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A prevalent caveolin-1 gene rs926198 variant is associated with type 2 diabetes mellitus in the Thai population

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This study investigated the associations between *CAV1* variants and metabolic syndrome (MetS), type 2 diabetes mellitus (T2DM), and cardiometabolic risk factors, as well as the influence of *CAV1* variants on *CAV1* mRNA expression. We genotyped 743 T2DM patients for *CAV1* variants. Multiple logistic regression was conducted to adjust for sex, age, and body mass index (BMI), and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. The expression of mRNA was measured by reverse transcription polymerase chain reaction. The rs926198 variant, but not the rs3807989 variant, was associated with T2DM. Crude ORs were 1.87 (95% CI: 1.32–2.69, $p = 0.0005$) and adjusted ORs were 1.81 (95% CI: 1.12–2.96, $p = 0.016$), respectively. Additionally, patients with Mets and T2DM who had the rs926198 variant exhibited a significant 44.3% reduction in *CAV1* mRNA expression ($P < 0.05$). Clinical samples revealed that the rs926198 variant is strongly linked to T2DM, with significantly reduced *CAV1* mRNA. Our findings suggest a crucial role for the rs926198 variant in T2DM, indicating its potential for prevention, diagnosis, and intervention purposes.

Keywords Cardiometabolic risk factors, *CAV1* gene, Insulin resistance, Metabolic syndrome, rs926198 variant, Type 2 diabetes mellitus

Metabolic syndrome (MetS), type 2 diabetes mellitus (T2DM), and related conditions, such as insulin resistance, elevate cardiometabolic risk factors and increase the risk of cardiovascular disease mortality[1,2]. Various factors and associated proteins, including caveolin-1 (CAV1), regulate metabolic status. The caveolin-1 protein is encoded by the 36.4 kb *CAV1* gene on chromosome 7 (7q31.1). This gene has been found to play a significant role in regulation of cell metabolism[3]. *CAV1* facilitates insulin secretion by interacting with cdc42; the gene is also a vital component of insulin secretion vesicles[4]. In pancreatic β-cells, *CAV1* is implicated in insulin receptor signaling, insulin secretion, and potentially diabetes development[4]. Caveolin-1 and adiponectin receptor 1 also form a signalosome associated with lipids, insulin sensitivity, and glucose homeostasis[5–8].

In vitro studies have demonstrated that caveolin-1 associates with lipid bodies, which are the primary structures that store triacylglycerol molecules in adipocytes[9–11]. In vivo, *CAV1* depletion enhances insulin secretion, and compared with control mice, *CAV1* knockout mice exhibit hyperinsulinemia, hypertriglyceridemia, and insulin resistance[12,13]. In humans, a homozygous *CAV1* gene mutation causes congenital generalized lipodystrophy type 3 (CGL3), characterized by postprandial hyperinsulinemia and severe insulin resistance[14]. Additionally, lower *CAV1* gene expression levels in humans are linked to an increased risk of T2DM and MetS, albeit not as high as in *CAV1* null mice, indicating that reduced *CAV1* may contribute to these conditions[15,16]. Genetic variants in the

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CAV1 gene are known to influence MetS and T2DM, necessitating their identification. Identifying these variants supports individualizing diagnoses, predicting disease progression, monitoring therapy, and personalizing prevention and treatment strategies for diabetes care in patients[17].

CAV1 single-nucleotide polymorphisms have been implicated in MetS, a significant risk factor for diabetes and coronary artery disease. Studies have linked rs926198 and rs3807989 variants in the *CAV1* gene to insulin resistance, hypertension, and MetS in White and Hispanic populations[16,18]. The rs3807989 variant at the *CAV1/CAV2* locus has also been associated with increased coronary artery disease and myocardial infarction risk in the Chinese Han population, potentially through upregulation of *CAV1* expression[19]. These findings suggest that rs926198 and rs3807989 may be predictive markers for disease development.

However, the functional impact of these variants on *CAV1* regulation remains unclear. Our study aimed to investigate the associations between these variants and MetS, T2DM and cardiometabolic risk factors in the Thai population. Additionally, we quantified *CAV1* mRNA levels in patients carrying these variants to elucidate their potential regulatory effects.

