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1 . 1 . 2 . 3 . 1

Fibrinogen, Factor VII and Plasminogen Activator Inhibitor-1 Genotypes and the Risk of Coronary Artery Disease

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Objective : The aims of this study were to investigate the extent to which specific known polymorphisms of fibrinogen, factor VII (FVII) and PAI-1 genes are associated with their respective plasma levels. And also we examined whether these genotypes were linked to coronary artery disease (CAD).

Methods : We performed a case-control study of 165 patients which included 156 CAD and 9 peripheral artery obstructive disease and 188 healthy controls without a history of cardiovascular disease. The four polymorphisms of fibrinogen (-455G/A, 448Arg/Lys), FVII (353Arg/Gln) and PAI-1 (4G/5G) gene were measured, together with their plasma levels.

Results : There was a difference between patients and controls in the frequency of the fibrinogen 448Lys allele (0.206 vs 0.106, $P < 0.001$), but there were no significant frequency differences in fibrinogen -455A (0.537 vs 0.529), FVII 353Gln (0.079 vs 0.080) and PAI-1 4G (0.146 vs 0.113) Allele. Plasma fibrinogen

level was higher in patients (372.8 ± 112.0 mg/dL) than in controls (300.4 ± 70.9 mg/dL) and patients with genotype 448LysLys (457.8 ± 134.4 mg/dL) or 448ArgLys (397.3 ± 120.8 mg/dL) had higher fibrinogen levels than those with β 448ArgArg (354.9 ± 102.3 mg/dL). Using multivariate logistic regression, the 448 ArgLys or LysLys genotype was associated with over twice the risk of CAD (odds ratio 2.25) compared with the 448ArgArg genotype. Hypertension is more potent risk factor for the person who has the 448Lys allele of fibrinogen.

Conclusions : These data provide evidence that a polymorphism of the fibrinogen 448Arg/Lys is associated with an increased risk of CAD and that hypertension is more potent risk factor for CAD in person who have the 448Lys allele of fibrinogen. (*Korean J Hematol 2001;36:79-89*)

Key Words : Fibrinogen, Factor VII, PAI-1, Polymorphism, Coronary artery disease

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(coronary artery disease)

¹⁾ (fibrinogen), VII (FVII), plasminogen activator inhibitor-1 (PAI-1), tissue type plasminogen activator (t-PA), von Willebrand factor

²⁾ 가 가

³⁾ 50 kb , , 37가
4

⁴⁾ RsaI (312Thr/Ala), HindIII (-148C/T), HaeIII (-455A/G), Alu (-488C/T), MnlI (488Arg/Lys), AvaII (1688T/G), BclI (3' flanking region), ⁵⁾ HaeIII, AluI, MnlI BclI (allele)가

가 가 ,
가 가
가 ^{3, 6 8)}

FVII 13 ⁹⁾
FVII 353Arg/ Gln,
(promoter) 10 (-323ins 10), intron 7
variable number of tandem repeat (VNTR)

¹⁰⁾ 353Arg/ Gln 353Gln 가
FVII 가 20 25%
가 가

^{3, 11, 12)} PAI-1 plasminogen activator
12.2kb 7
PAI-1 HindIII (3' re-
gion), intron 3 CA dinucleotide repeat,
4G/ 5G ^{13, 14)} 4G/ 5G

4G PAI-1 가
가 가 가
^{3, 13, 15)}

(multifactorial) ¹⁶⁾
가

¹⁷⁾ RsaI MnlI
¹⁸⁾ FVII 353Arg/ Gln , PAI-1 4G/ 5G
^{19, 20)}

-455A/ G (HaeIII)
448Arg/ Lys (MnlI) , FVII 353Arg/ Gln
, PAI-1 4G/ 5G

, FVII PAI-1

1.
156
9 (Table 1, 2).

