

PAI-1 유전자 다형성(4G/5G)과 심혈관질환 발생에 관한 정량적 메타분석

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Genetic Polymorphism of PAI-1 Gene and Cardiovascular Disease : Meta-analysis of Case-Control Studies

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ABSTRACT

Background : Previous reports have suggested that alleles at the plasminogen activator inhibitor-1 (PAI-1) gene are associated with increased risk of developing coronary artery disease, including myocardial infarction and stroke through their effect on PAI-1 levels. **Method** : We attempted to search English literatures for all reports of possible effects of PAI-1 gene on cardiovascular disease in human published prior to November 1998. We used a Mantel-Haenszel method (fixed effect model) and random effect model, respectively, to perform a meta-analysis of 7 case-control studies that provided information related to the effects of PAI-1 gene on risk of cardiovascular disease. **Results** : From 7 studies for diagnosed cardiovascular disease, the relative frequencies of the three genotypes among controls was (5G/5G) (homozygous normal), 24.5% ; (4G/5G) (heterozygous), 48.2%, and (4G/4G) (homozygous for the mutant, 675 GGGG), 27.3%. These relative frequencies in cases were 21.7% for 5G/5G, 48.0% for 4G/5G, and 30.3% for 4G/4G. In fixed effect model, compared with those with genotype (5G/5G), the overall odds ratio (OR) for cardiovascular disease among those with (4G/5G) was 1.12 (95% CI, 0.93 to 1.34), and it was 1.20 (1.01 to 1.44) for the (4G/4G) genotype. For five studies with myocardial infarction as the outcome, the overall OR of myocardial infarction was 1.20 (0.99 to 1.47) for those with (4G/5G) and 1.24 (1.00, 1.54) for those with (4G/4G) genotypes, respectively. **Conclusion** : Our findings provide support for the weak association between PAI-1 gene and cardiovascular disease, in particular, myocardial infarction. (**Korean Circulation J 1999;29(4):366-373**)

KEY WORDS : Gene · Cardiovascular disease · Plasminogen activator inhibitor-1 · Meta-analysis.

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서 론

plasminogen activator inhibitor - 1 (PAI - 1) ¹⁾ , ²⁾ 가 ³⁾ . PAI - 1 가 . PAI - 1 가 7 q21.3 - q22 ⁴⁾ 3 CA ⁵⁾ HindIII PAI - 1 ⁵⁾ PAI - 1 promotor (I/D 4G/5G, insertion/deletion) allele 4 gua - nosines(4G) 가 , 5 (5G) 가 ⁶⁾ Promotor 4G가 5G 가 PAI - 1 ⁶⁻⁹⁾ allele가 ⁷⁾ 4G 가 , PAI - 1

Ericksson (1995)⁷⁾ PAI - 1 4G/5G 가 ¹⁰⁾ PAI - 1 4G/5G (quantitative meta - analysis) . 가

대상 및 방법

연구논문의 수집 (MEDLINE) 1998

11 4G/5G PAI - 1, 4G/5G, (ICD 9 410 - 414, ischemic heart disease), (ICD 9 410, myocardial infarction), (ICD 9 430 - 438, cerebrovascular disease) 가 . 7 ¹⁾²⁾⁶⁾⁷⁾⁹⁻¹¹⁾ () 1) , 2) , 3) 분석정보의 추출 (1 ,) , 4G/5G (PCR) , Hardy - Weinberg (equili - brium)

통계적 분석방법 Hardy - Weinberg ²⁾ PAI - 1 4G/5G 가 1 4G/4G 4G/4G (overall odds ratio) (fixed effect model) (random effect model)

(true effect) 가 가 1 . 7 3
 가 , .
 4,536
 .¹²⁻¹⁵⁾ 1,964 , 2,572 .
 PAI - 1 4G/5G
 , 95% , (two tail test) Dawson (1993) 675
 (level of significance), 가
 Joseph Lau가 (Table 2).
 Meta - Analysis
 0.988 (1990 1995) ¹⁶⁾ . 연구 문헌의 Hardy-Weinberg 평형 검정
 결 과 가 Hardy - Weinberg(H - W)
 가 Dawson
 연구 문헌의 정성적 메타분석 결과 (1993)⁵⁾ H - W 가
 7 allele 가 ,
 1993 1998 H - W 가
 (Table 1). 5 , Ye (1995)⁹⁾
 , 1 , 1 H - W H - W
 가 45 가 (Table 3).
 2 70