Results

Associations between *CAV1* genotypes and clinical/biochemical characteristics

Table 1 presents the general characteristics of patients based on the *CAV1* variants rs926198 and rs3807989. For rs926198, parameters such as obesity (BMI, waist circumference, total body fat, and visceral fat), insulin resistance (HOMA-IR), dyslipidemia (total cholesterol, TG, low-density lipoprotein cholesterol, and HDL-C), and other metabolic profiles (HbA1c, fasting insulin, uric acid, microalbuminuria, and high-sensitivity C-reactive protein) were comparable between the variant (T/C + C/C) and wild type (T/T) alleles. Parameters including age, systolic blood pressure, pulse wave velocity (left and right), fasting blood glucose, and Framingham risk score were elevated in individuals with the minor alleles (T/C + C/C) compared to those with the wild-type allele. For rs3807989, most parameters of the minor allele (G/A + A/A) were similar to those of the wild-type (G/G) allele. The exceptions were fasting insulin, TG, and uric acid levels (Table 1).

Parameters	rs926198			rs3807989		
	Major allele homozygote ($n = 561$) TT	Minor allele carriers ($n = 182$) CT + CC	*P* value*	Major allele homozygote ($n = 456$) GG	Minor allele carriers ($n = 287$) AG + AA	*P* value*
Sex (F/M)	374/187	114/68		287/169	201/86	
Age (y)	51.01 ± 15.51	54.54 ± 15.62	***0.004***	52.16 ± 15.40	51.42 ± 15.93	0.499
BMI (kg/m^2)	25.48 ± 4.77	25.48 ± 4.26	0.522	25.60 ± 4.72	25.29 ± 4.53	0.626
WC (cm)	86.42 ± 11.99	87.53 ± 11.39	0.155	86.86 ± 11.84	86.43 ± 11.88	0.876
TBF (%)	31.17 ± 6.27	30.94 ± 6.70	0.998	31.33 ± 6.37	30.77 ± 6.38	0.279
VF (%)	10.40 ± 6.31	11.09 ± 6.10	0.098	10.89 ± 6.32	10.06 ± 6.14	0.087
SBP (mmHg)	124.15 ± 19.87	126.54 ± 17.04	***0.038***	125.65 ± 20.14	123.29 ± 17.62	0.250
DBP (mmHg)	73.67 ± 12.69	73.62 ± 12.74	0.941	74.01 ± 12.76	73.10 ± 12.59	0.409
PWV left	1494.21 ± 365.16	1613.13 ± 426.17	***0.007***	1545.24 ± 365.58	1510.65 ± 389.86	0.108
PWV right	1505.56 ± 364.32	1615.90 ± 440.22	***0.002***	1538.65 ± 378.12	1500.71 ± 401.72	0.079
FBG (mg/dL)	109.41 ± 28.58	114.88 ± 26.49	***0.0007***	112.00 ± 30.23	108.76 ± 24.44	0.331
HbA1c (%)	5.98 ± 1.00	6.00 ± 0.88	0.717	6.01 ± 1.02	5.95 ± 0.86	0.592
Fasting insulin (mU/L)	15.55 ± 9.00	15.21 ± 8.01	0.984	16.08 ± 9.29	14.50 ± 7.80	0.019
TC (mg/dL)	189.31 ± 36.38	187.44 ± 40.48	0.270	188.12 ± 37.52	190.02 ± 37.26	0.433
TG (mg/dL)	130.62 ± 77.58	124.46 ± 68.39	0.319	134.33 ± 77.81	120.83 ± 70.85	0.008
LDL-C (mg/dL)	119.05 ± 34.44	117.66 ± 38.04	0.389	117.15 ± 36.02	121.17 ± 15.41	0.135
HDL-C (mg/dL)	59.92 ± 15.76	56.10 ± 15.29	0.467	56.56 ± 15.80	56.98 ± 15.41	0.664
Uric acid (mg/dL)	5.55 ± 1.46	5.63 ± 1.46	0.786	5.65 ± 1.47	5.44 ± 1.43	0.031
MAU (mg/g Cr)	75.62 ± 422.35	50.20 ± 266.76	0.297	85.58 ± 454.02	62.49 ± 240.24	0.428
hs-CRP (mg/dL)	3.34 ± 8.33	2.77 ± 4.43	0.843	3.76 ± 9.39	2.32 ± 2.79	0.144
Framingham risk score (%)	3.84 ± 5.71	5.23 ± 6.72	***0.008***	4.29 ± 5.97	4.00 ± 6.04	0.289

Table 1. Demographic and biochemical characteristics of patients with the *CAV1* variants rs926198 and rs3807989. The data are presented as the means ± SDs. * *P* values were evaluated by Mann–Whitney U test. Significant P values are shown in bold italics. BMI, body mass index; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MAU, microalbuminuria; PWV, pulse wave velocity; SBP, systolic blood pressure; TBF, total body fat; TC, total cholesterol; TG; triglyceride, VF, visceral fat; WC, waist circumference.

