Int J Clin Exp Med 2015;8(2):2097-2107
www.ijcem.com /ISSN:1940-5901/IJCEM0004727

Original Article

PAI-1 4G/5G polymorphism and coronary artery disease risk: a meta-analysis

Zhongshu Liang, Weihong Jiang, Mao Ouyang, Kan Yang

Department of Cardiology, The Third Xiangya Hospital of Central South University 138 Tongzipo Road, Changsha 410013, Hunan, China

Received December 11, 2014; Accepted February 6, 2015; Epub February 15, 2015; Published February 28, 2015

Abstract: Many epidemiologic studies have investigated the plasminogen activator inhibitor-1 (PAI-1) gene 4G/5G polymorphism and this association with coronary artery disease (CAD). But definite conclusions can not be drawn. Related studies were identified from PubMed, Springer Link, Ovid, Chinese Wanfang Data Knowledge Service Platform, Chinese National Knowledge Infrastructure (CNKI), and Chinese Biology Medicine (CBM) till 10 August 2014. Pooled ORs and 95% CIs were used to assess the strength of the associations. A total of 53 studies including 20921 CAD cases and 18434 controls were included. Significantly elevated CAD risk was found in overall analysis (OR = 1.13, 95% CI: 1.05-1.21, *P* = 0.0009). In the subgroup analysis by races, significantly increased risk was found in Caucasians (OR = 1.11, 95% CI: 1.03-1.20, *P* = 0.005) and Asians (OR = 1.20, 95% CI: 1.01-1.42, *P* = 0.04). In the subgroup analysis by gender, significant association was found in males (OR = 1.15, 95% CI: 1.06-1.25, *P* = 0.0008), but was not found in females (OR = 1.05, 95% CI: 0.92-1.20, *P* = 0.47). In the subgroup analysis by age, young populations showed increased CAD risk (OR = 1.19, 95% CI: 1.02-1.37, *P* = 0.02), but old populations did not show this association (OR = 1.01, 95% CI: 0.82-1.24, *P* = 0.93). This meta-analysis provides the evidence that *PAI-1* 4G/5G polymorphism may contribute to the CAD development.

Keywords: Coronary artery disease, PAI-1, meta-analysis, polymorphism

Introduction

Coronary artery disease (CAD) is a complex disease with the interplay of multiple genetic and environmental factors precipitating its development [1]. Several risk factors for CAD have been well established including heavy alcohol consumption, family history, hypertension, diabetes and hyperlipidemia [2] and it is widely believed that CAD and its associated risk factors are largely under genetic control [3].

Plasminogen activator inhibitor-1 (PAI-1) is considered to be an important regulatory element in fibrinolysis. The suppression of fibrinolysis due to high plasma concentrations of PAI-1 and increased plasma concentrations of factor VII, fibrinogen, and von Willebrand factor are associated with the development of myocardial infarction (MI). Elevated PAI-1 levels appear to increase the risk of atherothrombotic events and may also promote the progression of vascular disease [4]. Renckens et al. reported that PAI-1 deficiency mice showed a reduction in the early induction of IL-6, a main inflammatory cytokine, in plasma and tissues with subsequently lower acute phase protein levels [5]. Thus, PAI-1 could have a proinflammatory property, thereby participating in CAD.

Plasma PAI-1 concentrations can be affected by several polymorphisms in the promoter region of the PAI-1 gene, including a common single-base polymorphism (4 or 5 guanine) in the promoter region of the gene, 675 base pairs upstream of the transcriptional start site [6]. Subjects homozygous for the 4G allele have plasma PAI-1 concentrations approximately 25% higher than those of subjects who are homozygous for the 5G allele [7]. A series of studies have investigated the association between the *PAI-1* 4G/5G polymorphism and CAD susceptibility, but provided controversial or inconclusive results [6-56]. In order to lessen the impact of different genetic background, we performed this meta-analysis to assess the

