Factor XII 46C → T Gene Polymorphism in Chilean Subjects with Coronary Artery Disease and Controls

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Key Words

F12 gene • Coagulation factors • Coronary artery disease • C46T polymorphism

Abstract

Objective: To investigate the possible association between *factor XII (F12)* gene variant and the presence of coronary artery disease (CAD) in Chilean subjects. **Methods:** A total of 112 unrelated patients with a diagnosis of CAD confirmed by angiography (33–74 years old) and 107 healthy controls (30–68 years old) were included in this study. PCR-RFLP was used to evaluate the 46C → T polymorphism of the *F12* gene. **Results:** The genotype distribution for the 46C → T variant of the *F12* gene in CAD patients (CC: 41%, CT: 39%, TT: 20%) and controls (CC: 38%, CT: 48%, TT: 14%) was comparable ($p = 0.365$). Similarly, the allelic frequency was equivalent ($p = 0.833$). The odds ratio for CAD associated with the mutated 46T allele was 1.06 (95% CI = 0.72–1.56) confirming the absence of an association. **Conclusion:** This study showed that the *F12* 46C → T gene polymorphism is not related to CAD in the studied population. However, this study is limited by its sample size and the use of controls not matched by age and sex.

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Introduction

Coronary artery disease (CAD) is the main cause of mortality in Chile [1]. Although there is substantial evidence that genetic factors contribute to CAD [2], a small number of such studies have been carried out in Chile [3, 4]. To date different genes have been related to CAD, among them, the genes encoding the coagulation factors [5–7].

Common genetic variants at factors I, II, V, VII and XIII have been associated with cardiovascular diseases in several populations [8, 9]. In addition, a common polymorphism at the *factor XII (F12)* gene, 46C → T (rs1801020), has been related to CAD risk [10–12]. Santamaría et al. [11, 12] reported that the homozygosity for the T allele of the 46C → T polymorphism of the *F12* gene increased the risk of ischemic stroke and acute CAD. Similarly, the WOSCOPS study showed that individuals carrying the mutated T allele have a high risk of developing acute coronary disease [10]. In addition, Tirado et al. [13] showed that the 46C → T polymorphism is an independent risk factor for venous thrombosis.

However, these findings are not in accordance with previous observations of Endler et al. [14, 15], who suggested that the presence of the T allele for the 46C → T

polymorphism at *F12* could represent a protective factor for CAD considering that this genetic variation is associated with decreased F12 activity [15]. In view of these contradictory results, the aim of the present study was to evaluate the possible association between the 46C → T gene polymorphism of the *F12* gene and CAD in Chilean subjects.

Subjects and Methods

Subjects

The *F12* polymorphism was analyzed in 112 unrelated Chilean patients (83 men and 29 women), ages 33–74 years, with a diagnosis of CAD documented by angiography (coronary artery stenosis >70%), admitted to the Cardiology Service of the Hernán Henríquez Hospital of Temuco city, Chile. For the control group consisting of 107 unrelated individuals (61 men and 46 women), ages 30–68 years, from Temuco city, we used a structured questionnaire to identify disease-free controls and to exclude subjects who were suspected of having any form of vascular disease. Controls with a familial history of CAD, determined by interviewing, were also excluded from the study.

Demographic data and history of hypertension, diabetes mellitus, cigarette smoking, and hypercholesterolemia were assessed in each subject. In both groups, there was no preselection of serum lipid levels. Subjects with a history of diabetes or basal glycemia ≥ 126 mg/dl were defined as diabetic. The study protocol was approved by the ethics committee of our university, and all subjects gave written informed consents.

Serum Measurements

Biochemical measurements were determined from blood samples collected by venipuncture after overnight (>12 h) fast. Previously described enzymatic methods [3] were used to determine the levels of serum glucose, uric acid, triglycerides, total cholesterol and high-density lipoprotein cholesterol (HDL-C). Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald equation when the triglyceride concentrations did not exceed 400 mg/dl.

DNA Analysis

Genomic DNA was extracted from blood leukocytes by a salt-ing-out method optimized by Salazar et al. [16]. The 46C → T polymorphism of the *F12* gene was detected using PCR followed by enzymatic restriction according to conditions described by Zito et al. [17]. The correct assessment of genotypes for the 46C → T polymorphism of the *F12* gene was evaluated using a homozygous sample for the restriction site as a positive control. In addition, all gels were reread blindly by two persons (J.C. and L.A.S.) without any change, and 10% of the analyses were repeated randomly.

