# Original article

## Relationship of plasminogen activator inhibitor 1 gene 4G/5G polymorphisms to hypertension in Korean women

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***Keywords:*** *hypertension; plasminogen activator inhibitor 1; polymorphism*

**Background** Hypertension (HTN) is a major determinant of various cardiovascular events. Plasma levels of plasminogen activator inhibitor 1 (PAI-1) modulate this risk. A deletion/insertion polymorphism within the PAI-1 loci (4G/4G, 4G/5G, 5G/5G) affects the expression of this gene. The present study investigated the association between PAI-1 loci polymorphisms and HTN in Korean women.

**Methods** Korean women (*n*=1312) were enrolled in this study to evaluate the association between PAI-1 4G/5G gene polymorphisms and HTN as well as other metabolic risk factors. PAI-1 loci polymorphisms were investigated using polymerase chain reaction amplification and single-strand conformation polymorphism analysis.

**Results** The three genotype groups differed with respect to systolic blood pressure (*P*=0.043), and diastolic blood pressure (*P*=0.009) but not with respect to age, body mass index, total cholesterol, low or high density lipoprotein cholesterol, triglycerides, or fasting blood glucose. Carriers of the PAI-1 4G allele had more hypertension significantly (PAI-1 4G/5G vs. PAI-1 5G/5G, *P*=0.032; PAI-1 4G/4G vs. PAI-1 5G/5G, *P*=0.034). When stratified according to PAI-1 4G/5G polymorphism, there was no significant difference in all metabolic parameters among PAI-1 genotype groups in patients with HTN as well as subjects with normal blood pressure. The estimated odds ratio of the 4G/4G genotype and 4G/5G for HTN was 1.7 (*P*=0.005), and 1.6 (*P*=0.015), respectively.

**Conclusion** These findings might indicate that PAI-1 loci polymorphisms independently contribute to HTN and that gene-environmental interaction may be not associated in Korean women.

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Hypertension (HTN) is an important risk factor associated with increased cardiovascular morbidity and mortality.[1] It is an enormous public health burden with substantial health care expenditures, affecting almost one-fourth of all adults in Korea; consequently, prevention of HTN is a public health priority. Blood pressure (BP) is considered a complex trait influenced by several environmental and genetic factors, with 30%–60% of individual variations in BP being attributed to additive genetic factors.[2] It is well-established that HTN clusters in families[3] and that a positive family history represents a major risk factor for future HTN in non-hypertensive offspring.[4] The underlying pathophysiology of HTN is, however, not completely understood.

Differences in lifestyle, such as diet composition, smoking habits, stress, and obesity may be only partially responsible for changes in the incidence rate of systemic vascular disease. In recent years, epidemiological studies have shown that identifying abnormalities in some hemostatic parameters may help predict the risk of ischemic events. An increased risk for arterial thrombosis has been associated with high plasma levels of coagulation and fibrinolytic factors.[5] Low fibrinolytic activity is related to elevated plasma levels of plasminogen activator inhibitor-1 (PAI-1) and has been documented in subjects who develop myocardial infarction (MI).[6] Evidence for a strong genetic component in the pathogenesis of cardiovascular ischemia has been provided.[7] These findings support the hypothesis that genetic factors play a significant role in MI and vascular risk factors.[8] PAI-1 is the primary physiologic inhibitor of plasminogen activation in the blood.[9] Recently, elevated PAI-1 plasma levels have been shown to be related to a single-base-pair guanine deletion/insertion (4G/5G) polymorphism.[10]

On the other hand, elevated PAI-1 has been linked to insulin resistance syndrome,[11,12] which is a collective of dyslipidemia, glucose intolerance, obesity, hyperinsulinemia, and HTN. However, a correlation of plasma PAI-1 activity on triglyceride (TG) level among the 4G/5G genotypes was shown to be different in diabetics[13,14] and dyslipidemics.[15]

Studies concerning the relationship between HTN, metabolic features, and PAI-1 gene 4G/5G polymorphism in Korean women are lacking. The present study was undertaken to investigate the relationship between HTN, metabolic parameters and the PAI-1 loci polymorphism in

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this cohort.