Table 1. Data of the included studies

First author/Year	Race	Gender	Age of case	No. of case	No. of control	Case			Control			HWE	Score
						4G/4G	4G/5G	5G/5G	4G/4G	4G/5G	5G/5G		
Dawson/1993	Caucasian	Mixed	< 45	107	73	29	51	27	23	24	26	Yes	5
Eriksson/1995	Caucasian	Male	< 45	93	100	40	38	15	26	54	20	Yes	7
Ye/1995	Caucasian	Male	25-64	476	601	148	230	98	189	271	141	Yes	8
Mansfield/1995	Caucasian	Male	61-70	38	122	20	15	3	37	67	18	Yes	5
Burzotta/1997	Caucasian	Mixed	> 45	108	175	32	46	30	52	86	37	Yes	6
Ridker/1997	Caucasian	Male	62.9	374	495	101	191	82	133	247	115	Yes	7
Ossei-Gerning/1997	Caucasian	NA	59.8	158	150	59	73	26	36	65	49	Yes	8
Iwai/1998	Asian	Mixed	59.3	204	148	83	99	22	53	76	19	Yes	7
Kohler/1998	Caucasian	Mixed	57-59	181	188	66	91	27	54	86	48	Yes	7
Pastinen/1998	Caucasian	Mixed	58.1	151	150	46	74	31	30	80	40	Yes	8
Junker/1998	Caucasian	Male	38.6	241	179	86	112	43	52	93	34	Yes	7
Sugano/1998	Asian	Mixed	63.1	66	62	5	28	33	6	27	29	Yes	6
Ardissino/1999	Caucasian	Mixed	40.7	200	200	38	93	69	32	102	66	Yes	7
Anderson 1/1999	Caucasian	Mixed	63.7	375	978	105	193	77	303	457	218	Yes	7
Anderson 2/1999	Caucasian	Mixed	62.5	898	329	267	433	198	97	155	77	Yes	7
Doggen/1999	Caucasian	Male	56.1	331	302	88	170	73	84	150	68	Yes	6
Gardemann 1/1999	Caucasian	Male	62.7	1791	594	624	985	362	167	305	122	Yes	9
Gardemann 2/1999	Caucasian	Male	62.2	1214	1351	382	606	226	409	684	258	Yes	9
Grancha/1999	Caucasian	Female	56.0	41	62	6	23	12	11	30	21	Yes	8
Beneš/2000	Caucasian	Male	49.5	175	222	53	91	31	77	103	42	Yes	8
Canavy/2000	Caucasian	Mixed	55.0	244	244	48	97	56	64	121	59	Yes	7
Hooper/2000	African	Mixed	60.7	110	185	7	42	59	11	79	104	Yes	6
Mikkelsson/2000	Caucasian	Male	47.9	68	164	18	38	12	29	78	57	Yes	5
Song/2000	Asian	Mixed	60.7	158	139	62	64	32	54	60	25	Yes	6
Fu/2000	Asian	Mixed	51.3	87	92	39	29	19	25	45	22	Yes	8
Viitanen/2001	Caucasian	Mixed	56.0	118	110	29	65	24	28	51	31	Yes	6
Ortlepp/2002	Caucasian	Mixed	58	100	100	36	48	16	24	54	22	Yes	5
Yamada/2002	Asian	Female	62.5	589	704	215	300	75	315	316	73	Yes	6
ATVB/2003	Caucasian	Mixed	< 45	1210	1210	335	589	286	342	588	280	Yes	7
Crainich/2003	Caucasian	Mixed	73.5	264	753	70	136	58	200	387	166	Yes	9
Juhan-Vague/2003	Caucasian	Male	< 60	483	507	125	249	109	133	269	105	Yes	8
Leander 1/2003	Caucasian	Male	58.3	851	1051	256	415	153	283	542	203	Yes	7

Leander 2/2003	Caucasian	Female	61.5	361	505	103	180	61	153	226	110	Yes	7
Petrovič/2003	Caucasian	Mixed	58.3	154	194	45	74	35	68	89	37	Yes	6
Zhan/2003	Asian	Mixed	67.1	56	83	40	14	2	25	52	6	Yes	5
Tobin/2004	Caucasian	Mixed	61.9	547	505	159	280	108	162	237	106	Yes	7
Pegoraro/2005	Asian	NA	< 45	195	300	42	99	54	65	132	103	Yes	8
Whiting	Caucasian	NA	NA	881	261	263	427	191	78	121	62	Yes	6
Su/2006	Asian	Mixed	54.5	812	931	272	390	150	275	446	210	Yes	8
Morange/2007	Caucasian	Male	51.91	510	543	105	236	120	96	254	124	Yes	5
Sampaio/2007	Caucasian	Mixed	34.4	115	104	23	47	45	16	45	43	Yes	7
Taymaz/2007	Caucasian	NA	NA	115	41	31	58	26	15	20	6	Yes	8
Onalan/2008	Caucasian	Mixed	59.0	156	281	51	75	30	73	112	96	Yes	7
Sarecka/2008	Caucasian	Mixed	43.8	178	202	38	94	46	69	103	30	Yes	6
Isordia-Salas/2009	Caucasian	Mixed	40.0	127	127	9	64	54	17	38	72	Yes	7
Tàssies/2009	Caucasian	Mixed	60.0	248	200	56	121	71	48	92	60	Yes	9
Var/2009	Caucasian	Mixed	55.3	86	90	43	24	19	24	36	30	Yes	7
Abboud/2010	African	Mixed	59.0	305	328	88	156	61	42	180	106	Yes	7
Cao/2010	Asian	Mixed	64.6	116	60	61	41	14	15	27	18	Yes	8
Koch/2010	Caucasian	Mixed	64 .0	3657	1211	1091	1787	779	360	590	261	Yes	9
Ahmed/2011	Caucasian	Mixed	52.1	229	217	64	86	79	52	89	76	Yes	8
Ashavaid/2011	Asian	Mixed	58.6	446	473	112	218	116	113	247	113	Yes	8
Lima/2011	Caucasian	Mixed	60.0	123	38	46	34	43	12	12	14	Yes	6