Table 1. Characteristics of the study populations

Parameters	Patients (n=165)	Controls (n=188)	P-value*
Age (years)	59.9 ± 9.6	58.3 ± 9.1	0.108
Male : Female (n)	121 : 44	109 : 79	0.003
BMI (kg/m ²)	24.2 ± 2.6	23.9 ± 2.6	0.263
Smokers (n)	108	92	0.001
Hypertension (n)	93	46	<0.001
Diabetes mellitus (n)	58	20	<0.001
Triglycerides (mg/dL)	143.7 ± 81.4	157.3 ± 95.9	0.166
Total cholesterol (mg/dL)	197.4 ± 44.2	201.0 ± 42.7	0.434
HDL-C (mg/dL)	42.2 ± 11.1	51.7 ± 12.5	<0.001
LDL-C (mg/dL)	125.7 ± 37.7	118.6 ± 38.9	0.089
Total cholesterol/LDL-C	4.97 ± 1.87	4.03 ± 0.97	<0.001
Fibrinogen (mg/dL)	372.8 ± 112.0	300.4 ± 70.9	<0.001
Factor VII (%)	124.0 ± 30.0	126.7 ± 27.9	0.388
PAI-1 (ng/mL)	13.3 ± 12.3	11.5 ± 8.7	0.112

* Chi-square test for categorical and t-test for continuous variables were used

Values are given as mean ± SD or number of subjects
Abbreviations : BMI, body mass index; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol

Table 2. Plasma levels (mean±SD) of PAI-1, factor VII and fibrinogen according to the clinical diagnosis and the extent of coronary stenosis in the patient population

	n	Fibrinogen (mg/dL)	Factor VII (%)	PAI-1 (ng/mL)
Clinical diagnosis				
Stable angina	72	352.2±95.2	127.4±30.8	12.4±9.7
Unstable angina	59	372.7±113.4	125.0±30.8	14.1±15.9
Acute myocardial infarct	25	407.5±137.7	112.8±19.9	12.9±7.5
PAOD		442.1±115.4	121.4±38.2	18.0±15.7
<i>P</i> -value*		0.039	0.213	0.588
Degree of coronary stenosis				
minimal vessel disease	14	356.9±141.3	135.0±29.0	12.3±9.8
single vessel disease	51	364.2±111.1	123.4±29.1	13.4±16.5
double vessel disease	42	358.4±83.5	122.5±29.7	14.3±10.3
triple vessel disease	49	385.9±122.6	123.2±30.5	12.1±8.6
<i>P</i> -value†		0.251	0.719	0.725

* One-way analysis of variance was performed in total patient population (n=165)

† One-way analysis of variance was performed in patients with coronary artery disease (n=146)

Abbreviation : PAOD, peripheral artery obstructive disease

72, 59, Stago, France) PAI-1
 25, ELISA kit Imulyse™ fibrin (Biopool, Sewden)
 1, 2)
 3)
 21) 30 (high density lipoprotein-cholesterol, HDL-C) Hitachi 747 (Hitachi, Nakashi, Japan)
 Q, CK-MB 2 (low density lipoprotein-cholesterol, LDL-C) Friedewald
 22) 50%
 23)
 3) -455A/G 448Arg/Lys, FVII
 353Arg/Gln, PAI-1 4G/5G
 Genomic DNA Easy-DNA kit (Invitrogen, USA)
 (minimal vessel) 가 (PCR), FVII PAI-1
 3 (primer) (,)
 188) PCR
 5, 24, 25) thermocycler GeneAmp PCR
 9600 (Perkin Elmer, USA)
 455A/G 448Arg/Lys HaeIII, MnlI
 3%, 2.5% agarose gel
 1) PAI-1, FVII
 0.129 M trisodium citrate 가 UV transilluminator -455A/
 2,500 xg 15, G -455G 575 383 bp, -455A
 -70 958 bp 448Arg/Lys
 FVII STA Fibrinogen Factor 150 63 bp 488Arg,
 VII Deficient Substrate Plasma (Diagnostica Stago, 340 bp 488Lys .⁵⁾ FVII
 France) STA (Diagnostica 353Arg/Gln 312 bp MspI

205, 67, 40 bp 353Arg 272, 40 bp
 353Gln .²⁴⁾ PAI-1
 287 bp 4G
 5G 178 bp
 .²⁵⁾

4) , ,
 (body mass index, BMI), , FVII
 PAI-1 , , HDL-C, LDL-
 C *t-* , FVII PAI-1
 , FVII PAI-1
 positive skewness가

Hardy-Weinberg
²⁶⁾ -
 , FVII PAI-1
 (covariate)
 가

가
 , BMI, ,
 FVII
 가
 (-455AG/
 GG vs -455AA; 448ArgLys/LysLys vs 448ArgArg;
 353ArgGln/ GlnGln vs 353ArgArg)

448Arg/ Lys (, HDL-C)
 448Arg/ Lys 가
 , FVII PAI-1 , BMI,
 Pearson
 Window SAS version 6.12
 , *P* 0.05 가

1. , FVII, PAI-1
 BMI
 (Table 4).