## METHODS

### Study subjects

The study population consisted of subjects who visited the Health Promotion Center, Cheil Hospital, Seoul, South Korea, from 2002–2004. Following informed consent, 1312 Korean women were enrolled in this study to evaluate the relationship between PAI-1 4G/5G gene polymorphisms and HTN as well as other metabolic risk factors. The study was performed in accordance with the *Declaration of Helsinki* and was approved by the Institutional Review Board of Cheil Hospital. All patients provided written informed consent to participate to the study after full explanations from the investigators.

### Study design

Routine blood chemistry, lipid levels, anthropometry, and medical history data were gathered over a 3-year period. The presence of obesity, HTN, and related metabolic parameters were compared according to PAI-1 4G/5G gene polymorphisms. HTN was diagnosed if there was either systolic BP≥140 mmHg or diastolic BP ≥90 mmHg on at least three separate occasions, or if there was a history of antihypertensive drug medication. None of the study subjects had a history or clinical evidence of stroke, acute MI, heart failure, or renal insufficiency. There was no apparent cause of secondary HTN identified clinically in any participant. Hypertriglyceridemia was defined as plasma TG≥ 150 mg/dl. Diabetes was diagnosed if the fasting plasma glucose was higher than 126 mg/dl on two separate occasions or there was a history of antdiabetic medication.

### Measurements

*Anthropometry and laboratory tests*

The height and body weight of the participants were measured while they wore light clothing without shoes. Weight was measured to the nearest 0.1 kg and height to the nearest centimeter. Body mass index was calculated as the weight divided by height squared (BMI, kg/m$^2$). Trained nurses measured BP after the participants had been at rest for at least 15 minutes. BP measurements were recorded using a TM-2655P apparatus (PMS Instruments, Japan). Additionally, all of the subjects underwent the following blood tests: standard enzymatic measurements of total cholesterol, high-density lipoprotein (HDL) cholesterol, TG, low density lipoprotein (LDL) cholesterol and fasting glucose from fresh serum samples. These measurements were recorded using a TBA-200FR apparatus (Toshiba, Japan).

*PAI-1 4G/5G genetic analysis*

The PAI-1 4G/5G polymorphism was evaluated by polymerase chain reaction (PCR) amplification and single-strand conformation polymorphism (SSCP) analysis as described previously.[17] Genomic DNA was extracted from 100 µl buffy coat using an IsoQuick Nucleic Acid Extraction Kit (Micro-Probe, Bothell, USA). The 5′ and 3′ PCR primers were TAA-CCC-CTG-GTC-CCG-TTC and CAG-AGG-ACT-CTT-GGT-CTT-TCC, respectively. The target sequence around the 4G/5G polymorphism using a Perkin-Elmer/Applied DNA thermal cycler 2400 (Perkin-Elmer Corporation-Applied Biosystems, Foster City, USA) was amplified. Denatured PCR product (6 µl) with the GenePhor electrophoresis unit was applied and disentangled on a GeneGel Excel 12.5/24. Following staining with a DNA silver staining kit (Amersham Pharmacia Biotech, Uppsala, Sweden), three patterns were visualized on the gel. The representative PCR products were sequenced to recognize the 4G/4G, 4G/5G, and 5G/5G genotypes.

### Statistical analysis

All group data were reported as mean ± standard deviation (SD). Analysis of variance (ANOVA) tests were used to compare means of continuous variables such as various metabolic parameters across PAI-1 4G/5G gene polymorphism groups and HTN. Multivariate Logistic analysis was done to evaluate the odds ratio controlling for all potential confounding factors. A statistically significant difference was assumed to be present at $P$ <0.05.

