

Peripheral Vascular Disease Susceptibility Based on Diabetes Mellitus and rs17367504 Polymorphism of the MTHFR Gene

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Purpose: Peripheral vascular disease (PVD) is a life-threatening condition affecting the lower extremities. Common risk factors include type 2 diabetes (T2D), hypertension, dyslipidemia, smoking, and older age. There is a little-documented research on the genetic basis of the disease in Taiwan. We examined the impact of T2D and the blood pressure-associated rs17367504 variant of the *Methylenetetrahydrofolate reductase (MTHFR)* gene on PVD risk.

Materials and Methods: In this population-based association study, we linked data from 8992 participants in Taiwan Biobank (TWB) to their medical records in the National Health Insurance Research Database (NHIRD). Participants were 30 to 70 years old at recruitment and included those assessed between 2008 and 2015. We tested for association of PVD with rs17367504 and T2D using multiple logistic regression models. The rs17367504 variant was assessed using the Axiom-Taiwan Biobank Array Plate (TWB chip: Affymetrix, Inc., Santa Clara, CA, USA).

Results: Among cases with T2D (n = 1294), 158 (12.21%) were identified with PVD. T2D was associated with PVD (odds ratio [OR], 1.52; 95% confidence interval [CI], 1.21–1.91; p < 0.001) whereas rs17367504 variant was not (OR, 0.96; CI, 0.76–1.21; p = 0.728 in AG/GG compared to AA homozygotes). However, T2D and rs17367504 had an interactive effect on PVD (p for interaction = 0.0076). Results from our stratified analyses displayed OR of 1.75 (CI, 1.35–2.26; p < 0.001) in AA individuals with DM and 0.94 (CI, 0.56–1.58; p = 0.811) in AG+GG individuals with T2D. Using the AA genotype and no T2D as the reference group, the respective OR of PVD was 1.77 (CI, 1.38–2.28; p < 0.001) in AA individuals with T2D; 1.18 (CI, 0.91–1.55; p = 0.215) in AG+GG individuals with no T2D, and 1.03 (CI, 0.66–1.60; p = 0.892) in AG+GG individuals with T2D.

Conclusion: We found that type 2 diabetes was associated with increased risk of peripheral vascular disease, particularly in AA genotype carriers of the rs17367504 variant in Taiwan.

Keywords: peripheral vascular disease, type 2 diabetes, genomics, atherosclerosis

Introduction

Peripheral vascular disease, also known as peripheral artery disease (PAD) is an atherosclerotic disease affecting approximately 10% of the world's population.¹ It is more common in older individuals no matter their gender, resulting in occlusion of noncoronary blood vessels, particularly those of the lower extremities.² Classical risk factors include T2D, dyslipidemia, smoking, hypertension, and older age.³ T2D is a complex metabolic disorder characterized by chronic hyperglycemia.⁴ According to a systematic review and analysis, PVD is more frequent in South East Asians aged 45 to 54 and in Americans and Europeans aged 55 to 64 and 65 to 74, respectively.⁵

Atherosclerotic risk factors such as dyslipidemia, smoking, diabetes, hypertension exist for PVD.⁶ Among them, diabetes has shown a stronger association with disease prevalence and mortality.^{7–9} The risk of developing PVD is approximately 2–4 times higher in patients with diabetes.¹⁰ According to findings from a previous study, PVD was more frequent in about 20–30% of people with diabetes.⁶ In a study to assess the prevalence of asymptomatic peripheral vascular disease and related risk factors, Chen et al, found that diabetes was more frequent in approximately 36% of elderly individuals with asymptomatic PVD in Taiwan.¹¹ Studies have suggested that approximately 50% of PAD burden is linked to atherosclerotic risk factors while genetic and environmental factors account for the other factors.^{3,12}

Previous studies have shown that various polymorphisms of particular genes are either causative^{13–15} or protective for PVD.^{16,17} Researchers have also reported associations between common polymorphic variants of specific genes and PVD in patients with diabetes.^{18,19} Among them is the *MTHFR* gene that is crucial in controlling homocysteine (Hcy) metabolism. This gene also plays a role in mediating diabetes complications.²⁰ Hyper-homocysteinemia has been linked to PVD and cardiovascular disease (CVD) risk in patients with T2D, hypertension, and other health conditions.^{21–24} Rs17367504, one of the variants within the

MTHFR gene, has shown significant associations with hypertension^{25,26} and Hcy levels.²⁷

Of note, T2D is an atherosclerotic risk factor for PVD and CAD, both of which often occur together in approximately 50% of patients.^{14,28} It frequently occurs alongside hypertension, and each variable is a significant predictor of the other.²⁹ Peripheral artery disease and its common atherosclerotic risk factors have already been described.¹¹ However, there is a little-documented research on the genetic underpinnings of the disease in Taiwan. Using data collected between 2008 and 2015 from Taiwan Biobank participants aged 30 to 70 years, we assessed the impact of T2D and the *MTHFR* rs17367504 variant on PVD risk. We replicated this variant because of its significant links with PVD risk factors, including hypertension and hyperhomocysteinemia.³⁰ We included T2D in our analyses because PVD is frequent in patients with this condition.³¹ We hypothesized that the *MTHFR* rs17367504 variant would influence the relationship between PVD and T2D.