HWE, Hardy-Weinberg equilibrium; NA, not available.

Table 2. Meta-analysis of the association between *PAI-1* 4G/5G polymorphism and risk of CAD

	Association		Heterogeneity	
	OR (95% CI)	*P* Value	*P* Value	I^2 (%)
Overall	1.13 (1.05-1.21)	0.0009	0.001	41
Caucasian	1.11 (1.03-1.20)	0.005	0.02	34
Asian	1.20 (1.01-1.42)	0.04	0.02	48
Male	1.15 (1.06-1.25)	0.0008	0.16	39
Female	1.05 (0.92-1.20)	0.47	0.65	0
Young (≤ 50 years)	1.19 (1.02-1.37)	0.02	0.21	0
Old (> 50 years)	1.01 (0.82-1.24)	0.93	0.03	51

relationship of *PAI-1* 4G/5G polymorphism with risk of CAD.

Materials and methods

Search for publications

We searched databases containing PubMed, Springer Link, Ovid, Chinese Wanfang Data Knowledge Service Platform, Chinese National Knowledge Infrastructure (CNKI), and Chinese Biology Medicine (CBM) up to 10 August 2014, using the following Mesh terms: ("coronary artery disease" [MeSH] or "coronary heart disease") and ("PAI-1" or "plasminogen activator inhibitor-1"). The references from retrieved articles were also searched. There was no language restriction.

Inclusion and exclusion criteria

Studies included in this meta-analysis have to meet the following criteria: (1) case-control study or cohort study studying on associations between *PAI-1* 4G/5G polymorphism and risk of CAD; (2) sufficient published data about sample size, odds ratio (OR), and their 95% confidence interval (CI); (3) the distribution of the genotypes in control groups was in the Hardy-Weinberg equilibrium (HWE). Studies were excluded when they were: (1) not case-control study or cohort study; (2) duplicate of previous publication; (3) based on incomplete data; (4) meta-analyses, letters, reviews, or editorial articles.

Data extraction and qualitative assessment

Data were independently extracted by two reviewers using a standardized data extraction form. Discrepancies were resolved by discussion and if consensus was not achieved the decision was made by all the reviewers. The title and abstract of all potentially relevant articles were screened to determine their relevance. Full articles were also scrutinized if the title and abstract were ambiguous. The following information was collected from each study: authors, year of publication, sample size, ethnicity of subjects, gender, age, numbers of cases and controls, genotype frequency of *PAI-1* 4G/5G polymorphism.

Two reviewers completed the quality assessment independently. The Newcastle-Ottawa Scale (NOS) was used to evaluate the methodological quality, which scored studies by the selection of the study groups, the comparability of the groups, and the ascertainment of the outcome of interest. We considered a study awarded 0-3, 4-6, or 7-9 as a low-, moderate-, or high-quality study, respectively. Discrepancies were resolved by consensus and discussion.

Statistical analysis

Statistical analysis was conducted by using STATA statistical package (version 10, STATA, College Station, TX). The distributions of genotypes in controls were tested by HWE using the Chi-square test. The association of polymorphisms of *PAI-1* 4G/5G polymorphism and CAD risk was estimated by odds ratio (ORs) with 95% confidence intervals (CIs). The heterogeneity was tested by the Q-statistics with *P*-values < 0.1, and its possible sources of heterogeneity were assessed by Galbraith plot. The random effect model (DerSimonian and Laird) was selected to summarize the combined OR and their 95% CI. The significance of the pooled OR was determined by the Z test. Cumulative meta-analysis was also conducted. Publication bias was investigated with the funnel plot, in which the Standard Error (SE) of log OR of each study was plotted against its OR. Funnel-plot asymmetry was further assessed by the method of Egger's linear regression test [57]. All the *P* values were two sided. *P* value less than 0.05 was considered statistically significant.