,
 (Table 1).
 , LDL-C
 HDL-C
 FVII

PAI-1
 FVII PAI-1
 , 가 ,
 (Table 2).
 FVII PAI-1
 . (338.7 ±
 104.4 mg/dL)가 (328.8 ± 93.8 mg/dL)
 (*P*=0.372).

PAI-1 (, 13.0 ± 11.6; 11.3 ±
 8.2 ng/mL) (, 334.0 ± 104.6; , 335.4 ±
 88.6 mg/dL) (*P*=0.151,
P=0.899) FVII (120.7 ± 27.6%)
 (134.3 ± 29.4%) (*P*<0.001).

2. -455A/G 448Arg/Lys, FVII
 353Arg/ Gln, PAI-1 4G/5G

가 Hardy-Weinberg
 가 -
 455A/G 448Arg/Lys (link-
 age disequilibrium) (*D'*=0.85, *P*<0.001).
 -455A (0.146) 가 (0.113)
 488Lys (0.206) (0.106)
 (Table 3). FVII 353Gln
 (0.079) (0.080) 가 , PAI-1
 4G (0.537) (0.529) 가
 , FVII PAI-1
 () .

3. , FVII PAI-1
 -455A/G
 -455GA -455AA가 -455GG
 488Arg/Lys
 (Table 4).

Table 3. Genotype frequencies for fibrinogen (-455G/A, 488Arg/Lys), factor VII (353Arg/Gln) and PAI-1 (4G/5G)

Genotype	% in each group (n)			P-value [‡]
	Patients (165)	Controls (188)	Total (353)	
Fibrinogen [*] -455GG	72.6 (119)	80.1 (149)	76.6 (268)	0.146
-455GA	25.6 (42)	17.2 (32)	21.1 (74)	
-455AA	1.8 (3)	2.7 (5)	2.3 (8)	
Frequency of -455A allele	0.446	0.113	0.29	0.187
Fibrinogen 488ArgArg	61.2 (101)	78.7 (148)	71.1 (249)	<0.001
488ArgLys	36.4 (60)	21.3 (40)	28.6 (100)	
488LysLys	2.4 (4)	0 (0)	1.1 (4)	
Frequency of 488Lys(A) allele	0.206	0.106	0.153	0.001
Factor VII 353ArgArg	84.8 (140)	84.0 (158)	84.4 (298)	0.532
353ArgGln	14.5 (24)	16.0 (30)	15.3 (54)	
353GlnGln	0.6 (1)	0 (0)	0.3 (1)	
Frequency of 353Gln(A) allele	0.079	0.080	0.079	0.961
PAI-1 [†] 5G5G	21.7 (35)	20.9 (39)	21.3 (74)	0.815
5G4G	49.1 (79)	52.4 (98)	50.9 (177)	
4G4G	29.2 (47)	26.7 (50)	27.9 (97)	
Frequency of 4G allele	0.537	0.529	0.533	0.836

^{*}Data on -455AG were missing in 1 patient and 2 controls

[†]Data on 4G/5G were missing in 4 patients and 1 control

[‡]Each genotype and allelic frequency of the patients was compared to those of the controls using a chi-square test

Table 4. Plasma levels (mean±SD) of fibrinogen, factor VII and PAI-1 according to the genotypes