Materials and Methods

Data Source and Study Population

Using specific identification number, data from participants in TWB were linked to the medical records in the NHIRD through the Health and Welfare Data Science

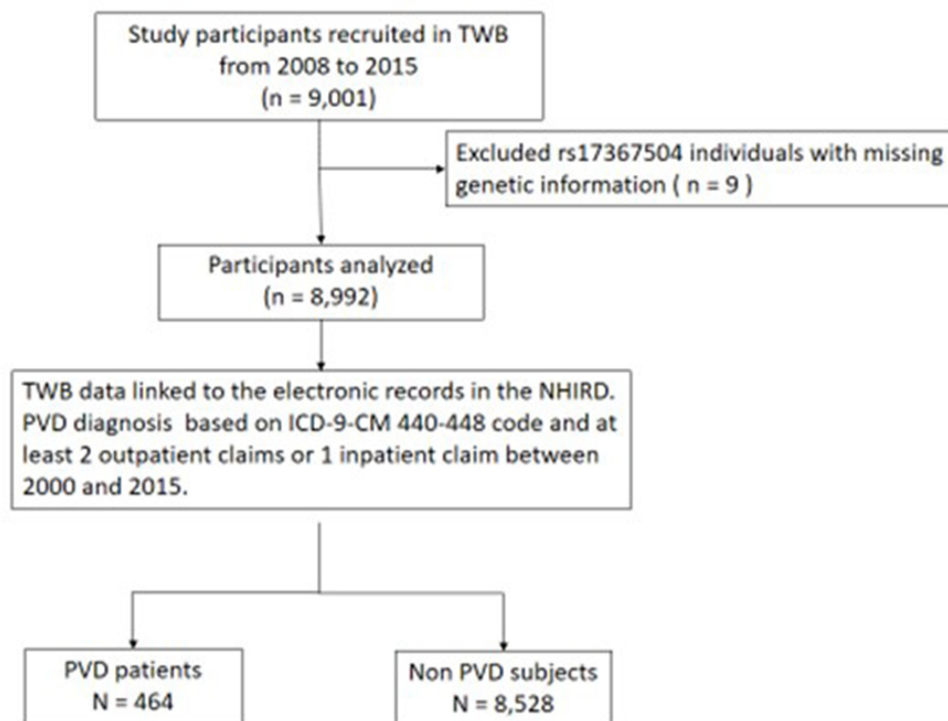


Figure 1 Flowchart of study participants.

Table 1 Baseline Characteristics of Study Population

	No T2D (n=7698)		T2D (n=1294)		p-value
	N	%	N	%	
Peripheral vascular disease					<0.001
No	7392	(96.02)	1136	(87.79)	
Yes	306	(3.98)	158	(12.21)	
MTHFR rs17367504					0.355
AA	5862	(76.15)	970	(74.96)	
AG+GG	1836	(23.85)	324	(25.04)	
Sex					<0.001
Female	4176	(54.25)	630	(48.69)	
Male	3522	(45.75)	664	(51.31)	
Age (yr)					<0.001
30 to 39	2030	(26.37)	64	(4.95)	
40 to 49	2252	(29.25)	204	(15.77)	
50 to 59	2160	(28.06)	476	(36.79)	
60 to 70	1256	(16.32)	550	(42.50)	
Smoking					0.005
No	6001	(77.96)	963	(74.42)	
Yes	1697	(22.04)	331	(25.58)	
Alcohol drinking					0.005
No	6911	(89.78)	1128	(87.17)	
Yes	787	(10.22)	166	(12.83)	
Physical activity					<0.001
No	4612	(59.91)	574	(44.36)	
Yes	3086	(40.09)	720	(55.64)	
BMI (kg/m ²)					<0.001
<18.5	212	(2.75)	16	(1.24)	
18.5–24	3822	(49.65)	455	(35.16)	
24–27	2259	(29.35)	443	(34.23)	
≥27	1405	(18.25)	380	(29.37)	
Hypertension					<0.001
No	6281	(81.59)	550	(42.5)	
Yes	1417	(18.41)	744	(57.5)	
Hyperlipidemia					<0.001
No	5905	(76.71)	310	(23.96)	
Yes	1793	(23.29)	984	(76.04)	
Atrial fibrillation					0.007
No	7665	(99.57)	1281	(99.00)	
Yes	33	(0.43)	13	(1.00)	
Tea consumption					0.932
No	4821	(62.63)	812	(62.75)	
Yes	2877	(37.37)	482	(37.25)	
Coffee consumption					0.002
No	5182	(67.32)	928	(71.72)	
Yes	2516	(32.68)	366	(28.28)	