Associations between *CAV1* variants and clinical cardiometabolic risk factors

Table 2 outlines the associations of the *CAV1* variants rs926198 and rs3807989 with MetS, T2DM, cardiometabolic risk factors (dyslipidemia [high TG and low HDL-C levels]), hypertension, and obesity under a dominant model of genetic transmission. The rs926198 variant was significantly associated with MetS (OR 1.44, $P = 0.036$), T2DM (OR 1.87, $P = 0.0005$), HOMA-IR (OR 1.47, $P = 0.013$), visceral fat (OR 1.44, $P = 0.034$), and the Framingham risk score (OR 1.78, $P = 0.008$). These associations lost significance after adjusting for sex, age, and BMI, except for T2DM, which remained significant (OR 1.81, $P = 0.016$). In contrast, the rs3807989 variant was inversely associated with high levels of TG (OR 0.66, $P = 0.014$) and uric acid (OR 0.57, $P = 0.016$). These inverse associations persisted after adjusting for sex, age, and BMI (OR 0.68, $P = 0.032$ for TG; OR 0.61, $P = 0.044$ for uric acid; Table 2).

mRNA expression profile according to *CAV1* genotype

Previous studies on *CAV1*-deficient mice have indicated a predisposition to T2DM and MetS[11]. Both mice and humans with reduced *CAV1* gene expression have shown an increased likelihood of developing these conditions, albeit to a lesser extent than do *CAV1* null mice, suggesting that reduced *CAV1* expression may contribute to these pathologies[11,12]. We hypothesized that the rs926198 variant, located in the noncoding region of the *CAV1* gene, might negatively affect *CAV1* mRNA levels. Consequently, we measured *CAV1* mRNA levels in groups of patients with different variants.

A cohort of 38 patients with the rs926198 variant was selected for analysis (Supplementary Table 2). These patients exhibited a high prevalence of T2DM and MetS, with 22 having high visceral fat (≥ 10%) and 23 (16 females and 7 males) exhibiting high waist circumference. However, 24 patients with the rs926198 variant had a more normal body mass index (BMI < 25 kg/m^2). Additionally, we evaluated 26 patients with the rs3807989 variant (Supplementary Table 2). This group also had a high frequency of T2DM and high visceral fat (≥ 10%), but nearly all were non-MetS, with a normal waist circumference and BMI.

We extracted mRNA from white blood cells and analyzed *CAV1* mRNA expression using semiquantitative PCR to compare *CAV1* mRNA levels between the variant and wild-type groups. The results indicated a significant reduction in mean *CAV1* mRNA expression (a 44.3% decrease) in patients with the rs926198 variant compared

	rs926198				rs3807989			
	Minor allele carriers versus major allele homozygous				Minor allele carriers versus major allele homozygous			
	Crude		Adjusted †		Crude		Adjusted †	
Cardiometabolic risks	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
MetS *	1.44 (1.02–2.02)	***0.036***	1.33 (0.89-2.00)	0.166	0.99 (0.73–1.34)	0.952	1.01 (0.70–1.47)	0.938
T2DM *	1.87 (1.32–2.67)	***0.0005***	1.81 (1.12–2.96)	***0.016***	0.96 (0.71–1.29)	0.713	1.06 (0.70–1.61)	0.768
HOMA-IR *	1.47 (1.01–2.12)	***0.013***	1.54 (0.92–2.53)	0.09	0.71 (0.46–1.09)	0.127	0.75 (0.46–1.20)	0.231
High TG *	1.08 (0.74–1.54)	0.693	1.00 (0.68–1.45)	0.987	0.66 (0.47–0.92)	***0.014***	0.68 (0.48–0.96)	***0.032***
Low HDL-C *	0.90 (0.60–1.32)	0.587	0.91 (0.60–1.36)	0.641	0.95 (0.67–1.33)	0.759	0.95 (0.66–1.36)	0.776
Hypertension *	1.04 (0.71–1.51)	0.848	0.92 (0.62–1.35)	0.667	0.70 (0.50–0.99)	***0.046***	0.72 (1.50–1.02)	0.069
High PWV *	1.44 (1.01–2.09)	0.05	1.01 (0.60–1.69)	0.982	0.79 (0.58–1.08)	0.140	0.78 (0.50–1.21)	0.268
High BMI †	1.26 (0.90–1.77)	0.171	1.15 (0.81–1.62)	0.423	0.96 (0.72–1.30)	0.811	1.00 (0.74–1.36)	0.982
High WC †	1.43 (1.01–2.05)	***0.045***	1.32 (0.92–1.93)	0.138	1.30 (0.96–1.76)	0.096	1.29 (0.94–1.78)	0.122
High VF †	1.44 (1.03–2.03)	***0.034***	1.25 (0.85–1.85)	0.254	0.86 (0.64–1.16)	0.316	0.97 (0.69–1.36)	0.841
High uric acid *	1.16 (0.72–1.84)	0.535	1.05 (0.62–1.72)	0.854	0.57 (0.38–0.89)	**0.016**	0.61 (0.37–0.98)	***0.044***
MAU *	1.09 (0.69–1.70)	0.706	0.99 (0.62–1.56)	0.972	1.11 (0.73–1.68)	0.615	1.15 (0.75–1.75)	0.525
hs-CRP *	0.99 (0.59–1.63)	0.974	1.03 (0.61–1.72)	0.900	0.75 (0.47–1.17)	0.212	0.75 (0.47–1.18)	0.216
FRS *	1.78 (1.16–2.69)	***0.008***	1.67 (0.82–3.37)	0.154	0.91 (0.61–1.37)	0.664	1.15 (0.60–2.19)	0.675

