

플라즈미노겐 활성인자 억제제-1 유전자의 4G/5G 다형성이 관동맥 질환에 미치는 영향

강현재 · 한기훈 · 최성준 · 김효수 · 손대원
오병희 · 이명묵 · 박영배 · 최윤식 · 이영우

4G/5G Polymorphism of Plasminogen Activator Inhibitor-1 Gene and Its Effects on Coronary Artery Disease

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ABSTRACT

Background : 4G allele of one base pair insertion/deletion polymorphism (4G/5G) at plasminogen activator inhibitor-1 (PAI-1) was associated with increased plasma activity of PAI-1. Increased plasma PAI-1 activity was associated with increase risk of coronary artery disease (CAD). However, there was a controversy whether 4G allele increases the risk of CAD. We investigated relationship between 4G/5G genetic polymorphism and CAD in Korean population. **Methods** : We studied 453 patients-145 patients with normal coronary angiogram (NL), 106 with stable angina (SA), 104 with unstable angina (UA) and 98 with myocardial infarction (MI)-characterized by coronary angiography. **Results** : 1) Korean had higher 4G allele frequency than Caucasian (4G : 5G = 0.60 : 0.40 in Korean). 2) There were no allele or gene frequency difference of 4G/5G polymorphism between CAD group and NL group (4G : 5G = 0.61 : 0.39 in CAD, 0.59 : 0.41 in NL, $p = 0.58$). 3) 4G allele was not associated with increased risk of acute coronary syndrome (4G : 5G = 0.60 : 0.40 in SA, 0.59 : 0.41 in UA, and 0.57 : 0.43 in MI, $p = 0.84$). 4) 4G allele had no influence on progression of coronary atherosclerosis (4G : 5G = 0.58 : 0.42 in single vessel disease, 0.58 : 0.42 in two vessel disease, and 0.56 : 0.44 in three vessel disease, $p = 0.82$). 5) 4G was not an independent risk factor of CAD even after adjusted with other risk factors. **Conclusion** : In Korean, 4G/5G polymorphism of PAI-1 gene has no relationship with development, progression of coronary artery disease. (Korean Circulation J 1998;28(7):1105-1111)

KEY WORDS : Plasminogen activator inhibitor-1 · 4G/5G polymorphism · Coronary artery disease.

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 601 ECTIM study⁴⁾
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 . PAI - , Ridker PM ¹²⁾ 14,916 가 Phy -
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 4G/5G 4G
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 가 , PAI - 1 가 453 (: 310 , : 143)
 .⁴⁾⁶⁻⁸⁾ 50%
 PAI - 1 가 4G/5G 308 ,
 4G/5G 106 , 104 ,
 . Eriksson P ⁹⁾ 98 .
 1995 45 94
 100 4G 가가 145
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 Mansfield MW ¹⁰⁾ 150
 , Ossei - Gerning N ¹¹⁾ 446
 4G/4G

방 법

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PAI - 1 PAI - 1
675 4G, 5G
PAI - 1
Mansfield

MW 1995
8) 4G 5' - GTC TGG ACA CGT GGG
GG - 3', 5G 5' - GTC TGG ACA CGT GGG
GA - 3', 5' - AAG CTT TTA CCA
TGG TAA CCC CTG GT - 3' 5' - TGC AGC
CAG CCA CGT GAT TGT CTA G - 3'

PCR 25 μ L DNA 25ng, 10 \times
reaction buffer 2.5 μ L (Tris - HCl 10 mmol/L (pH
8.3), MgCl₂ 1.5 mmol/L, KCl 40 mmol/L, DTT 1
mmol/L, BSA 50 g/ml), dNTP 3.75 nmol

4G 5G 17 μ 27 μ
15 pmol, Taq polymerase 1 U
DNA thermal cycler (Perkin - Elmer)

94 1 denaturation, 53 1
annealing, 72 1 extension
4 cycle 30 23
cycle 27 cycle . PCR

1.5% agarose gel

4G, 5G 2
PCR 287
가 4G 5G
178 가
(Figs. 1 and 2).

² - test,
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logistic regression . SAS rel -
ease 6.12 (SAS institute Inc.)

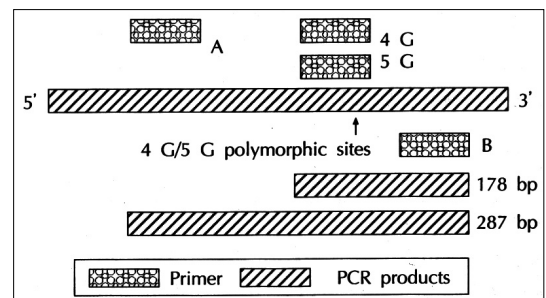


Fig. 1. Scheme of PCR for detection of 4G/5G polymorphism. 4G, 5G : primer for detection of 4G, 5G region, A,B : common primer, 178bp product : product of primer B and 4G or 5G, 287bp product : product of primer A and B.

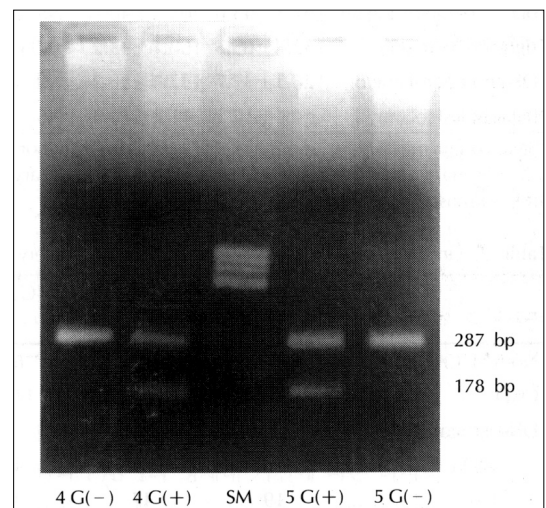


Fig. 2. Results of PCR : We performed two separate polymerase chain reactions for Single sample : first, PCR with one of the allele specific primer (4G or 5G) and two common primers. Then, with another allele specific primer and two common primers.