(Continued)

Table 1 (Continued).

	No T2D (n=7698)		T2D (n=1294)		p-value
	N	%	N	%	
Diet Type					0.030
Omnivore	6873	(89.28)	1185	(91.58)	
Lacto-ovo vegetarian	130	(1.69)	21	(1.62)	
Strict vegetarian	695	(9.03)	88	(6.80)	

Note: Data are presented as n (%).**Abbreviations:** T2D, type 2 diabetes; yr, year; MTHFR, methylenetetrahydrofolate reductase; BMI, body mass index; AA and AG+GG, genotypes of rs17367504 polymorphism.

Center (HWDC) repository. These individuals had been recruited through 29 assessment centers distributed across Taiwan. Taiwan Biobank had obtained written (signed) informed consent from each participant before enrollment. These participants had completed questionnaires on a wide range of social, medical, and lifestyle information and provided blood samples for DNA analysis. The QIAamp DNA Mini Kit (Qiagen, Valencia, CA, USA) was used to isolate DNA from the participants' blood samples.³² This study was conducted in accordance with the Declaration of Helsinki. The Institutional Review Board of Chung Shan Medical University approved this study (IRB: CS1-20009).

In our study, we obtained genetic data for 9001 TWB participants assessed between 2008 and 2015. We excluded 9 individuals with missing or incomplete genetic information, leaving 8992 individuals for analysis. In the final analysis, there were 468 cases with PVD and 8528 controls (Figure 1).

Disease Assessment

Disease identification was based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) coding.³³ The diagnosis codes used were 440–448 for peripheral vascular disease, 250 for T2D (ICD-9-CM: 250), 401–405 for hypertension, and 272 for hyperlipidemia, together with either an inpatient admission or two outpatient consultations.

SNP Selection and Genotyping

We chose the rs17367504 genetic variant using search engines including but not limited to PubMed, Snpedia, Google Scholar, and the National Center for

Biotechnology Information (NCBI). In TWB, genotyping is performed by Affymetrix using the Axiom™ Genome-Wide Array Plate System (Affymetrix, Santa Clara, CA, USA).³² Genotyping experiments are typically conducted in Academia Sinica by the National Center for Genome Medicine.

Statistical Analyses

We performed all statistics using PLINK version 1.09 beta and the statistical analysis system (SAS) package, version 9.4. The chi-square test and Student's *t*-test were used for the categorical and continuous variables. Effects of T2D and rs17367504 on PVD risk were tested in multiple logistic regression models, and results were presented as ORs along with their respective CIs. For our quality control, the missing rate of the rs17367504 variant was 0.00099, and the minor allele frequency (MAF) was 0.1278. The *p*-value for the Hardy-Weinberg equilibrium (HWE) test was 0.1549.

Results

Of the 8992 eligible participants, diabetes cases were older than the controls (mean age [standard deviation, SD], 55.78 [9.02] years against 48.34 [10.73] years; *p*<0.001; data not shown). There were 1294 cases with diabetes mellitus and 7698 controls (Table 1). Among cases with T2D, 158 (12.21%) were identified with PVD. We found an association between T2D and PVD (OR, 1.52; CI, 1.21–1.91) as shown in Table 2. Rs17367504 variant was not associated with PVD (OR, 0.96; CI, 0.76–1.21 in AG/GG compared to AA individuals). Also associated with PVD was hypertension (OR, 1.55; CI, 1.24–1.94), hyperlipidemia (OR, 1.69; CI, 1.35–2.12) smoking (OR, 1.34; CI, 1.01–1.77), obesity (OR, 1.34; CI, 1.1.04–1.72), and older age 40–49 years [OR, 1.92; CI 1.20–3.05]; 50–59 years [OR, 3.33; CI, 2.14–5.18], and 60–70 years ([OR, 5.06; CI, 3.21–7.98], respectively). We observed an interaction between T2D and rs17367504 (*p* = 0.0076). Results from our stratified analyses displayed OR of 1.75 (CI, 1.35–2.26) in AA individuals with T2D and 0.94 (CI, 0.56–1.58) in AG+GG individuals (Table 3). Using the AA genotype and no T2D as the reference group (Table 4), the respective ORs were 1.77 (CI, 1.38–2.28) in AA individuals with T2D; 1.18 (CI, 0.91–1.55) in AG+GG individuals with no