	Genotype	Patients	P-value [*]	Controls	P-value [*]	Total	P-value [*]	
Fibrinogen (mg/dL)	-455GG	362.7±104.2	0.165	295.7±72.7	0.214	325.7±94.2	0.008	
	-455GA	399.4±133.2		322.1±63.3		365.9±114.7		
	-455AA	391.3±53.3		395.8±51.9		331.6±69.2		
	Factor VII (%)	488ArgArg	354.9±102.3	0.020	297.3±72.5	0.311	320.9±90.3	<0.001
		488ArgLys	397.3±120.8		311.8±64.4		363.1±110.0	
		488LysLys	457.8±134.4		-		457.8±134.4	
PAI-1 (ng/mL)	353ArgArg	124.3±31.0	0.171	129.1±28.0	0.006	126.9±29.5	0.013	
	353ArgGln	119.7±21.4		113.6±24.0		116.3±22.9		
	353GlnGln	179.0		-		179.0		
PAI-1 (ng/mL)	5G5G	12.9±11.4	0.973	11.6±10.5	0.133	12.2±10.9	0.415	
	5G4G	13.6±14.3		10.4±7.2		11.8±11.0		
	4G4G	13.8±9.7		13.3±9.5		13.6±9.5		

^{*}One-way analysis of covariance (with age as covariate) was performed to test whether genetic variation was associated with plasma level of hemostatic factor

488ArgLys
 488LysLys 가 488ArgArg 4.
 가 .
 FVII 353ArgGln 353ArgArg
 353GlnGln FVII ,
 PAI-1 PAI-1 가 3.74 , 가 3.51 ,
 HDL-C (<35 mg/dL) 가 4.94
 (Table 5). , FVII PAI-1
 (SD) 99.2 mg/dL, 28.9%

Table 5. Risk factors of coronary artery disease in univariate or multivariate logistic regression analysis

Risk factors	Odds ratio (95% confidence interval)		
	Univariate analysis		Multivariate analysis [†]
Age (years)	0.98	(0.96 1.00)	0.99 (0.96 1.01)
Sex (male vs female)	1.08	(0.70 1.67)	0.68 (0.33 1.42)
BMI (<25 vs >25 kg/m ²)	1.07	(0.70 1.65)	1.03 (0.69 1.71)
Smokers (no vs yes)	0.94	(0.61 1.44)	0.83 (0.43 1.61)
Hypertension (no vs yes)	3.96 [†]	(2.52 6.23)	3.74 [†] (1.87 6.62)
Diabetes mellitus (no vs yes)	4.55 [†]	(2.59 8.00)	3.51 [†] (1.87 6.62)
Total cholesterol (<210 vs ≥210 mg/dL)	0.73	(0.47 1.14)	0.81 (0.47 1.39)
HDL-C (<35 vs ≥35 mg/dL)	6.58 [†]	(3.17 13.7)	4.97 [†] (2.22 11.10)
Fibrinogen (per 99.2 mg/dL)	2.65 [†]	(1.94 3.61)	2.46 [†] (1.67 3.63)
Factor VII (per 28.9 %)	0.91	(0.74 1.13)	0.91 (0.68 1.21)
PAI-1 (per 10.6 ng/mL)	1.20	(0.96 1.56)	1.20 (0.89 1.63)
Fibrinogen genotype			
-455GA/AA (base group; -455GG)	1.52 [‡]	(0.93 2.50)	1.72 [‡] (0.98 3.02)
488ArgLys/LysLys (base group; 488ArgArg)	2.35 [‡]	(1.48 3.75)	2.25 [‡] (1.28 3.96)
Factor VII genotype (base group; 353ArgArg)			
353ArgGln/GlnGln	0.94	(0.53 1.68)	0.83 (0.42 1.64)
PAI-1 genotype (base group; 5G5G)			
4G5G	0.83	(0.47 1.41)	0.94 (0.50 1.78)
4G4G	0.96	(0.53 1.75)	1.06 (0.52 2.16)

[†]Adjusted for age, sex, body mass index, and history of hypertension, diabetes, smoking, and acute myocardial infarction

[‡]P<0.001, [†]P<0.05, [‡]P<0.1. Odds ratio for coronary artery disease associated with one standard deviation difference of hemostatic variables
Abbreviation : see Table 1

Table 6. Combined effects of fibrinogen genotype (488Arg/Lys) and hypertension, diabetes and low HDL-C on risk of coronary artery disease