Statistical Analysis

Statistical analysis was carried out using the Sigma Stat Software, ver. 2.0 (Jandel Sci., San Rafael, Calif., USA). Data are presented as mean $\pm$ SD. The Student t test or one-way ANOVA was used to evaluate differences between the means of continuous

variables. The allelic frequencies and genotype distribution were estimated by gene counting. Multiple comparisons were performed by the Tukey method. Differences between noncontinuous variables, and Hardy-Weinberg equilibrium were tested by χ^2 analysis. ORs and their 95% CIs associated with the mutated 46T allele were also calculated. Statistical significance was set at $p < 0.05$.

Results

Clinical Variables

The clinical, anthropometric and laboratory characteristics of the study subjects are given in table 1. The CAD subjects had an elevated body mass index (BMI) and a higher prevalence of traditional risk factors for CAD, including smoking, diabetes, hypertension, hypercholesterolemia and familial history of CAD ($p < 0.001$). The baseline serum concentrations of triglycerides, glucose and uric acid were higher in CAD patients than controls. In addition, CAD subjects presented lower HDL-C levels ($p < 0.001$). There was no significant difference in the mean serum concentrations of total cholesterol and LDL-C between the CAD and control groups ($p = 0.053$). Similarly, there was no significant difference in the mean values of diastolic and systolic blood pressures between CAD and control subjects ($p = 0.156$ and 0.235 , respectively).

Allele Frequencies

The genotype distribution and the relative allele frequency of the 46C → T polymorphism of the *F12* gene in CAD patients and controls are given in table 2. For both groups, CAD and control subjects, the distribution of genotypes was as expected from the Hardy-Weinberg equilibrium (CAD patients: $\chi^2 = 3.48$, $p = \text{NS}$; controls: $\chi^2 = 0.018$, $p = \text{NS}$). The genotype distribution for the 46C → T polymorphism in CAD patients and controls was similar ($p = 0.365$). Similarly, the allelic frequency was equivalent in both groups ($p = 0.833$). Moreover, the OR for CAD related to the 46T allele was 1.06 (95% CI = 0.72–1.56) confirming the absence of an association. A possible association between the 46C → T polymorphism and traditional risk factors for CAD was also explored. We observed that the individuals carrying the TT genotype exhibited a higher BMI and higher levels of uric acid when compared to other genotypes (table 3). A comparison of various studies involving mostly Caucasians with our study (Amerindians) is given in table 4.

Table 1. Clinical and demographic characteristics of the Chilean subjects with CAD (n = 112) and controls (n = 107)

	CAD	Controls	p
Age, years	59.7 ± 9.9	41.8 ± 9.4	<0.001
Male, %	74	56	0.007
Diabetes, %	39	5	<0.001
SBP, mm Hg	129 ± 21	125 ± 21	0.235
DBP, mm Hg	77 ± 11	80 ± 16	0.156
BMI	27.6 ± 4.9	25.5 ± 3.3	<0.001
Smoking, %	64	41	0.001
Hypercholesterolemia, %	80	20	<0.001
Hypertension, %	79	26	<0.001
Angina, %	77	0	<0.001
AMI, %	64	0	<0.001
Family history of CAD, %	36	0	<0.001
Diseased vessels, %			
Single vessel	32.2	0	–
Double vessel	27.6	0	–
Triple vessel	40.2	0	–
Total cholesterol, mg/dl	184 ± 54	198 ± 53	0.053
LDL-C, mg/dl	116 ± 37	115 ± 42	0.913
HDL-C, mg/dl	32 ± 8	52 ± 12	<0.001
Triglycerides, mg/dl	182 ± 193	136 ± 96	0.029
Fasting glucose, mg/dl	112 ± 42	96 ± 40	0.005
Uric acid, mg/dl	5.6 ± 1.6	4.5 ± 1.5	<0.001

BMI = Body mass index; DBP = diastolic blood pressure; SBP = systolic blood pressure; AMI = acute myocardial infarction. p values from Student's t test or χ^2 test.

