarcopenia. We categorized each participant according to the EWGSOP conceptual stages of sarcopenia and separated patients into three groups: pre-sarcopenia, sarcopenia, and severe sarcopenia. In this article, 'pre-sarcopenia' referred to having low muscle mass with normal muscle strength and physical performance; 'sarcopenia' was defined by low muscle mass combined with low muscle strength or low physical performance; 'severe sarcopenia' means that muscle mass, strength and physical performance were all low.

Polymerase chain reaction (PCR)-restriction fragment length polymorphism genotyping conditions. Genomic DNA of each participant was prepared from peripheral blood leucocytes using a QIAamp Blood Mini Kit (Blossom, Taipei, Taiwan) and further

Table II. *The primer sequences, polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP) conditions for caveolin-1 gene single nucleotide polymorphisms (SNPs).*

Polymorphism	Primer sequences	Restriction enzyme	SNP sequence	DNA fragment size (bp)
C521A (rs1997623)	F: 5'-GTGTCCGCTTCTGCTATCTG-3'	*Avr* II	C	485 bp
	R: 5'-GCCAAGATGCAGAAGGAGTT-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.

processed according to our previous articles (24-26). The 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 II.

Statistical analyses. 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 polymorphisms 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. The associations between the *CAV1* polymorphisms and sarcopenia risk were estimated by computing odds ratios (ORs) and their 95% confidence intervals (CIs) from unconditional logistic regression analysis with the adjustment for possible confounders. A value of $p<0.05$ was considered statistically significant, and all statistical tests were two-sided.

Results

In Table I, the distribution of age, gender and BMI of the control, pre-sarcopenia, sarcopenia and severe sarcopenia groups are summarized and analyzed. There was no difference in the distributions of age and gender among the four groups (Table I). However, the percentages of those with BMI less than 18.5 kg/m^2 were much lower in the control group (0.61%) than those in the pre-sarcopenia (16.07%), sarcopenia (17.46%), and severe sarcopenia (17.86%) groups. On the contrary, the percentage of those with BMI of 27.0 kg/m^2 or more was much higher in the control group (20.18%) than those in the pre-sarcopenia (0%), sarcopenia (3.18%), and severe sarcopenia (8.93%) groups ($p<0.0001$)

In the beginning, we classified the patients in pre-sarcopenia, sarcopenia and severe sarcopenia groups together according to their genotypes to compare them against those in control group. Thus, the genotypic frequencies for *CAV-1* C521A, G14713A, G21985A, T28608A, T29107A and G32124A in the control and the whole-sarcopenia groups are shown in Table III. Among the single nucleotide polymorphisms (SNPs) investigated, the genotypic distribution of *CAV1* G14713A was significantly different between the sarcopenia and control groups, and the *p*-value for trend was significant ($p=0.0235$). The percentage of A allele carriers in the patient group was higher than that in the control group (Table III). Those with AG and AA genotypes had 1.65- and 1.78-fold increased odds of having sarcopenia (95% CI=1.09-2.49 and 0.96-3.31, respectively) (Table III). For *CAV-1* C521A, G21985A, T28608A, T29107A and G32124A, there was no difference between patient and control groups in the distribution of the genotypic frequency (Table III). To sum up, the genotypic frequency distribution analysis indicated that individuals carrying AG for *CAV1* G14713A were at significant risk of sarcopenia.

The results of allelic distribution analysis of *CAV1* C521A, G14713A, G21985A, T28608A, T29107A and G32124A among the controls and patients are shown in Table IV. Among the SNPs investigated, only the distribution of *CAV1* G14713A was differentially distributed ($p=0.0041$). In detail, the percentage of the A allele was much higher in the patients (28.9%) than in the controls (20.8%) (Table IV). For other SNPs, there was no difference between the two groups in the distribution of allelic frequencies of these SNPs (Table IV). Supporting the idea deduced from the results in Table III, the allelic frequency distribution analysis indicated that individuals carrying an A allele for *CAV1* G14713A were at higher risk of sarcopenia.

Table III. *Distribution of caveolin-1 genotypes in patients with sarcopenia and controls*.

Genotype	Controls		Patients		*p*-Value[a]	Odds ratio (95% CI)
	N	%	N	%		
C521A rs1997623					0.6165	
CC	320	97.9%	170	97.1%		1.00 (Reference)
AC	7	2.1%	5	2.9%		1.34 (0.42-4.30)
AA	0	0.0%	0	0.0%		
G14713A rs3807987					0.0235*	
GG	218	66.7%	95	54.3%		1.00 (Reference)
AG	82	25.1%	59	33.7%		1.65 (1.09-2.49)*
AA	27	8.2%	21	12.0%		1.78 (0.96-3.31)
G21985A rs12672038					0.6955	
GG	195	59.6%	98	56.0%		1.00 (Reference)
AG	107	32.7%	61	34.9%		1.13 (0.76-1.69)
AA	25	7.7%	16	9.1%		1.27 (0.65-2.50)
T28608A rs3757733					0.7040	
TT	193	59.0%	110	62.9%		1.00 (Reference)
AT	109	33.3%	53	30.3%		0.85 (0.57-1.28)
AA	25	7.7%	12	6.8%		0.84 (0.41-1.74)
T29107A rs7804372					0.5176	
TT	175	53.5%	103	58.8%		1.00 (Reference)
AT	120	36.7%	57	32.6%		0.81 (0.54-1.20)
AA	32	9.8%	15	8.6%		0.80 (0.41-1.54)
G32124A rs3807992					0.8453	
GG	161	49.2%	89	50.8%		1.00 (Reference)
AG	133	40.7%	71	40.6%		0.97 (0.66-1.42)
AA	33	10.1%	15	8.6%		0.82 (0.42-1.60)

95% CI, 95% Confidence interval; [a]Based on chi-square test. *Statistically significant.