## RESULTS

### Hypertension and metabolic parameters of Korean women by PAI-1 genotype

As shown in Table 1, age ranged from 33–94 years and368 of the study subjects (28.0%) were HTN. The

**Table 1.** HTN and metabolic parameters of Korean women by PAI-1 genotypes

| Variables | PAI-1 genotypes | | | Total ($n$=1312) |
|---|---|---|---|---|
| | 5G/5G ($n$=230) | 4G/5G ($n$=634) | 4G/4G ($n$=448) | |
| Age (years) | 59.0±7.2 | 58.9±7.3 | 59.4±6.9 | 59.1±7.1 |
| BMI (kg/m$^2$) | 24.0±2.9 | 23.4±2.9 | 24.0±2.7 | 23.9±2.8 |
| SBP (mmHg)* | 123.8±16.6 | 126.6±17.2 | 127.3±17.2 | 126.3±17.1 |
| DBP (mmHg)* | 76.0±11.1 | 78.3±10.8 | 78.6±10.3 | 78.0±10.7 |
| Total cholesterol (mg/dl) | 199.7±38.1 | 201.7±34.7 | 202.6±36.5 | 201.6±36.0 |
| HDL cholesterol (mg/dl) | 56.1±14.8 | 55.5±14.8 | 55.7±13.7 | 55.7±14.4 |
| LDL cholesterol (mg/dl) | 108.3±47.6 | 110.1±44.5 | 110.5±45.9 | 109.9±45.5 |
| Triglyceride (mg/dl) | 122.9±76.2 | 129.8±77.5 | 129.8±76.4 | 128.5±76.9 |
| FBS (mg/dl) | 95.8±17.0 | 97.8±73.0 | 96.3±16.1 | 96.9±52.0 |
| Hypertension (%)† | 47 (20.4) | 187 (29.4) | 134 (29.9) | 368 (28.0) |

ANOVA test for continuous variables was used; means (standard deviation) are indicated. *$P$ <0.05. †PAI-1 4G/5G vs. PAI-1 5G/5G, $P$=0.032; PAI-1 4G/4G vs. PAI-1 5G/5G, $P$=0.034 by scheffe. BMI: body mass index. SBP: systolic blood pressure. DBP: diastolic blood pressure. HDL: high density lipoprotein. LDL: low density lipoprotein. FBS: fasting blood glucose.

**Table 2.** Biochemical characteristics by PAI-1 4G/5G polymorphism in subjects with and without hypertension

| Variables | Genotype | | | *P* values |
|---|---|---|---|---|
| | 4G/4G | 4G/5G | 5G/5G | |
| Hypertension (+) | | | | |
| Age (years) | 61.98±6.49 | 60.32±7.91 | 61.69±7.41 | 0.177 |
| BMI (kg/m$^2$) | 24.45±2.86 | 24.53±3.00 | 25.43±2.57 | 0.153 |
| Triglyceride (mg/dl) | 145.46±73.17 | 147.69±87.02 | 150.67±95.91 | 0.940 |
| Total cholesterol (mg/dl) | 205.85±40.95 | 207.84±35.41 | 200.93±39.66 | 0.581 |
| HDL cholesterol (mg/dl) | 55.62±13.93 | 54.55±14.02 | 55.36±12.05 | 0.817 |
| LDL cholesterol (mg/dl) | 109.79±51.53 | 115.50±43.88 | 103.26±51.99 | 0.301 |
| FBS (mg/dl) | 97.34±13.69 | 97.21±13.62 | 99.24±21.29 | 0.730 |
| Hypertension (–) | | | | |
| Age (years) | 58.66±6.94 | 58.25±6.64 | 57.78±6.36 | 0.379 |
| BMI (kg/m$^2$) | 23.73±2.57 | 23.35±2.81 | 23.48±2.81 | 0.182 |
| Triglyceride (mg/dl) | 128.01±75.29 | 125.28±71.07 | 119.02±71.14 | 0.424 |
| Total cholesterol (mg/dl) | 200.94±34.30 | 198.73±34.59 | 196.94±37.03 | 0.462 |
| HDL cholesterol (mg/dl) | 56.05±13.89 | 56.71±14.10 | 57.30±12.66 | 0.619 |
| LDL cholesterol (mg/dl) | 111.51±42.71 | 109.36±42.93 | 108.74±44.43 | 0.739 |
| FBS (mg/dl) | 95.65±16.55 | 93.70±13.12 | 93.55±12.07 | 0.139 |