Table 2. Association between the *CAV1* variants rs926198 and rs3807989 and clinical cardiovascular risk factors. Metabolic syndrome (MetS) was defined according to the IDF definition. Type 2 diabetes mellitus (T2DM) was diagnosed according to the American Diabetes Association definition. High TG levels were classified as triglyceride levels ≥ 150 mg/dL. Low HDL-C was defined as HDL levels < 40 mg/dL in men and < 50 mg/dL in women. Hypertension was defined as an SBP ≥ 140 mmHg or a DBP ≥ 90 mmHg. A high BMI was defined as a BMI ≥ 25 kg/m^2. High WC ≥ 90 cm in men and ≥ 80 cm in women. Insulin resistance was at the 85th percentile of HOMA-IR in this study (HOMA-IR ≥ 6.55). hs-CRP was defined as high-sensitivity C-reactive protein ≥ 3.0 mg/L. High uric acid ≥ 7.2 mg/dL. Microalbuminuria ≥ 30 mcg/mg creatinine. High visceral fat rating ≥ 10. High pulse wave velocity ≥ 1400 cm/s. The Framingham risk score was ≥ 10%. Significant P values are shown in bold italics. *Adjusted by age, sex and BMI; † adjusted by age and sex. ‡ Significant P values are shown in bold italics. BMI, body mass index; FRS, Framingham risk score; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; MAU, microalbuminuria; Mets, metabolic syndrome; PWV, pulse wave velocity; T2DM, type2 diabetes mellitus; TBF, total body fat; TC, total cholesterol; TG; triglyceride, VF, visceral fat; WC, waist circumference.

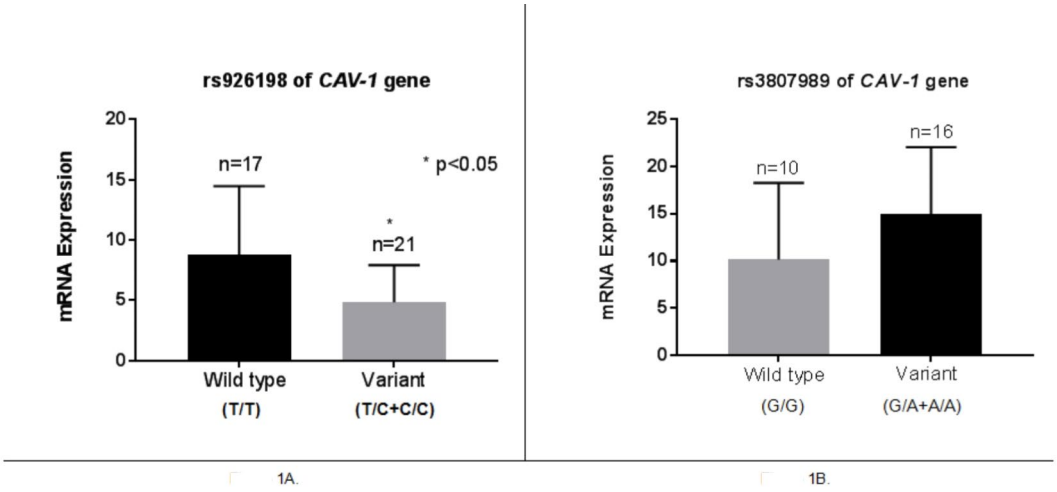

Fig. 1. Comparative analysis of the mRNA levels of rs926198 (**A**) and rs3807989 (**B**) in the CAV1 gene.