Results

Characteristics of studies

According to the inclusion criteria, 53 case-control studies [6-56] were included. The publica-

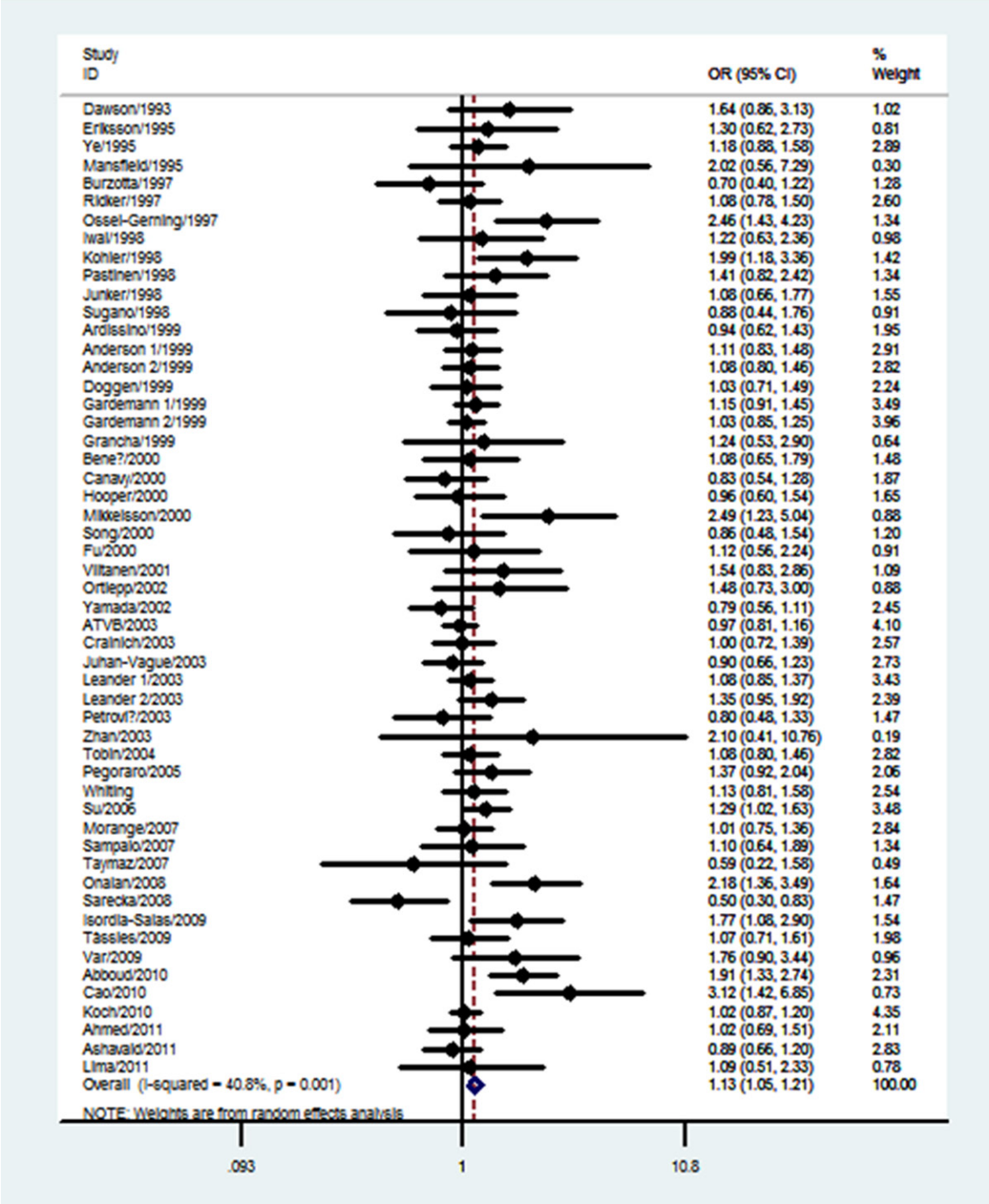

Figure 1. Meta-analysis for the association between *PAI-1* 4G/5G polymorphism and risk of CAD.

tion year of involved studies ranged from 1993 to 2011. In total, 20921 CAD cases and 18434 healthy controls were involved in this meta-analysis, which evaluated the relationship between *PAI-1* 4G/5G polymorphism and CAD risk. The characteristics of the included studies are summarized in **Table 1**.