Table 2 Peripheral Vascular Disease Risk in Overall Participants

	OR	95% CI	p-value
rs17367504 (ref: AA) AG+GG	0.96	(0.76–1.21)	0.728
T2D (ref: No) Yes	1.52	(1.21–1.91)	<0.001
Sex (ref: Female) Male	0.62	(0.48–0.78)	<0.001
Age, yr (ref: 30 to 39)			
40 to 49	1.92	(1.20–3.05)	0.006
50 to 59	3.33	(2.14–5.18)	<0.001
60 to 70	5.06	(3.21–7.98)	<0.001
Smoking (ref: No) Yes	1.34	(1.01–1.77)	0.044
Alcohol drinking (ref: No) Yes	1.1	(0.79–1.54)	0.574
Physical activity (ref: No) Yes	1.2	(0.98–1.47)	0.082
BMI (ref: 18.5≤BMI<24)			
BMI<18.5	0.49	(0.18–1.35)	0.166
24≤BMI<27	0.98	(0.78–1.24)	0.854
BMI≥27	1.34	(1.04–1.72)	0.025
Hypertension (ref: No) Yes	1.55	(1.24–1.94)	<0.001
Hyperlipidemia (ref: No) Yes	1.69	(1.35–2.12)	<0.001
Atrial fibrillation (ref: No) Yes	0.87	(0.30–2.49)	0.794
Tea consumption (ref: No) Yes	0.78	(0.63–0.97)	0.028
Coffee consumption (ref: No) Yes	0.98	(0.79–1.22)	0.881
Diet Type (ref: Omnivore)			
Lacto-ovo vegetarian	1.2	(0.57–2.50)	0.630
Strict vegetarian	0.65	(0.42–0.99)	0.048

Abbreviations: T2D, type 2 diabetes; OR, odds ratio; CI, confidence interval; BMI, body mass index; AA and AG+GG, genotypes of rs17367504 polymorphism; yr, year.

T2D, and 1.03 (CI, 0.66–1.60) in AG+GG individuals with T2D.

Discussion

In our study, we linked genetic data in TWB to the electronic health records in the NHIRD. Our analyses

Table 3 Peripheral Vascular Disease Risk in Study Participants According to rs17367504 Genotypes

	rs17367504 (AA)			rs17367504 (AG+GG)		
	OR	95% CI	p-value	OR	95% CI	p-value
T2D (ref: No) Yes	1.75	(1.35–2.26)	<0.001	0.94	(0.56–1.58)	0.811
Sex (ref: Female) Male	0.63	(0.48–0.84)	0.001	0.55	(0.33–0.90)	0.019
Age, yr (ref: 30 to 39)						
40 to 49	1.61	(0.94–2.75)	0.081	3.32	(1.24–8.92)	0.017
50 to 59	2.96	(1.80–4.88)	<0.001	5.27	(2.00–13.93)	0.001
60 to 70	4.88	(2.93–8.14)	<0.001	5.73	(2.07–15.86)	0.001
Smoking (ref: No) Yes	1.44	(1.05–1.98)	0.025	1.00	(0.54–1.86)	1.000
Alcohol drinking (ref: No) Yes	0.93	(0.63–1.37)	0.710	1.94	(0.99–3.80)	0.054
Physical activity (ref: No) Yes	1.28	(1.02–1.62)	0.037	1.01	(0.66–1.55)	0.956
BMI (ref: 18.5≤BMI<24)						
BMI<18.5	0.52	(0.16–1.65)	0.265	0.44	(0.06–3.34)	0.428
24≤BMI<27	0.97	(0.74–1.26)	0.792	1.02	(0.63–1.63)	0.952
BMI≥27	1.55	(1.16–2.06)	0.003	0.77	(0.43–1.37)	0.372
Hypertension (ref: No) Yes	1.39	(1.08–1.79)	0.012	2.31	(1.44–3.72)	0.001
Hyperlipidemia (ref: No) Yes	1.76	(1.36–2.28)	<0.001	1.50	(0.94–2.39)	0.093
Atrial fibrillation (ref: No) Yes	0.77	(0.23–2.58)	0.666	1.49	(0.17–12.84)	0.716
Tea consumption (ref: No) Yes	0.85	(0.67–1.09)	0.196	0.56	(0.35–0.91)	0.019
Coffee consumption (ref: No) Yes	0.99	(0.77–1.26)	0.924	1.00	(0.64–1.57)	0.993
Diet Type (ref: Omnivore)						
Lacto-ovo vegetarian	0.80	(0.29–2.23)	0.668	2.56	(0.86–7.63)	0.092
Strict vegetarian	0.60	(0.37–0.98)	0.040	0.90	(0.38–2.15)	0.818

Note: The p-value for the interaction between rs17367504*diabetes is 0.0076.