Diseases	Category†	rs926198 CAV1 variant minor allele carriers versus major allele homozygous		
		*OR_{adj}	95% CI	*P* value‡
Metabolic syndrome	Nonobese	2.14	1.07–4.27	***0.032***
	Obese	1.69	0.94–3.06	0.081
Type 2 diabetes mellitus	Nonobese	2.48	1.37–4.50	***0.003***
	Obese	0.54	0.24–1.22	0.138

Table 3. Adjusted odds ratios for metabolic syndrome and type 2 diabetes according to *CAV1* genotype rs926198 stratified by obesity status and homeostatic model assessment of insulin resistance status. Significant P values are shown in bold italics. †Participants were categorized as nonobese (BMI < 25 kg/m^2, $n = 389$) or obese (BMI ≥ 25 kg/m^2, $n = 354$). ‡OR_{adj} was adjusted for age, sex and body mass index as fixed effects and relatedness as a random effect.

to the wild type (Fig. 1A). Conversely, no significant change in *CAV1* mRNA levels was detected in patients with the rs3807989 variant compared to those with the wild type (Fig. 1B). Therefore, the rs926198 variant—but not the rs3807989 variant—was associated with decreased *CAV1* mRNA expression ($P < 0.05$; Fig. 1A).

Exploratory analysis of the role of the CAV1 rs926198 variant in nonobese patients at risk of MetS and T2DM

Given the significant association of MetS with the rs926198 minor allele and its lack of correlation with high BMI risk (Table 2), we explored the predictive role of the *CAV1* rs926198 genotype for MetS and T2DM in obese versus nonobese individuals. In the nonobese subgroup, the presence of the minor allele significantly enhanced the predictive capacity for MetS, demonstrating a more than twofold increased likelihood of MetS occurrence after adjusting for confounding factors (OR 2.14, 95% CI 1.07–4.27, $P = 0.032$; Table 3). Similarly, the risk of T2DM was twice as high in nonobese individuals carrying the rs926198 minor allele compared to major allele homozygotes (OR 2.48, 95% CI 1.37–4.50, $P = 0.003$; Table 3).

Haplotype analyses of cav1 variants (rs926198-rs3807989) and disease statuses (T2DM and Mets)

We analyzed the association between haplotypes and disease status, focusing on T2DM and Mets. Haplotypes were constructed using the SNP markers rs926198 and rs3807989, and four common haplotypes were identified (Table 4). Among these, the C/G haplotype was significantly associated with an increased risk of MetS ($P < 0.001$, OR = 2.47, 95% CI = 1.48–4.10). After adjusting for sex and age, this association remained statistically significant ($P_{adj} = 0.03$, OR = 1.83, 95% CI = 1.06–3.16). Similarly, the C/G haplotype was associated with an elevated risk of T2DM ($P < 0.001$, OR = 3.10, 95% CI = 1.72–5.60), and this association also persisted after adjusting for sex and age ($P_{adj} = 0.04$, OR = 2.10, 95% CI = 1.02–4.29) (Table 4). This suggests that the C/G haplotype may play a significant role in increasing susceptibility to both MetS and T2DM, even when accounting for common demographic factors such as age and sex.

Haplotype (rs926198-rs3807989)	Mets* (frequency)	Non-mets (frequency)	Crude		Adjusted‡	
			OR (95% CI)	*P* value	OR (95% CI)	*P* value
T/G	0.7059	0.7508	1.00	–	1.00	–
T/A	0.1271	0.1430	0.94 (0.68–1.30)	0.710	1.04 (0.73–1.48)	0.830
C/A	0.0846	0.0710	1.29 (0.84–1.89)	0.260	1.27 (0.81–1.99)	0.300
C/G	0.0824	0.0352	2.47 (1.48–4.10)	< ***0.001***	1.83 (1.06–3.16)	***0.031***
Haplotype (rs926198-rs3807989)	**Type 2 diabetes (frequency)**	**No-type 2 diabetes (frequency)**	**OR (95% CI)**	***P* value**	**OR (95% CI)‡**	***P* value**
T/G	0.7132	0.7552	1.00	–	1.00	–
T/A	0.1252	0.1493	0.88 (0.65–1.21)	0.430	1.05 (0.70–1.57)	0.810
C/A	0.0835	0.0691	1.27 (0.84–1.91)	0.250	1.46 (0.85–2.50)	0.170
C/G	0.0780	0.0265	3.10 (1.72–5.60)	< ***0.001***	2.10 (1.02–4.29)	***0.043***

Table 4. Distribution of haplotype frequencies in study patients. *Metabolic syndrome (MetS) was defined according to the IDF definition. †Type 2 diabetes was defined according to the American Diabetes Association (ADA) definition. Significant P values are shown in bold italics. ‡Multiple logistic regression adjusted by age and sex.