ANOVA test for continous variables were used; means (standard deviation) are indicated. BMI: body mass index. HDL: high density lipoprotein. LDL: l ow density lipoprotein. FBS: fasting blood glucose.

three genotype groups differed with respect to systolic BP (*P*=0.043), and diastolic BP (*P*=0.009) but not with respect to age, BMI, total cholesterol, HDL cholesterol, LDL cholesterol, TG, or fasting blood glucose. Carriers of the PAI-1 4G allele had significantly more hypertension (PAI-1 4G/5G vs. PAI-1 5G/5G, *P*=0.032; PAI-1 4G/4G vs. PAI-1 5G/5G, *P*=0.034). The frequencies observed were not significantly different from those predicted by Hardy-Weinberg equilibrium. Additionally, subjects who are taking HTN or diabetes medication were excluded because medications for HTN and diabetes can affect BP and blood glucose values. Based on 1112 subjects without antihypertensive medication history and 1200 subjects without antidiabetic medication history, the three genotype groups differed with respect to systolic BP (*P*=0.040) and diastolic BP (*P*=0.010) but not with respect to age, BMI, total cholesterol, HDL cholesterol, LDL cholesterol, TG, or fasting blood glucose. A frequency of the 4G allele of the PAI-1 gene polymorphism was significantly higher in hypertensive patients (*P*=0.021) (data not shown).

### Biochemical characteristics by PAI-1 4G/5G polymorphism in subjects with and without hypertension

When stratified according to PAI-1 4G/5G polymorphism, there was no significant difference in age, BMI, TG, total cholesterol, HDL cholesterol, LDL cholesterol and fasting blood glucose among PAI-1 genotype groups in hypertensive patients as well as subjects with normal BP (Table 2). Additional analysis of 1112 subjects without antihypertensive medication history and 1200 subjects without antidiabetic medication history also found that there was no significant difference in all biochemical characteristics among PAI-1 genotype groups in patients with HTN as well as subjects with normal BP (data not shown).

### Odds ratios of hypertension according to PAI-1 genotypes

To assess the relationship of PAI-1 with and without HTN, multiple regression analysis models were employed (Table 3). It was estimated that the odds ratio of the 4G/4G genotype and 4G/5G for HTN was 1.7 (*P*=0.005), and 1.6 (*P*=0.015), respectively. In addition, age, BMI, and TG independently contributed to HTN. For 1112 subjects without antihypertensive medication history, the 4G allele showed a significant association of the PAI-1 4G/5G polymorphism with HTN (PAI-1 4G/5G vs. PAI-1 5G/5G, *OR*=1.827, *P*=0.001; PAI-1 4G/4G vs. PAI-1 5G/5G, *OR*=1.727, *P*=0.005) as well as age (*P* <0.001), BMI (*P*=0.001), and TG (*P*=0.027) (data not shown). For 1200 subjects without antidiabetic medication history, the 4G allele showed a significant association of the PAI-1 4G/5G polymorphism with HTN (PAI-1 4G/5G vs. PAI-1 5G/5G, *OR*=1.851, *P*=0.004; PAI-1 4G/4G vs. PAI-1 5G/5G, *OR*=1.709, *P*=0.002) as well as age (*P* <0.001), BMI (*P* <0.001), and both LDL cholesterol and HDL cholesterol (*P*=0.018) (data not shown).