Table IV. *Distribution of alleles for caveolin-1 gene in patients with sarcopenia and controls*.

Allele	Controls		Patients		*p*-Value[a]	Odds ratio (95% CI)
	N	%	N	%		
C521A rs1997623					0.6187	
Allele C	647	98.9%	345	98.6%		1.00 (Reference)
Allele A	7	1.1%	5	1.4%		1.34 (0.42-4.25)
G14713A rs3807987					0.0041*	
Allele G	518	79.2%	249	71.1%		1.00 (Reference)
Allele A	136	20.8%	101	28.9%		1.54 (1.15-2.08)*
G21985A rs12672038					0.3704	
Allele G	497	76.0%	257	73.4%		1.00 (Reference)
Allele A	157	24.0%	93	26.6%		1.15 (0.85-1.54)
T28608A rs3757733					0.4104	
Allele T	495	75.7%	273	78.0%		1.00 (Reference)
Allele A	159	24.3%	77	22.0%		1.14 (0.84-1.54)
T29107A rs7804372					0.2650	
Allele T	470	71.9%	263	75.1%		1.00 (Reference)
Allele A	184	28.1%	87	24.9%		0.85 (0.63-1.14)
G32124A rs3807992					0.6043	
Allele G	455	69.6%	249	71.1%		1.00 (Reference)
Allele A	199	30.4%	101	28.9%		0.93 (0.70-1.23)

95% CI, 95% Confidence interval. [a]Based on chi-square test. *Statistically significant.

Table V. *The contribution of caveolin-1 G14713A genotypes to risk of pre-sarcopenia, sarcopenia and severe sarcopenia.*

G14713A rs3807987	Controls N (%)	Pre-sarcopenia N (%)	Odds ratio (95% CI)	Sarcopenia N (%)	Odds ratio (95% CI)	Severe sarcopenia N (%)	Odds ratio (95% CI)
GG	218 (66.7)	38 (67.9)	1.00 (Reference)	31 (49.2)	1.00 (Reference)	26 (46.4)	1.00 (Reference)
AG	82 (25.1)	15 (26.8)	1.05 (0.55-2.01)	23 (36.5)	1.97 (1.09-3.58)*	21 (37.5)	2.15 (1.15-4.03)*
AA	27 (8.2)	3 (5.3)	0.64 (0.18-2.21)	9 (14.3)	2.34 (1.01-5.45)*	9 (16.1)	2.79 (1.19-6.59)*
p-Value[a]		0.7488		0.0278*		0.0115*	

95% CI, 95% Confidence interval. [a]Based on chi-square test. *Statistically significant.

Discussion

CAV1 is the major member of the caveolin family and it was reported that skeletal muscle fibers from male *CAV1*$^{-/-}$ mice exhibit striking abnormalities, such as tubular aggregates, mitochondrial proliferation/aggregation, and increased numbers of M-cadherin-positive satellite cells. Notably, these skeletal muscle defects were more pronounced with increasing age (27). Sarcopenia is an age-related disease defined by decreased muscle mass and function. In literature, the contribution of personal genotype to sarcopenia has not been studied. Previously, the association of *CAV1* genotypes with several types of cancer has been established (28-38). In the present article we aimed to examine the genotypic contribution of *CAV1* to sarcopenia. As the first step, we combined the patients of pre-sarcopenia, sarcopenia and severe sarcopenia in a single group to compare with the age- and gender-matched control group. After the genotypic frequency distribution analysis, it was found that individuals with the AG genotypes were at 1.65-fold higher risk of sarcopenia compared to those carrying wild-type GG genotype for *Cav1* G14713A (Table III). As for other SNPs we investigated, there was no differential genotype distribution among cases and controls (Table III). Similar findings for AA *versus* GG genotype in Table III (OR=1.78, 95%CI=0.96-3.31, p=0.0235) and A *versus* G allele (OR=1.54, 95%CI=1.15-2.08, p=0.0041) supported the idea that the presence of an A allele for *Cav1* G14713A may serve as a novel biomarker for sarcopenia. As the second step, we further investigated whether there is a difference in the *Cav1* G14713A genotype among the subgroups of patients we enrolled, and whether the A allele on *Cav1* G14713A could still serve as a biomarker in the subgroups. The results given in Table V show that individuals carrying the AG and GG genotypes were at 1.97- and 2.34-fold higher risk of sarcopenia, and of 2.15- and 2.79-fold higher risk of severe sarcopenia, compared with those carrying wild-type GG genotype for *Cav1* G14713A. Interestingly, the genotype seemed not to contribute to pre-sarcopenia risk (Table V).

The functional investigation of mRNA and protein levels for the role of *CAV1* in sarcopenia has not been previously studied. It is also still not well-understood what the genotype-phenotype correlation is for variant *CAV1* G14713A. In 2002, it was reported that *CAV1*-knockout mice were viable and fertile, despite the fact that they lack morphologically identifiable caveolae in endothelia, adipocytes, smooth muscle cells, skeletal muscle fibers, and cardiac myocytes (39). Thus, it is very possible that a subtle genetic variation of *CAV1* may alter skeletal muscle development and degradation homeostasis and somehow contribute to personal susceptibility to sarcopenia. In this pilot population-based study, we found that the A allele of *CAV1* G14713A may be a biomarker associated with higher risk of sarcopenia or severe sarcopenia, but not of pre-sarcopenia (Table V).

In conclusion, the present study found as far as we are aware for the first time, that the *CAV1* G14713A variant genotypes were associated with sarcopenia risk in Taiwanese, and the carrying of an A allele for *CAV1* G14713A may serve a predictor for higher risk of sarcopenia and severe sarcopenia.

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