Table 1. Participants and study design characteristics of 7 case-control studies

Study No.	Authors	Year	Country	Age, years		% of male	Outcomes
				Mean	Range		
1	Dawson et al.	1993	UK	<45	NA	NA	MI
2	Eriksson et al.	1995	Sweden	<45	NA	100	MI
3	Ye et al.	1995	UK	44.5	25.0 - 64.0	100.0	MI
4	Ridker et al.	1997	USA	59.0	NA	100.0	MI
5	Catto et al.	1997	UK	73.0	64.0 - 80.0	49.2	Stroke
6	Ossei-Gerning et al.	1997	UK	58.5	NA	70.6	MI
7	Margaglione et al.	1998	Italy	44.0	22.0 - 66.0	77.0	CAD history

NA : not available MI : Myocardial Infarction CAD : Coronary Artery Disease

Table 2. Number of subjects by each genotype of 7 case-control studies

Study No.	Authors	Year	Case				Controls			
			4G/4G	4G/5G	5G/5G	Total	4G/4G	4G/5G	5G/5G	Total
1	Dawson et al.	1993	29	51	27	107	23	24	26	73
2	Eriksson et al.	1995	40	38	15	93	26	54	20	100
3	Ye et al.	1995	148	230	98	476	189	271	141	601
4	Ridker et al.	1997	101	191	82	374	134	252	109	495
5	Catto et al.	1997	150	274	134	558	56	80	36	172
6	Ossei-Gerning et al.	1997	59	73	26	158	36	65	49	150
7	Margaglione et al.	1998	68	85	45	198	239	493	249	981
Total			595	942	427	1964	703	1239	630	2572

Table 3. Allele frequencies and Hardy-Weinberg equilibrium of 7 case-control studies

Study No.	Authors	Year	Allele frequencies		p value for Hardy-Weinberg equilibrium	
			4G	5G	Case	Control
1	Dawson et al.	1993	NA	NA	NA	NA
2	Eriksson et al.*	1995	0.53	0.47	p>0.05	p>0.05
3	Ye et al.	1995	0.54	0.46	p>0.05	p<0.05
4	Ridker et al.	1997	0.52	0.48	p>0.05	p>0.05
5	Catto et al.*	1997	0.56	0.44	p>0.05	p>0.05
6	Ossei-Gerning et al.	1997	0.54	0.46	p>0.05	p>0.05
7	Margaglione et al.	1998	0.49	0.51	p>0.05	p>0.05

NA : not available *allele frequencies from control group only.

Table 4. Random and fixed effect of 4G/5G versus 5G/5G on cardiovascular diseases of 7 case-control studies

	Random effect model						Fixed effect model				
	OR	95% CI	Q	Z	P	OR	95% CI	Z	P		
Overall	1.12	0.93, 1.34	6.81	1.21	0.23	1.12	0.95, 1.32	1.31	0.19		
Catto's et al *	1.16	0.95, 1.42	5.98	1.42	0.16	1.15	0.96, 1.38	1.56	0.12		
Margaglione's et al **	1.22	0.96, 1.55	5.06	1.61	0.11	1.20	0.99, 1.47	1.83	0.07		
Dawson et al ***	1.23	0.92, 1.64	5.05	1.37	0.17	1.20	0.99, 1.48	1.74	0.08		

*Catto's study was excluded

** Catto's and Margaglione's study were excluded.

***Catto's, Margaglione's and Dawson's study were excluded P : p-value for two tails test.

심혈관 질환 발생에 유전자다형성(4G/5G)의 영향 분석

4G/5G

6.81 (p>0.05)

5G/5G 4G/5G 4G/4G

(effect size)

가 0.72 3.09

(overall odds ratio)

(fixed effect)

(random effect)

가

4G/5G 1.23

(0.93, 1.34) , 1.12(0.95, 1.32)

(Table 4).