*Left 2 lanes : with primer designed for detection of 4G region and common primers, Right 2 lanes : with primer designed for detection of 5G region and common primers, SM : size marker.

관동맥 질환의 발생과의 관련성

4G/5G 유전자의 비율

$$453 \quad ($$

$$+ \quad) \quad 4G : 5G$$

$$0.60 : 0.40 \quad ,$$

$$(4G : 5G \quad = 0.50 \sim 0.54 : 0.46$$

$$\sim 0.50) \quad 4G \quad , \quad ^{4)12)13)}$$

$$5G/ \quad 5G : 4G/$$

$$5G : 4G/4G = 0.19 : 0.43 : 0.38 \quad ,$$

Hardy - Weinberg Equilibrium

Body mass index (Table 1). 4G : 5G (308) = 0.59 : 0.41, (145) = 0.61 : 0.39 (p=0.58). 5G/5G : 4G/5G : 4G/4G = 0.18 : 0.46 : 0.36, = 0.20 : 0.38 : 0.42, Hardy - Weinberg Equilibrium (Table 2).

관동맥 질환의 임상상에 따른 비교 (Table 2)

Table 1. Patients characteristics

	Normal CAG	CAD	P-value
Number	145	308	
Age (years old)	53.9 ± 9.5	58.6 ± 9.1	NS
Sex (M : F)	80 : 65	230 : 78	<0.01
Hypertension	13.7%	28.6%	<0.01
Diabetes mellitus	48.0%	49.1%	NS
History of smoking	26.2%	55.9%	<0.01
BMI (kg/m ²)	24.7 ± 3.2	24.4 ± 2.4	<0.01
Total cholesterol (mg/dl)	197.3 ± 43.6	205.7 ± 40.5	NS
Triglyceride (mg/dl)	132.7 ± 65.5	160.1 ± 93.2	<0.05
LDL-cholesterol (mg/dl)	126.5 ± 37.7	132.4 ± 36.2	NS
HDL-cholesterol (mg/dl)	44.4 ± 12.2	41.2 ± 10.9	NS

*BMI : body mass index, normal CAG : patients with normal coronary angiography, CAD : patients with coronary artery disease, NS : P-value 0.05.

$(106 \quad), (104 \quad),$
 $(98 \quad) \quad 4G : 5G$
 $0.60 : 0.40, 0.59 : 0.41, 0.57 : 0.43 \quad$ 가
 $(p=0.84). \quad 5G/5G : 4G/5G : 4G/4G$
 $= 0.17 : 0.45 : 0.38,$
 $= 0.18 : 0.45 : 0.37,$
 $= 0.20 : 0.47 : 0.33 \quad,$
 Hardy - Weinberg Equilibrium

관동맥 경화증의 진행에 따른 비교 (Table 2)

(70) , 1 (114) , 2
 3 (86)
 $4G : 5G$

Table 2. Univariate analysis-Risk factors for coronary artery disease

	5G / 5G	4G / 5G	4G / 4G	<i>P</i> -value	4G	5G	<i>P</i> -value
	(number of patients)				(proportion)		
Normal CAG	29	55	61	NS	0.61	0.39	NS
CAD	55	142	111		0.59	0.41	
Disease category							
CSA	18	48	40	NS	0.60	0.40	NS
UA	19	47	38		0.59	0.41	
MI	20	46	32		0.57	0.43	
Extent of CAD							
1VD	22	51	41	NS	0.58	0.42	NS
2VD	9	38	23		0.58	0.42	
3VD	17	38	31		0.56	0.44	

*CSA : patients with chronic stable angina, UA : patients with unstable angina, MI : patients with myocardial infarction, 1VD : 1 vessel disease, 2VD : 2 vessel disease, 3VD : 3 vessel disease.

PAI - 1
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PAI - 1
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PAI - 1
PAI - 1
PAI - 1
4G/5G
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PAI - 1
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4G/5G
4G/5G
PAI - 1
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PAI - 1
재료 및 방법 :
308
PAI - 1
145
¹³⁾가
, 4G/5G
4G/5G
PAI - 1
결 과 :
1) 453 4G : 5G
0.60 : 0.40 ,
4G
(5G/5G : 4G/5G : 4G/4G=0.19 : 0.43 :
0.38). 2) (CAD : 308)
(NL : 145) 4G/5G
(CAD=0.61 : 0.39, NL=0.59 :
0.41, p=0.58). 3) (SA : 106) ,

(UA : 104), (MI : 98)
 4G : 5G 가
 (SA = 0.60 : 0.40, UA = 0.59 : 0.41, MI = 0.57 :
 0.43, p = 0.84).⁴⁾ 1 (1VD : 114), 2
 (2VD : 70), 3 (3VD : 86
) 4G : 5G
 가 (1VD = 0.58 : 0.42, 2VD =
 0.58 : 0.42, 3VD = 0.56 : 0.44, p = 0.82). 5) 4G
 가 : Odds
 Ratio가 0.90 가
 (95% CI : 0.65~1.24). , , , ,
 , 4G
 가 .
 결 론 :
 PAI - 1 (4G/5G)
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 중심 단어 : - 1 · 4G/5G
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 감사문 _____
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