Discussion

Genetic studies have explored associations between *CAV1* variants and metabolic traits across various populations, including European, Latin American, and Asian groups[20–23]. However, no prior studies have investigated these associations in the Thai population. This study examined the association between *CAV1* variants (rs926198 and rs3807989) and metabolic syndrome (MetS), type 2 diabetes mellitus (T2DM), and cardiometabolic risk factors in a Thai population. Our findings revealed that the rs926198 variant was associated with MetS, T2DM, insulin resistance, but not with dyslipidemia (high TG and low HDL-C levels), hypertension, high uric acid, or obesity. After adjusting for age and sex, only the association with T2DM remained statistically significant (OR = 1.81 [95% CI = 1.12–2.96], $P = 0.016$) (Table 2). While rs926198 has been extensively studied in White and other populations, its impact on the Thai population was previously unconfirmed. Our results align with studies in White and Hispanic hypertensive individuals, where rs926198 was linked to MetS, T2DM, insulin resistance, and dyslipidemia[16,18]. Additionally, we found that rs926198 was associated with high waist circumference and visceral fat, both cardiometabolic risk factors, though these associations lost significance after adjusting for sex, age, and BMI. In non-obese individuals, the minor allele of rs926198 was associated with increased odds of MetS (OR = 2.14) and T2DM (OR = 2.48) (Table 3). This association in the Thai population aligns with previous studies in non-obese White individual[16], suggesting a potential universal link between rs926198 and MetS across Thai and White populations. While the underlying mechanisms remain unclear, these findings highlight the potential of rs926198 as a valuable biomarker for MetS and T2DM in non-obese individuals. However, other studies have shown that while the rs11773845 variant was significantly associated with MetS (OR = 1.53), the rs926198 variant did not show significant associations with metabolic traits[23]. Similarly, the rs1997623 variant of *CAV1* was associated with MetS in Arab patients (OR = 1.81), but this association was not replicated in South Asian or Southeast Asian populations[22].

The rs3807989 variant was inversely associated with hypertension, elevated triglyceride levels, and uric acid. However, after adjusting for age, sex and BMI, only the associations with elevated triglyceride levels and uric acid remained statistically significant (Table 2). These novel findings have not been previously reported in the NHGRI-EBI GWAS Catalog[24] or the NCBI dbSNP database[25] and should be validated in other populations. Previous studies have shown that rs3807989 was significantly associated with higher fasting insulin levels and increased HOMA-IR in White populations[21]. In the Chinese Han population, rs3807989 was significantly associated with CAV1 expression and an increased risk of coronary artery disease and myocardial infarction[19]. Additionally, we investigated the association between haplotypes and disease status, focusing on T2DM and Mets. Haplotype analysis of *CAV1* variants (rs926198 T/C and rs3807989 G/A) identified four haplotypes: T/G, T/A, C/A, and C/G (Table 4). The C/G haplotype was associated with an increased risk of Mets and T2DM compared to the wild-type T/G reference genotype (Table 4). In contrast, the T/A and C/A haplotypes were not associated with these conditions. These results suggest that the C allele of rs926198 may interact with the G allele of rs3807989 in the development of Mets and T2DM, with alterations in the C allele potentially serving as a strong indicator for these conditions.

CAV1 regulates insulin signaling and insulin receptor stability by binding directly to the insulin receptor in adipocytes[12]. Disruption of this complex impairs insulin signaling, leading to insulin resistance[26]. In silico analysis of expression quantitative trait loci (eQTLs) identified lower *CAV1* expression in carriers of the rs926198 variant in White and Hispanic populations, with minor allele homozygotes showing the lowest expression levels. This reduced expression was confirmed in our patient cohort, suggesting a potential role for rs926198 in the development of MetS and T2DM[16]. To validate these results, we measured *CAV1* mRNA levels in our patient cohort and confirmed significantly reduced *CAV1* expression in patients carrying the rs926198 variant (Fig. 1). This reduction may contribute to Mets and T2DM, highlighting the potential of rs926198 as a biomarker and therapeutic target. The specific mechanism by which rs926198 affects *CAV1* expression remains to be elucidated. Further research is needed to clarify how rs926198 influences disease risk. We propose that *CAV1* gene polymorphisms, along with other genetic and environmental factors, could be used to assess the risk for T2DM

and Mets. While these findings are promising, the study has limitations, including the lack of longitudinal follow-up and a replication cohort. Additional research is necessary to elucidate the mechanisms through which rs926198 affects disease risk, particularly in non-obese individuals.