Table 2. Genotype distribution and relative allele frequencies of the 46C → T polymorphism of the *F12* gene in Chilean subjects with CAD (n = 112) and controls (n = 107)

	Genotype			Allele	
	CC	CT	TT	C	T
CAD	46 (41%)	44 (39%)	22 (20%)	0.607	0.393
Controls	41 (38%)	51 (48%)	15 (14%)	0.622	0.378
	$\chi^2 = 2.01$; d.f. = 2; p = 0.365			$\chi^2 = 0.04$; d.f. = 1; p = 0.833	

Discussion

In several studies [10–14], the association between the 46C → T polymorphism of the *F12* gene and cardiovascular diseases has been investigated. However, the results are controversial. In the present study, we have investi-

Table 3. Clinical and demographic characteristics of subjects with CAD according to the 46C → T genotypes of the *F12* gene

	CC (n = 46)	CT (n = 44)	TT (n = 22)	p
Age, years	60 ± 7	58 ± 12	63 ± 12	0.565
Diabetes, %	35	31	25	0.732
SBP, mm Hg	128 ± 18	128 ± 18	136 ± 21	0.341
DBP, mm Hg	76 ± 13	77 ± 9	79 ± 11	0.570
BMI	28 ± 3.9	27.1 ± 3.7	30.7 ± 5.9	0.032
Hypercholesterolemia, %	70	62	50	0.314
Hypertension, %	70	58	55	0.391
Diseased vessels, %				
Single vessel	26	22	20	
Double vessel	15	29	20	0.679
Triple vessel	35	29	30	
Total cholesterol, mg/dl	187 ± 51	176 ± 42	196 ± 78	0.356
LDL-C, mg/dl	117 ± 39	115 ± 36	117 ± 37	0.968
HDL-C, mg/dl	33 ± 8	32 ± 8	31 ± 9	0.791
Triglycerides, mg/dl	193 ± 157	143 ± 85	254 ± 368	0.105
Uric acid, mg/dl	5.3 ± 1.4	5.4 ± 1.8	6.5 ± 1.4	0.018

DBP = Diastolic blood pressure; SBP = systolic blood pressure. p values from one-way ANOVA or χ^2 test. Comparisons by the Tukey method: BMI, TT vs. CT (p = 0.025), TT vs. CC (p = 0.088); uric acid, TT vs. CT (p = 0.029), TT vs. CC (p = 0.021).

gated, for the first time in Chile, the possible association between the *F12* 46C → T polymorphism and CAD.

The observed higher serum levels of triglycerides, glucose and uric acid in CAD subjects compared with controls and the lower HDL-C concentrations confirmed the well-known associations between traditional risk factors and CAD. However, the concentrations of total cholesterol and LDL-C were similar in CAD subjects and controls probably due to statin therapy in CAD patients.

Our data also showed that the 46C → T polymorphism of the *F12* gene is not associated with CAD in Chilean subjects as the frequency of the 46T allele was similar in CAD and control subjects (39.3 vs. 37.8%). This finding is similar to others [18–21]. Orth et al. [18], in Germany, found no evidence that the 46C → T polymorphism is associated with CAD or thrombophilia. Likewise, Colhoun et al. [19] failed to establish an association between this polymorphism and coronary artery calcification in diabetic subjects and controls. Kohler et al. [20] did not find an association either between the 46C → T polymorphism and CAD. Recently, Bach et al. [21], in a hospital-based cohort study that evaluated 2,615 patients undergoing coronary angiography and 572 controls, did not

Table 4. Comparison of different studies investigating the 46C → T polymorphism of the *F12* gene

Reference	Study design	Cases/ controls	Ethnicity	CVD diagnosis	Frequency of 46T, cases/controls	Association with CVD
Zito et al. [10]	case-control ¹	441/990	Caucasian	fatal or non-fatal MI ²	0.29/0.26	yes ³
Santamaría et al. [11]	case-control ⁴	205/231	Caucasian	ischemic stroke ⁵	0.22/0.20	yes
Santamaría et al. [12]	case-control	174/211	Caucasian	acute CAD ⁶	0.23/0.20	yes
Endler et al. [14]	case-control	303/325	Caucasian	CAD ⁷	0.26/0.27	yes ⁸
Kohler et al. [20]	case-control	266/185	Caucasian	CAD ⁹	0.27/0.30	no
Bach et al. [21]	case-control	2,043/572	Caucasian	stable CHD, MI, ACS	0.25/0.23	no
Roldán et al. [22]	case-control	281/550	Caucasian	MI ¹⁰	0.18/0.21	yes
Present study	case-control	112/107	Amerindian	CAD ¹¹	0.39/0.38	no

CVD = Cardiovascular disease; MI = myocardial infarction; CHD = coronary heart disease; ACS = acute coronary syndromes.