Results of meta-analysis

The main results of this meta-analysis and the heterogeneity test were shown in **Table 2**. Significantly elevated CAD risk was found in overall analysis (OR = 1.13, 95% CI: 1.05-1.21, P = 0.0009, **Figure 1**). In the subgroup analysis

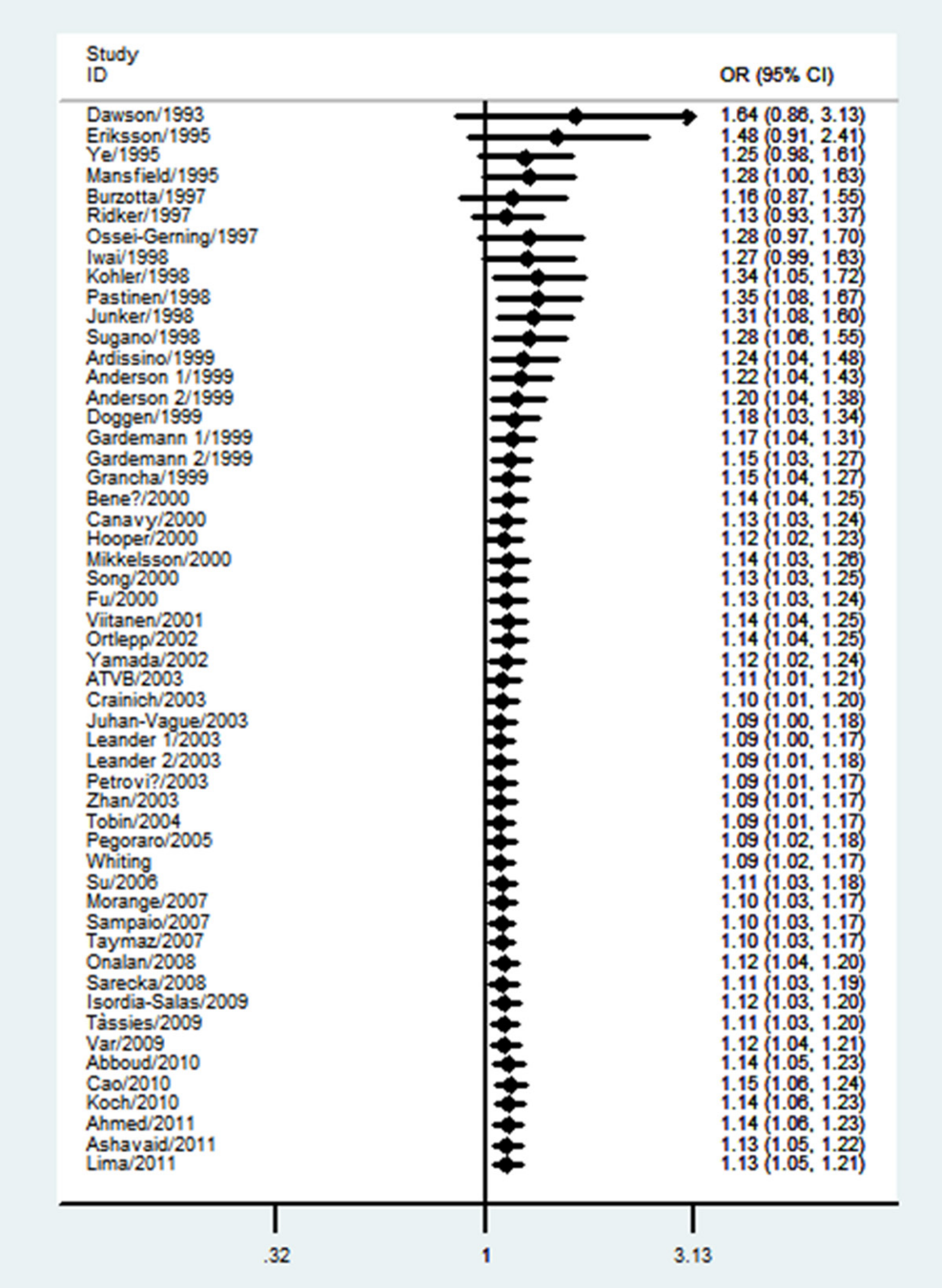

Figure 2. Cumulative meta-analysis of association between *PAI-1* 4G/5G polymorphism and risk of CAD.

by races, significantly increased risk was found in Caucasians (OR = 1.11, 95% CI: 1.03-1.20, *P* = 0.005) and Asians (OR = 1.20, 95% CI: 1.01-1.42, *P* = 0.04). In the subgroup analysis by