Abbreviations: T2D, type 2 diabetes; OR, odds ratio; CI, confidence interval; BMI, body mass index; AA and AG+GG, genotypes of rs17367504 polymorphism; yr, year.

indicated that PVD was independently associated with T2D but not the rs17367504 variant of the *MTHFR* gene. Despite these associations, both variables had an interactive effect on PVD risk. In our stratified models, we observed that T2D together with the AA (but not AG+GG) genotype was associated with increased risk of PVD among TWB individuals aged 30 to 70 years.

About 6.4% of adult population in Taiwan (n = 18,523,400) has T2D.³⁴ Tseng's previous findings suggested a higher prevalence (10%) of PVD among patients with T2D in Taiwan.³⁵ In the current study, we found that individuals with T2D were 1.5 times more likely to have PVD than those without the disease. To understand the genetic basis of PVD in Taiwan, we included the rs17367504 variant within the *MTHFR* gene in our analysis models. This gene is located on

Table 4 Peripheral Vascular Disease Risk Based on rs17367504 Genotype and the Presence or Absence of T2D

	OR	95% CI	p-value
rs17367504 genotype and disease status (ref: AA & no T2D)			
AA & T2D	1.77	(1.38–2.28)	<0.001
AG+GG & no T2D	1.18	(0.91–1.55)	0.215
AG+GG & T2D	1.03	(0.66–1.60)	0.892

Note: Adjusted for age, sex, smoking, alcohol drinking, physical activity, BMI, hypertension, hyperlipidemia, atrial fibrillation, tea and coffee consumption, and diet type.

Abbreviations: T2D, type 2 diabetes; OR, odds ratio; CI, confidence interval; BMI, body mass index; AA and AG+GG, genotypes of rs17367504 polymorphism; yr, year.

chromosome 1p36.3 and catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which is used for the remethylation of homocysteine to methionine.^{36,37} We chose the rs17367504 variant because of its association with hypertension, which shares a common pathway with T2D.³⁸ Both factors are known to influence PVD, as stated earlier. We found that T2D was associated with increased risk of PVD, particularly in AA genotype carriers of rs17367504. Our findings provide useful insights into the association of this variant with PVD in Taiwan. Despite this, the possible mechanisms mediating the interaction between T2D and rs17367504 on PVD susceptibility still need to be clarified. According to a previous meta-analysis, this variant has been widely explored in Europe but not Asia.³⁹ Further genomic studies would help to clarify the role of rs17367504 in disease pathogenesis in Asian populations.

We also found strong associations between PVD and hypertension, hyperlipidemia, smoking, obesity, and older age, most of which are potential risk factors for the disease.³ After stratification by rs17367504 genotypes, we observed that smoking, obesity, and hyperlipidemia remained significantly associated with PVD, especially in those with AA (but not AG+GG) genotype. However, hypertension was a risk factor irrespective of the genotype.

Our findings also indicated that individuals between the ages of 50 and 70 were more likely to develop the disease no matter the genotype. However, among those aged 40–49 years, only those with the combined AG+GG genotype were associated with an increased risk of the disease. According to a prior study, the prevalence of PVD rose sharply (about 20%) in men aged 80 years and older.⁴⁰ Taiwan Biobank data collection is restricted to adults between the age of 30 and 70. Therefore, we could not determine the genetic basis of those over 80. Another limitation of our study is that we used a blood pressure-associated variant. More replication studies are necessary to

substantiate our findings. Finally, diabetes and control groups were not matched by age and sex. Despite these limitations, the main strength of our study is the possession of genetic data from over nine thousand individuals.

Conclusion

Our study is the first to suggest an association between T2D and PVD susceptibility among Taiwanese adults with the *MTHFR* rs17367504 genetic variant. Our data indicated that among Taiwanese adults with the rs17367504 variant, those with T2D carrying the AA genotype are more likely to develop PVD. These findings may be relevant for studies assessing the importance of genetic determinants of PVD.

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Disclosure

The authors report no conflicts of interest in this work.

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