## DISCUSSION

The present study shows a positive association between the PAI-1 gene polymorphism and HTN in Korean women. A significant association was evident between PAI-1 loci polymorphisms and HTN after controlling for all potential confounding factors. However, when stratified according to PAI-1 4G/5G polymorphism, there was no significant difference in all metabolic parameters among PAI-1 genotype groups in patients with HTN as well as subjects with normal BP. A lack of association between the 4G/5G genotype and metabolic parameters in Korean women may be due to unknown gene variants or loci loosely linked to the PAI-1 4G/5G polymorphism.

### Association between PAI-1 loci polymorphisms and HTN

Patients with HTN had significantly greater 4G/4G genotype percentage and 4G allele frequency than those without this disorder. The association was also consistent with the subjects who did not take medications for HTN or diabetes. Studies of the association between PAI-1 loci polymorphisms and HTN have usually shown different

**Table 3.** Odds ratios of hypertension using multiple regression analysis according to PAI-1 genotypes

| Variables | B | SE | *OR* | *P* values | 95% *CI* |
|---|---|---|---|---|---|
| PAI-1 genotypes | | | | | |
| 5G/5G | | | 1 | | |
| 4G/5G | 0.533 | 0.192 | 1.704 | 0.005 | 1.170–2.483 |
| 4G/4G | 0.485 | 0.200 | 1.624 | 0.015 | 1.097–2.406 |
| Age (years) | 0.044 | 0.009 | 1.045 | <0.001 | 1.026–1.064 |
| BMI (kg/m$^2$) | 0.501 | 0.138 | 1.165 | <0.001 | 1.258–2.163 |
| Total cholesterol (mg/dl) | 0.006 | 0.002 | 9.323 | 1.006 | 1.001–0.011 |
| HDL cholesterol (mg/dl) | –0.005 | 0.005 | 0.995 | 0.389 | 0.985–1.006 |
| LDL cholesterol (mg/dl) | –0.004 | 0.002 | 0.996 | 0.048 | 0.993–1.000 |
| Triglyceride (mg/dl) | 0.002 | 0.001 | 1.002 | 0.017 | 1.000–1.002 |
| FBS (mg/dl) | 0.000 | 0.001 | 1.000 | 0.958 | 0.997–1.002 |

BMI: body mass index. HDL: high density lipoprotein. LDL: low density lipoprotein. FBS: fasting blood glucose. CI: confidence interval.

results. However, this study has significance since the result was from a large number of female subjects. The results of present study differ from the study involving Chinese subjects.[16] The study with Chinese subjects showed that patients with HTN had not significantly greater 4G/4G genotype percentage and 4G allele frequency than those without this disorder. However, the present result is supported by previous studies. Although the present study did not include circulating levels of PAI-1, an association between the polymorphism of angiotensin converting enzyme (ACE) gene and circulating levels of PAI-1 identified in a Korean study[17] was positively correlated. Also, a positive interaction between ACE-DD and PAI-1 4G/4G genotypes in the regulation of PAI-1 plasma levels has been reported,[18,19] leading us to hypothesize that the PAI-1 4G variant is associated with the increase of ACE, which subsequently contributes to an increase in BP.

The possible relationship between PAI-1 loci polymorphisms and HTN seems to be associated with HTN in pregnancy. Indeed, the present results are in accordance with a previous study[20] of the relationship between a single nucleotide insertion/deletion (4G/5G) polymorphism located in the promoter region of PAI-1 gene and the pathogenesis of pregnancy-induced HTN syndrome (PIHs). The genotype frequencies of PAI-1 gene in the PIHs group were 47.4% for 4G/4G, 41.5% for 4G/5G, and 11.1% for 5G/5G, suggesting that the PAI-1 gene polymorphism may be a susceptibility factor for pathogenesis of PIHs, and the 4G/4G genotype may be one of the major risk factors for PIHs in pregnant women.