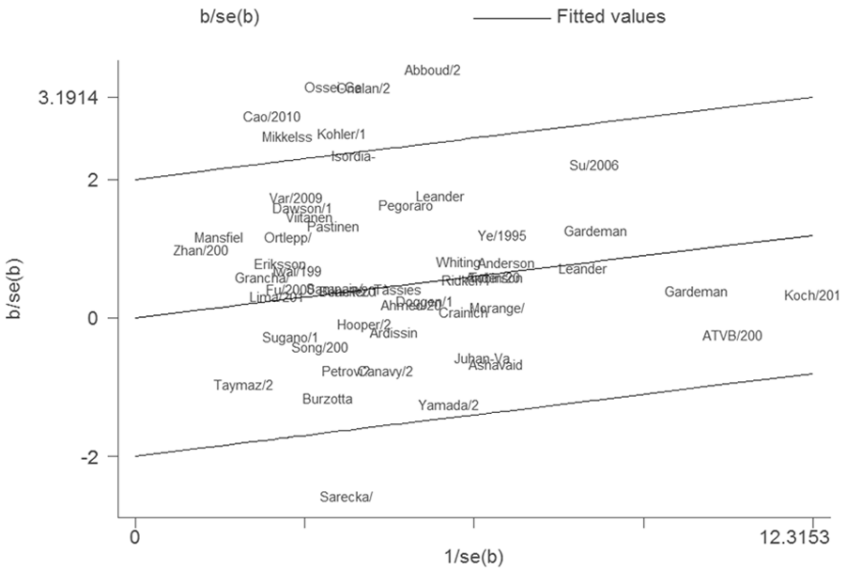

Figure 3. Galbraith plot of association between *PAI-1* 4G/5G polymorphism and risk of CAD.

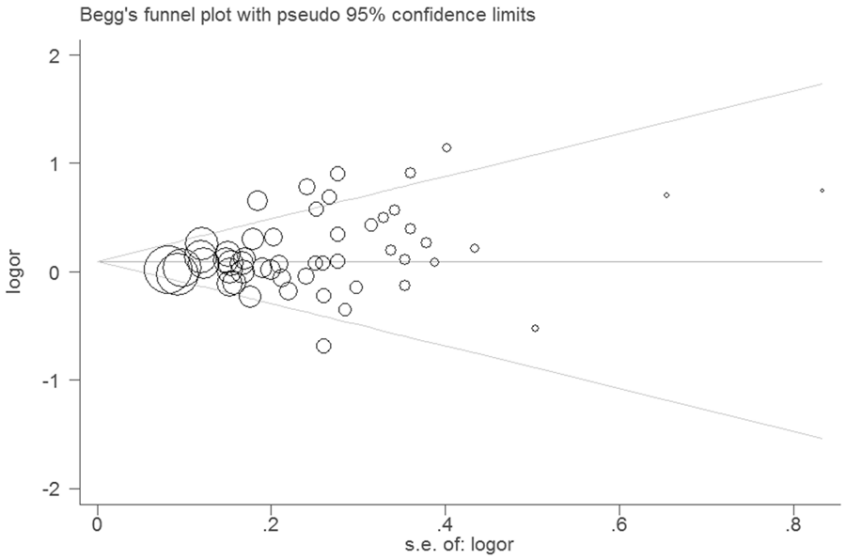

Figure 4. Funnel plot of associations between *PAI-1* 4G/5G polymorphism and risk of CAD.

gender, significant association was found in males (OR = 1.15, 95% CI: 1.06-1.25, *P* = 0.0008), but was not found in females (OR = 1.05, 95% CI: 0.92-1.20, *P* = 0.47). In the subgroup analysis by age, young populations showed increased CAD risk (OR = 1.19, 95% CI: 1.02-1.37, *P* = 0.02), but old populations did not show this association (OR = 1.01, 95% CI: 0.82-1.24, *P* = 0.93).

In order to compare the difference and evaluate the sensitivity of the meta-analyses, we used both models (the fixed effect model and random effect model) to evaluate the stability of the meta-analysis. All the results were not materially altered (data not shown). Cumulative meta-analysis also showed the result was stable and credible (**Figure 2**). In order to find the source of heterogeneity, Galbraith plot was used. Eight studies were found to be outliers (**Figure 3**). When these studies were excluded, the heterogeneity was disappeared.

The Begg's funnel plot and Egger's test were performed to assess the publication bias of literatures. The shape of the funnel plots did not reveal obvious asymmetry (**Figure 4**). Then, the Egger's test was used to provide statistical evidence of funnel plot symmetry. The Egger's test indicated that there was no obvious publication bias (*P* = 0.23).

Discussion

Although many studies analyzing the research results about the *PAI-1* 4G/5G polymorphism and CAD risk, definite conclusions cannot be drawn. Therefore, we did this meta-analysis to estimate the relationships between *PAI-1* 4G/5G polymorphism and susceptibility to CAD. The meta-analysis involved 53 articles and 39355 subjects. The results from this meta-analysis showed that the *PAI-1* 4G/5G polymorphism was significantly associated with CAD risk. When we performed the subgroup analyses by ethnicity, gender and age, significant associations with susceptibility for the development of CAD was found in Caucasians, Asians, males, and young

populations. On the one hand, it was possible that these differences might be affected by exposure to various environmental factors. However, no reported article was performed to assess the effect of *PAI-1*-environment interactions in different populations. In the future, more studies should be designed to analyze these associations. On the other hand, it was possible that considerable heterogeneity may have distorted the result.