Conclusions

Our study demonstrated that the rs926198 variant is significantly associated with type 2 diabetes mellitus (T2DM) in the Thai population, suggesting its potential as a diagnostic and predictive marker for personalized prevention. Additionally, the rs926198 variant may increase the risk of type 2 diabetes mellitus and metabolic syndrome (Mets) in non-obese patients. Further investigations are needed to confirm these findings and explore the underlying mechanisms involved.

Methods

Study design and population

This unmatched case–control study involved 850 Thai patients aged 25 years and older from the MetS-T2DM cohort at HRH Princess Maha Chakri Sirindhorn Medical Center, Srinakharinwirot University. Participants attended the outpatient department between 2013 and 2015.

MetS cases were defined using the 2009 International Diabetes Federation criteria[27]. These criteria required central obesity (using waist circumference for ethnicity-specific values) plus any two of the following:

- High triglyceride (TG) level (> 1.69 mmol/L or specific treatment for lipid abnormalities).
- Reduced high-density lipoprotein cholesterol (HDL-C) level (< 1.04 mmol/L in males, < 1.29 mmol/L in females, or specific treatment for lipid abnormalities).
- Raised blood pressure (systolic blood pressure ≥ 130 mmHg, diastolic blood pressure ≥ 85 mmHg, or treatment for previously diagnosed hypertension).
- Raised fasting blood glucose level (≥ 5.55 mmol/L or previously diagnosed T2DM). T2DM was diagnosed according to the 2010 American Diabetes Association guidelines[28].

The exclusion criteria were as follows:

- Underlying diseases, such as acute/chronic hepatitis, chronic renal failure, kidney dialysis, chronic inflammatory diseases, all cancer types, autoimmune diseases, Mendelian or rare genetic disorders, cognitive deficiencies, and type 1 diabetes mellitus.
- Pregnancy.
- Specific medications (steroids, thiazolidinediones, glucagon-like peptide-1 analogs, dipeptidyl peptidase-4 inhibitors, fenofibrate agents, insulin injections, and hormone treatments).

The controls were healthy individuals from the same health checkup service and met the same exclusion criteria as the patients.

As genotyping data for the rs926198 and rs3807989 *CAV1* variants were unavailable for 107 of the 850 patients, the final sample size was 743 participants.

All participants provided written informed consent prior to enrollment. The study received ethics approval from the Faculty of Medicine, Srinakharinwirot University, Bangkok, Thailand (SWUEC-EX12/2556). The research was conducted in accordance with the Declaration of Helsinki.

Anthropometric and biochemical measurements

Anthropometric measurements included body mass index (BMI; kg/m^2), waist circumference, total body fat, and visceral fat. Waist circumference was measured midway between the lower border of the ribs and the upper border of the pelvis using flexible tape in the horizontal plane. Total body fat and visceral fat were obtained through bioelectrical impedance analysis with a body fat analyzer (Omron BF511; Omron Healthcare United Kingdom Ltd, Milton Keynes, UK).

Systolic and diastolic blood pressures were measured using an automated Udex-Twin device (Intertech Medical Group, Bangkok, Thailand). Participants were seated and rested for 10 min prior to measurement, adhering to standard blood pressure assessment protocols. Additionally, blood samples were collected from participants following a 12-hour fast. These samples were analyzed for glucose, insulin, glycated hemoglobin (HbA1c), lipid profile, uric acid, high-sensitivity C-reactive protein, and microalbuminuria using an Abbott Architect ci8200 Chemistry Analyzer (Abbott Laboratories, Green Oaks, IL, USA). Insulin resistance was evaluated using the homeostatic model assessment of insulin resistance (HOMA-IR)[29].

The Framingham risk score, which estimates the 10-year cardiovascular risk, was calculated by incorporating age, sex, total cholesterol, HDL-C, hypertension treatment history, systolic blood pressure, and smoking status[30].

Genotyping

Genotyping was conducted on 743 patients, focusing on two common variants within the second intron of the *CAV1* gene: rs926198 (T/C) and rs3807989 (G/A). Peripheral blood leukocytes served as the DNA source, with extraction facilitated by the FlexiGene DNA Kit (Qiagen, Hilden, Germany). Extracted DNA was stored at -20 °C.

Polymerase chain reaction–restriction fragment length polymorphism methodology was used for genotyping. Supplementary Table 1 provides detailed information concerning primer sequences, polymerase chain reaction (PCR) product sizes, optimized PCR conditions, restriction enzymes, and resultant restriction products.

PCR amplification was carried out on a thermal cycler (Biometra, Göttingen, Germany). For rs926198, initial denaturation occurred at 94 °C for 5 min, followed by 33 cycles of 45 s at 94 °C, 30 s at 58.7 °C, and 30 s at 72 °C, with a final extension of 5 min at 72 °C. For rs3807989, the conditions comprised initial denaturation at 94 °C for 5 min, followed by 33 cycles of 45 s at 94 °C, 30 s at 58.2 °C, and 30 s at 72 °C, with a final extension at 72 °C for 5 min.