Risk factors	Odds ratio (95% confidence interval) of fibrinogen genotype 488Arg/Lys			
	Univariate analysis		Multivariate analysis*	
	ArgArg	ArgLys or LysLys	ArgArg	ArgLys or LysLys
History of hypertension				
Normotension	1	2.84 [†] (1.54 5.24)	1	2.76 [†] (1.39 5.48)
Hypertension	4.41 [†] (2.56 7.60)	9.79 [†] (4.29 22.30)	4.77 [†] (2.55 8.90)	11.29 [†] (4.56 28.20)
History of Diabetes				
Non-diabetes	1	1.93 [‡] (1.16 3.21)	1	2.37 [‡] (1.32 4.26)
Diabetes	0.58 (0.32 1.05)	3.40 (0.87 13.23)	0.92 (0.48 1.76)	5.33 (0.95 29.90)
HDL-C levels				
Normal HDL-C	1	2.09 [‡] (1.28 3.42)	1	2.40 [‡] (1.35-4.28)
Low HDL-C	0.66 (0.34 1.30)	5.44 (0.60 49.55)	0.79 (0.38 1.65)	5.86 (0.56-60.89)

* Adjusted for age, sex, body mass index, and history of hypertension, diabetes and smoking

[†]P<0.001, [‡]P<0.05, Low HDL-C signifies HDL-C <35.0 mg/dL

Abbreviation : see Table 1

10.6 ng/mL , 가 1 SD 가 1.72 (P< 2.46 0.1) . 488Arg/ 488ArgLys 488LysLys Lys , 488ArgLys 가 488ArgArg 2.25 488LysLys 가 -455GA -488AA 488ArgArg 가

Table 7. Univariate correlations for plasma levels of fibrinogen, factor VII and PAI-1 with continuous variables in all study population (n=353)

	Fibrinogen		Factor VII		PAI-1	
	r	P-value	r	P-value	r	P-value
Age	0.12	0.020	0.10	0.062	-0.11	0.039
BMI	0.07	0.215	0.14	0.010	0.16	0.003
Triglycerides	-0.01	0.802	0.36	<0.001	0.09	0.097
Total cholesterol	0.06	0.263	0.28	<0.001	0.04	0.461
HDL-C	-0.15	0.005	0.07	0.237	-0.09	0.089
LDL-C	0.13	0.018	0.13	0.014	0.03	0.531
Fibrinogen	-	-	0.20	<0.001	0.19	<0.001
Factor VII	-	-	-	-	0.15	0.006

Abbreviation : see Table 1

11.29
(Table 6). 488Arg/Lys
(, HDL-C)

5. , FVII PAI-1
, LDL-C, FVII PAI-1
, HDL-C

(Table 7). FVII BMI, ,
LDL-C, PAI-1 .
PAI-1 BMI ,

-455A/G 448Arg/Lys,
FVII 353Arg/Gln, PAI-1 4G/5G

가 . 488Arg
가 488ArgLys
488LysLys 가 가
488ArgLys 488LysLys 가
488ArgArg 2.25 , 488ArgLys
488LysLys 11.29
. Meilahn 28) 488Lys

Baumann 5) 가

488Arg/Lys
488Lys
-455G/A
3, 6 8)
-455A 가
-455GA 가
-455AA 가
-455GA -488AA 가
1.72
(P<0.1). Lee 2)
-455AA
(0.05<P<0.1)
가
가
2, 8)
가
3, 5, 6 8) 가
가 가
가
가가 가
가 가 2)
가 488ArgLys 488LysLys
가 가
가가 가
가 가
가 가 27)
가
488Arg
488ArgLys 가
488LysLys 가
488ArgArg 2.25 , 488ArgLys
488LysLys 11.29
. Meilahn 28) 488Lys
353Gln FVII
Green 11)
24, 29, 30)
353Gln FVII
가 plasmid FVII

, PAI-1

가

가

가

Lys, VII 353Arg/ Gln, PAI-1 4G/ 5G

가

165 156 9 188

VII PAI-1

(-455A/ G 448Arg/ Lys, FVII 353Arg/ Gln, PAI-1 4G/ 5G)

488Lys (0.206) (0.106) (P< 0.001). -455A (0.537 vs 0.529), FVII 353Gln (0.079 vs 0.080) PAI-1 4G (0.146 vs 0.113)

가 (372.8 ± 112.0 mg/ dL)

가 448ArgLys (397.3 ± 120.8 mg/ dL)

가 448ArgArg (354.9 ± 102.3 mg/ dL)

488ArgLys 488LysLys 가

488ArgArg 2.25

488ArgLys 488LysLys

가 488ArgArg

가

11.29

488Lys 가

가

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