¹ Matched by age and smoking habit.

² Individuals who, during the course of the (average) 4.8- to 5-year follow-up, experienced a definitive or suspect fatal or nonfatal MI, sudden coronary death or required coronary artery bypass graft or angioplasty were defined as cases.

³ Associated with a high risk of CHD in men with high cholesterol levels.

⁴ Matched by age, gender and ethnic origin.

⁵ Subjects who had at least 1 episode of ischemic stroke.

⁶ Acute CAD was confirmed on the basis of definitive ischemia or necrosis of the myocardium.

⁷ CAD with or without ACS.

⁸ The homozygosity of the T allele in patients with CAD + ACS is a protector factor.

⁹ CAD based on the presence of ≥50% stenosis in a major coronary artery or one of their branches.

¹⁰ Patients with acute MI before 45 years.

¹¹ CAD documented by angiography (coronary artery stenosis >70%).

observe any association between *F12* genotypes and clinical phenotype of cardiovascular diseases.

However, other studies have shown an association between the 46C → T polymorphism of the *F12* gene and CAD [10–14, 22–25]. Zito et al. [10] observed that this polymorphism is associated with a high risk of coronary disease in men with elevated levels of cholesterol. Roldán et al. [22] observed a synergistic association between hypercholesterolemia and the 46C → T *F12* polymorphism for developing premature myocardial infarction in Spanish subjects.

Soria et al. [23] and Tirado et al. [13] have reported that the 46C → T polymorphism is a genetic risk factor for thrombotic disease in a Spanish population. Recently, Cochery-Nouvellon et al. [24] observed that the homozygosity for the 46C → T polymorphism of the *F12* gene is a risk factor for venous thrombosis during the first pregnancy. Reuner et al. [25] have suggested that the 46C → T polymorphism may be a new independent risk factor for cerebral venous thrombosis, and that this genetic variant should be added to the panel of established risk factors. On the contrary, Endler et al. [14] suggested that the presence of the 46T allele protects against the development of acute coronary syndrome in patients with preexisting CAD.

Studies analyzing the possible role of gene variants and their respective gene products in cardiovascular diseases have often produced conflicting results. According to Bach et al. [26], the reasons for these discrepancies include the differences in study design, the definition of inclusion and exclusion criteria and the number and ethnicity of the subjects. The analysis of different studies investigating the association between the 46C → T polymorphism of the *F12* gene and cardiovascular disease (table 4) showed significant differences between the diagnostic criteria and study design. The contradictory results could be explained, at least in part, by undetected ethnic admixture in the cases and/or controls that falsely distorts allele frequencies in some situations. In a recent study [27], a significant interethnic allelic variation for the 46C → T polymorphism of the *F12* gene was described across populations, with a higher allele frequency in African-Americans (46%) and a minor frequency in Caucasians (22%) [27]. Gene-gene and gene-environmental interactions could also explain the contradictory results of the association between the 46C → T polymorphism of the *F12* gene and CAD. There exists evidence which emphasizes the importance of these interactions in circulatory disorders [28].

In addition, we evaluated possible associations between the *F12* 46C → T polymorphism and traditional risk factors for CAD. We observed that CAD patients carrying the homozygous TT genotype exhibited a higher BMI and higher serum levels of uric acid. Previous studies [29, 30] reported that F12a (activated form of F12) levels were significantly correlated with BMI, age, cholesterol, triglycerides and uric acid levels. Endler et al. [15] and Zito et al. [10, 17] reported that the 46C → T polymorphism is a determinant of F12 activity. In these studies, the T allele for the 46C → T polymorphism was associated with lower plasma F12a. The reduced fibrinolysis as a consequence of lower plasma F12a may be the mechanism leading to higher risk of CAD. However, in our study, we did not measure F12 activity. This limitation confines the discussion of our findings.

Conclusion

The present study suggests that the 46C → T polymorphism of the *F12* gene is not associated with CAD in Chilean individuals. However, this study is restricted by its sample size and the use of controls not matched by age and sex.

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