### Biochemical characteristics by PAI-1 4G/5G polymorphism in subjects with and without hypertension

When stratified according to PAI-1 4G/5G polymorphism, there was no significant difference in all metabolic parameters among PAI-1 genotype groups in patients with HTN as well as subjects with normal BP. Studies of the interaction of PAI-1 polymorphism with metabolic parameters in hypertensive patients have reported different correlations. A study from Jeng[16] showed that in hypertensive patients carrying the 4G/4G genotype, a higher TG was correlated with higher PAI-1, and this finding suggested a possible contribution of gene-environmental interaction to their high risk for atherothrombotic disease. On the other hand, Henry et al[15] demonstrated that interaction of PAI-1 polymorphism with TG, BMI, and total cholesterol was not significant. Another studies documented that lack of association between the 4G/5G genotype and TG level in a healthy population.[21,22] The association of gene-environmental interaction also was not observed in our data. This discrepancy can be explained as following. First, it may be due to unknown gene variants or loci loosely linked to the PAI-1 4G/5G polymorphism or variations in inclusion criteria for the subjects, sample size, and study design. Second, because the history of antilipidemic drugs was not included in the present study, the results might underestimate the association between the 4G/5G genotype and metabolic parameters.

There are some limitations associated with this study. First, the study was retrospective, and was unable to obtain all the clinical information from all the study patients. Second, it is not clear whether the analysis of this restricted patient group introduced a selection bias and these findings may or may not reflect the situation in the overall population. Third, the circulating levels of PAI-1 and the polymorphism of ACE gene were not measured in the current study. The ACE genetic and PAI-1 analysis might provide additional information with association between PAI-1 loci polymorphisms and HTN. Possible relationships between these factors and PAI-1 gene polymorphisms will require additional studies. Fourth, our data may not be robust to obtain the conclusion that the association of gene-environmental interaction is lacking in Korean women due to observation of a few environmental factors related to PAI-1 gene 4G/5G polymorphisms.

In conclusion, the present study shows a positive association between the PAI-1 gene polymorphism and HTN, and shows that PAI-1 loci polymorphisms independently contribute to HTN and that gene-environmental interaction may not be associated in Korean women. In future, a further large multicenter, population-based study with broad environmental factors is needed to observe some questions developed from the present data.