Several studies have demonstrated increased expression of PAI-1 in human atherosclerotic lesions [58, 59]. Immunohistochemical study demonstrated enhanced expression of PAI-1 in the macrophages and endothelial cells of atherosclerotic plaques [60]. Patients with type 2 diabetes show higher expression of PAI-1 in the atherosclerotic vascular wall than those without diabetes [61]. Thus, increased PAI-1 in the arterial wall may contribute directly to development of CAD.

Our meta-analysis has several strengths. First, we have followed the inclusion and exclusion criteria strictly to reduce possible selection bias. Second, a funnel plot and Egger's linear regression test were used to assess publication bias. Third, the sensitivity analysis and cumulative meta-analysis had been performed to confirm the reliability and stability of the results. Fourth, Galbraith plot was used to find the source of heterogeneity. In fact, the result was still significant when the outliers were excluded (OR = 1.06, 95% CI: 1.01-1.13, P = 0.02).

Some limitations should be addressed. First, there was only two case-control studies investigated the association of *PAI-1* 4G/5G polymorphism and CAD risk in Africans. Therefore, more studies with large sample sizes are needed to further identify the association among African. Second, because small negative studies are less likely to published, the possibility of publication bias cannot be ruled out completely, even though the Egger's test and funnel plots did not provide the evidence of publication bias in this meta-analysis. Third, a lack of original data from the eligible studies limited evaluation of the effects of the gene-gene and gene-environment interactions during CAD development.

In conclusion, our meta-analysis supports that *PAI-1* 4G/5G polymorphism might contribute to individual susceptibility to CAD. Concerning CAD with multifactorial etiology, to further evaluate gene-gene and gene-environment interactions on *PAI-1* 4G/5G polymorphism and CAD, larger studies in selected populations with different environmental background or other risk factors are required.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Kan Yang, Department of Cardiology, The Third Xiangya Hospital of Central South University, No. 138 Tongzipo Road, Changsha 410013 Hunan, China. Tel: 86-0731-88618072; E-mail: kanyang0731@163.com

References

[1] Lee IM, Sesso HD, Oguma Y, Paffenbarger RS Jr. Relative intensity of physical activity and risk of coronary heart disease. Circulation 2003; 107: 1110-6.

[2] Wild SH, Byrne CD. ABC of obesity. Risk factors for diabetes and coronary heart disease. BMJ 2006; 333: 1009-11.

[3] Hsu J, Smith JD. Genome-wide studies of gene expression relevant to coronary artery disease. Curr Opin Cardiol 2012; 27: 210-3.

[4] Vaughan DE. PAI-1 and atherothrombosis. J Thromb Haemost 2005; 3: 1879-83.

[5] Renckens R, Roelofs JJ, de Waard V, Florquin S, Lijnen HR, Carmeliet P, van der Poll T. The role of plasminogen activator inhibitor type 1 in the inflammatory response to local tissue injury. J Thromb Haemost 2005; 3: 1018-25.

[6] Dawson S, Hamsten A, Wiman B, Henney A, Humphries S. Genetic variation at the plasminogen activator inhibitor-1 locus is associated with altered levels of plasma plasminogen activator inhibitor-1 activity. Arterioscler Thromb 1991; 11: 183-90.

[7] Eriksson P, Kallin B, van't Hooft FM, Båvenholm P, Hamsten A. Allele-specific 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: 1851-5.

[8] Ye S, Green FR, Scarabin PY, Nicaud V, Bara L, Dawson SJ. The 4G/5G genetic polymorphism in the promoter of the plasminogen activator inhibitor-1 (PAI-1) gene is associated with differences in plasma PAI-1 activity but not with risk of myocardial infarction in the ECTIM study. Etude CasTemoins de I'nfarctus du Mycocarde. Thromb Haemost 1995; 74: 837-41.

[9] Mansfield MW, Stickland MH, Grant PJ. Plasminogen activator inhibitor-1 (PAI-1) promoter

polymorphism and coronary artery disease in non-insulin-dependent diabetes. Thromb Haemost 1995; 74: 1032-1034.

[10] Burzotta F, Di Castelnuovo A, Amore C, D'Orazio A, Donati MB, Iacoviello L. 4G/5G polymorphism in the promoter region of the PAI-1 gene is not a risk factor for familial myocardial infarction in subjects over 45 years. Thromb Haemost 1997; 78: 1294-5.