After PCR, the products were digested using the *BsaI* endonuclease for rs926198 and the *PciI* endonuclease for rs3807989. The resulting fragments were separated via 2.5% agarose gel electrophoresis and visualized under ultraviolet light. The genotype call rates were 87.0% for rs926198 and 92.0% for rs3807989.

Total RNA isolation and cDNA synthesis

Total RNA was isolated from buffy coats using RBC lysis solution, followed by extraction with GENEzol reagent (Geneaid Biotech, Taipei, Taiwan). Purification was accomplished with the PureLink RNA Mini Kit (Ambion, Austin, TX, USA) according to the manufacturer's guidelines. Residual DNA was removed using DNase treatment (Ambion). Total RNA was converted into cDNA via the Superscript III First-Strand Synthesis System (Invitrogen, Carlsbad, CA, USA) with random hexamer primers.

Primer sequences were designed to target exon 2 of *CAV1*, yielding a 151-bp PCR product (forward 5' ACA TCTCTACACCGTTCCCATCCG 3' and reverse 5' ATCGTTGAGGTGTTTAGGGTCGC 3'). Glyceraldehyde 3-phosphate dehydrogenase (*GAPDH*) served as an internal control with the following primers: forward 5' CCT CCAAAATCAAGTGGGGCGATG 3' and reverse 5' CGAACATGGGGGCATCAGCAGA 3'.

Quantitative real-time PCR was conducted in a 10 μL reaction volume, prepared from 2X Power SYBR Green PCR Master Mix (Applied Biosystems, Weiterstadt, Germany), which included AmpliTaq Gold DNA Polymerase LD, dNTPs with dUTP/dTTP blends, Passive Reference 1, and optimized buffer components. The real-time PCR amplification conditions for the Step One Real-Time PCR System (Applied Biosystems, Carlsbad, CA, USA) included an initial denaturation step at 95 °C for 10 min, followed by 40 cycles of 15 s of denaturation at 95 °C and then 1 min of annealing and extension at 60 °C for another 40 cycles.

The threshold cycle (Ct) values for *CAV1* and *GAPDH* were determined. The fold change in the expression level of *CAV1* relative to that of *GAPDH* was calculated using the following formula: $2^{\Delta Ct}/lowest\ value\ of\ 2^{\Delta Ct}$; where ΔCt = Ct of *GAPDH* – Ct of *CAV1*.

mRNA expression profile analysis

Patients with MetS and T2DM harboring the rs926198 variant were categorized into a variant group ($n = 21$) and a wild-type group ($n = 17$). For the rs3807989 variant, participants were similarly divided into variant ($n = 16$) and wild-type ($n = 10$) groups.

Statistical analysis

The baseline characteristics are reported as numbers and percentages for categorical variables, while the means and standard deviations describe continuous variables. Comparisons between groups were performed using the Mann–Whitney U test. To explore the association between *CAV1* variants and disease status (MetS and T2DM), odds ratios (ORs) and 95% confidence intervals were calculated using multiple logistic regression, adjusting for sex, age, and BMI.

Statistical analyses were performed using R software (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria). For gene expression analyses, mean values and standard deviations were computed, and comparisons were made using Student's t-test via GraphPad Prism, version 7.00 (GraphPad Software Inc, Boston, MA, USA). A P value < 0.05 was considered to indicate statistical significance. Hardy–Weinberg equilibrium was assessed using a fast exact test[31]. The haplotype analysis was performed to investigate the association between CAV1 variants (rs926198 and rs3807989) and both Mets and T2DM. We utilized the haplo.stats package in R to estimate haplotype frequencies and assess their associations through generalized linear regression analysis [32].

Data availability

The authors confirm that the data supporting the findings of this study are available within the article [and/or its supplementary materials]. The data that support the findings of this study are available on request from the corresponding author, [SC]. The data are not publicly available due to privacy or ethical restrictions.

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Author contributions

M.Y. researched and analyzed the data and wrote the manuscript. S.C. wrote the grant proposal, designed and analyzed the study, screened and examined all recruited patients, researched the data, and contributed to writing and reviewing the manuscript. SJ designed, and analyzed part of the study and contributed to writing and reviewed the manuscript. G.S. performed the experiments. P.E. performed the experiments. V.A. designed the study and provided trial advice. C.D. and T.H. provided trial advice. All authors approved the final version of the manuscript.

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Declarations

Competing interests
The authors declare no competing interests.

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