REFERENCES


1. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003; 42: 1206-1252.
2. Hottenga JJ, Boomsma DI, Kupper N, Posthuma D, Snieder H, Willemsen G, et al. Heritability and stability of resting blood pressure. Twin Res Hum Genet 2005; 8: 499-508.
3. Stamler R, Stamler J, Riedlinger WF, Algera G, Roberts RH. Family (parental) history and prevalence of hypertension. Results of a nationwide screening program. JAMA 1979; 241: 43-46.
4. Parikh NI, Pencina MJ, Wang TJ, Benjamin EJ, Lanier KJ, Levy D, et al. A risk score for predicting near-term incidence of hypertension: the Framingham Heart Study. Ann Intern Med 2008; 148: 102-110.
5. Ridker PM, Vaughan DE, Stampfer MJ, Manson JE, Hennekens CH. Endogenous tissue-type plasminogen activator and risk of myocardial infarction. Lancet 1993; 341: 1165-1168.
6. Hamsten A. Hemostatic function and coronary artery disease. N Engl J Med 1995; 332: 677-678.
7. Berg K. Twin research in coronary heart disease. In: Parisi GL, Nance WL, eds. Twin Research 3: Epidemiological and Clinical Studies. New York, NY: Alan R Liss; 1981: 117-130.
8. Sing CF, Moll PP. Genetics of variability of CHD risk. Int J Epidemiol 1989; 18(suppl 1): S183-S195.
9. Van Meijer M, Pannekoek H. Structure of plasminogen activator inhibitor 1 (PAI-1) and its function in fibrinolysis: an update. Fibrinolysis 1995; 9: 263-276.
10. Eriksson P, Kallin B, van t'Hooft FM, Bavhenolm P, Hamsten A. Allelicspecific increase in basal transcription of the plasminogen-activator inhibitor 1 gene is associated with myocardial infarction. Proc Natl Acad Sci U S A 1995; 92: 1851-1855.
11. Landin K, Tengborn L, Smith U. Elevated fibrinogen and plasminogen activator inhibitor (PAI-1) in hypertension are related to metabolic risk factors for cardiovascular disease. J Intern Med 1990; 227: 273-278.
12. Potter van Loon BJ, Kluft C, Radder JK, Blankenstein MA, Meinders AE. The cardiovascular risk factor plasminogen activator inhibitor type 1 is related to insulin resistance. Metab Clin Exp 1993; 42: 945-949.
13. Panahloo A, Mohamed-Ali V, Lane A, Green F, Humphries SE, Yudkin JS. Determinants of plasminogen activator inhibitor 1 activity in treated NIDDM and its relation to a polymorphism in the plasminogen activator inhibitor 1 gene. Diabetes 1995; 44: 37-42.
14. Mansfield MW, Stickland MH, Grant PJ: Plasminogen activator—inhibtor-1 (PAI-1) promoter polymorphism and coronary artery disease in non-insulin-dependent diabetes. Thromb Haemost 1995; 74: 1032-1034.
15. Henry M, Chomiki N, Scarabin PV, Alessi MC, Peiretti F, Arveiler D, et al. Five frequent polymorphisms of the PAI-1 gene: lack of association between genotypes, PAI activity, and triglyceride levels in a healthy population. Arterioscler Thromb Vascular Biol 1997; 17: 851-858.
16. Jeng JR. Association of PAI-1 gene promoter 4G/5G polymorphism with plasma PAI-1 activity in Chinese patients with and without hypertension. AJH 2003; 16: 290-296.
17. Kim DK, Kim JW, Kim S, Gwon HC, Ryu JC, Huh JE, et al. Polymorphism of angiotensin converting enzyme gene is associated with circulating levels of plasminogen activator inhibitor-1. Arterioscler Thromb Vasc Biol 1997; 17: 3242-3247.
18. Margaglione M, Cappucci G, d'Addedda M, Colaizzo D, Giuliani N, Vecchione G, et al. PAI-1 plasma levels in a general population without clinical evidence of atherosclerosis: Relation to environmental and genetic determinants. Arterioscler Thromb Vasc Biol 1998; 18: 562-567.
19. Margaglione M, Grandone E, Vecchione G, Cappucci G, Giuliani N, Colaizzo D, et al. Plasminogen activator inhibitor 1 (PAI-1) antigen plasma levels in subjects attending a metabolic ward: relation to polymorphisms of PAI-1 and angiotensin converting enzyme (ACE) genes. Arterioscler Thromb Vasc Biol 1997; 17: 2082-2087.
20. Guan LX, Du XY, Wang JX, Wang RL, Wu ZL, Jiang H. Relationship between the 4G/5G polymorphism of the plasminogen activator inhibitor-1 gene and the pathogenesis of pregnancy-induced hypertension syndrome. Chin J Med Genet (Chin) 2004; 21: 173-175.
21. Henry M, Tregouet DA, Alessi MF, Aillaud MF, Visvikis S, Siest G, et al. Metabolic determinants are much more important than genetic polymorphisms in determining the PAI-1 activity and antigen plasma concentrations: a family study with part of the Stanislas cohort. Arterioscler Thromb Vasc Biol 1998; 18: 84-91.
22. Mastsubara Y, Murata M, Isshiki I, Watanabe R, Zama T, Watanabe G, et al. Genotype frequency of plasmniogen activator inhibitor (PAI-1) 4G/5G polymorphism in healthy Japanese males and its relation to PAI-1 levels. Intern J Hematol 1999; 69: 43-47.


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