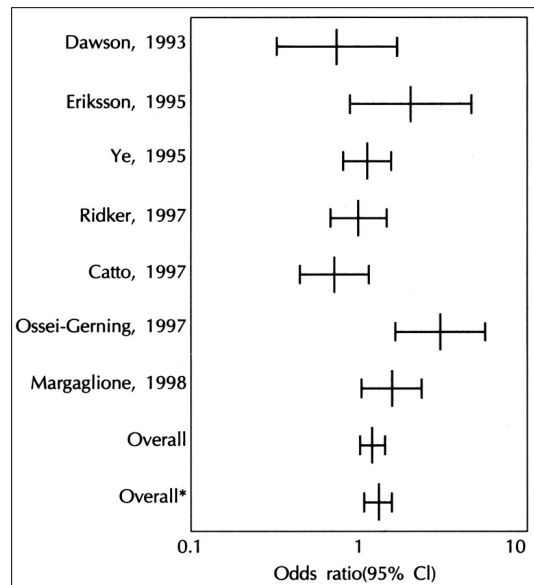


Fig. 1. Odds Ratios of 4G/4G versus 5G/5G on cardiovascular disease. * : Catto's study was excluded

(Table 4). , Catto (1997)²⁾

가
Margaglione (1998),¹⁾ H - W
Dawson (1993)⁶⁾

1)2)

6)

Table 5. Random and fixed effect of 4G/4G versus 5G/5G on cardiovascular diseases of 7 case-control studies

	Random effect model						Fixed effect model				
	OR	95% CI	Q	Z	P	OR	95% CI	Z	P		
Overall	1.26	0.90, 1.76	18.47	1.34	0.18	1.20	1.01, 1.44	2.04	0.04		
Catto et al*	1.39	0.99, 1.96	13.37	1.88	0.06	1.31	1.08, 1.58	2.75	0.01		
Margaglione's et al**	1.36	0.89, 2.08	12.38	1.40	0.16	1.24	1.00, 1.54	1.98	0.05		
Dawson et al***	1.51	0.94, 2.43	10.83	1.70	0.09	1.29	1.03, 1.62	2.24	0.03		

*Catto's study was excluded

**Catto's and Margaglione's study were excluded.

***Catto's, Margaglione's and Dawson's study were excluded.

P : p-value for two tails test.

가 , p 7 5

(Table 4).

4G/4G 4G/5G 가 , 가

가 . , 가

1.26(0.90, 1.76), 1.20(1.01, 1.44) (Fig. 1). , 가 (selection bias) 가 . ,

가 1.51(0.94, 2.43 ; p - value =0.09) , 가 PAI - 1 45

, 가 1.29(1.03, 1.62 ; p - value =0.03) (Table 5). 17) 18)

고 안

가 PAI - 1 19)

45 6)7) 45

plasminogen activator inhibitor - 1(PAI - 1) 4G/4G가 45

4G/5G 1998 11 7

5G/5G 4G/4G 가 20%

4G/5G 5G/5G 4G/4G 가 12%

PAI - 1 segregation PAI - 1 가 , Pankow (1998)²⁰⁾

4G/4G 가 PAI - 1 segregation PAI - 1

가 segregation PAI - 1 21)

가 (complex disease) , 22)가 1998

Pankow ²⁰⁾ 가 first relatives

가 가 segregation 가

PAI - 1

가

가

²³⁾

. Falk(1995)⁸⁾

가

308

4G/4G

52

(22.1%)

51

(34.7%)

가

가

가

가

가

7

Table 4 5

4G/4G

ferroni

. , Bon -

0.05

, Catto(1997)²⁾

0.05/k,(

k

)

가 76

, Ossei - Gerning(1996)¹¹⁾

PAI -

1

가

(3.09, 95%

1.64, 5.80)

, PAI -

MONICA

1 가

20%가

4G/5G가 PAI - 1

¹⁾

4G/5G가

²³⁾

가

가

가

PAI - 1

가

요 약

tissue

연구배경 :

plasminogen activator

PAI - 1

plasminogen activator inhibitor - 1(PAI - 1)

²⁴⁾

PAI - 1

PAI - 1

가

(body mass index)

PAI - 1

. Kwan (1994)²⁵⁾

방 법 :
 1998 1 (MEDLINE)
 4G/5G
 7
 Hardy - Weinberg(H - W)
 4G/5G
 결 과 :
 1) 1993 1998
 , 1 , 5
 가 , 1
 4,536
 1,964 , 2,572
 2) 가 H - W 가 H - W
 가
 3) 0.72 3.09
 . 4G/4G
 1.26(0.90, 1.76) , 1.20
 (1.01, 1.44)
 4) 가 , p - value
 가
 1.51(0.94, 2.43 ; p=0.09)
 1.29(1.03, 1.62 ; p=0.03)
 결 론 :
 4G/5G
 가
 가
 중심 단어 :
 (PAI - 1)
 98 (HMP -
 98 - M - 1 - 0004)

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