[11] Ridker PM, Hennekens CH, Lindpaintner K, Stampfer MJ, Miletich JP. Arterial and venous thrombosis is not associated with the 4G/5G polymorphism in the promoter of the plasminogen activator inhibitor gene in a large cohort of US men. Circulation 1997; 95: 59-62.

[12] Ossei-GerningN, MansfieldMW, SticklandMH, Wilson IJ, Grant PJ. Plasminogen activator inhibitor-1 promoter 4G/5G genotype and plasma levels in relation to a history of myocardial infarction in patients characterized by coronary angiography. Arterioscler Thromb Vasc Biol 1997; 17: 33-7.

[13] Iwai N, Shimoike H, Nakamura Y, Tamaki S, Kinoshita M. The 4G/5G polymorphism of the plasminogen activator inhibitor gene is associated with the time course of progression to acute coronary syndromes. Atherosclerosis 1998; 136: 109-14.

[14] Kohler HP, SticklandMH, Ossei-Gerning N, Carter A, Mikkola H, Grant PJ. Association of a common polymorphism in the factor XIII gene with myocardial infarction. Thromb Haemost 1998; 79: 8-13.

[15] Margaglione M, Cappucci G, Colaizzo D, Giuliani N, Vecchione G, Grandone E. The PAI-1 gene locus 4G/5G polymorphism is associated with a family history of coronary artery disease. Arterioscler Thromb Vasc Biol 1998; 18: 152-6.

[16] Pastinen T, Perola M, Niini P, Terwilliger J, Salomaa V, Vartiainen E, Peltonen L, Syvänen A. Array-based multiplex analysis of candidate genes reveals two independent and additive genetic risk factors for myocardial infarction in the Finnish population. Hum Mol Genet 1998; 7: 1453-62.

[17] Junker R, Heinrich J, Schulte H, Tataru M, Kohler E, Schonfeld R, Nowak-Göttl U, Assmann G. Plasminogen activator inhibitor-1 4G/5G-polymorphism and factor V Q506 mutation are not associated with myocardial infarction in young men. Blood Coagul Fibrinolysis 1998; 9: 597-602.

[18] Sugano T, Tsuji H, Masuda H, Nakagawa K, Nishimura H, Kasahara T. Plasminogen activator inhibitor-1 promoter 4G/5G genotype is not a risk factor for myocardial infarction in a Japanese population. Blood Coagul Fibrinolysis 1998; 9: 201-4.

[19] Ardissino D, Mannucci PM, Merlini PA, Duca F, Fetiveau R, Tagliabue L. Prothrombotic genetic risk factors in young survivors of myocardial infarction. Blood 1999; 94: 46-51.

[20] Anderson JL, Muhlestein JB, Habashi J, Carlquist JF, Bair TL, Elmer SP. Lack of association of a common polymorphism of the plasminogen activator inhibitor-1 gene with coronary artery disease and myocardial infarction. J Am Coll Cardiol 1999; 34: 1778-83.

[21] Doggen CJ, Bertina RM, Cats VM, Reitsma PH, Rosendaal FR. The 4G/5G polymorphism in the plasminogen activator inhibitor-1 gene is not associated with myocardial infarction. Thromb Haemost 1999; 82: 115-20.

[22] Gardemann A, Lohre J, Katz N, Tillmanns H, Hehrlein FW, Haberbosch W. The 4G4G genotype of the plasminogen activator inhibitor 4G/5G gene polymorphism is associated with coronary atherosclerosis in patients at high risk for this disease. Thromb Haemost 1999; 82: 1121-6.

[23] Grancha S, Estellés A, Tormo G, Falco C, Gilabert J, España F. Plasminogen activator inhibitor-1 (PAI-1) promoter 4G/5G genotype and increased PAI-1 circulating levels in postmenopausal women with coronary artery disease. Thromb Haemost. 1999; 81: 516-21.

[24] Beneš P, Mužík J, Benedík J, Frélich M, Elbl L, Vasků A, Znojil V, Vácha J. Single effects of apolipoprotein B, (a), and E polymorphisms and interaction between plasminogen activator inhibitor-1 and apolipoprotein (a) genotypes and the risk of coronary artery disease in Czech male caucasians. Mol Genet Metab 2000; 69: 137-43.

[25] Canavy I, Henry M, Morange PE, Tiret L, Poirier O, Ebagosti A. Genetic polymorphisms and coronary artery disease in the south of France. Thromb Haemost 2000; 83: 212-6.

[26] Hooper WC, Lally C, Austin H, Renshaw M, Dilley A, Wenger NK, Phillips DJ, Whitsett C, Rawlins P, Evatt BL. The role of the t-PA I/D and PAI-1 4G/5G polymorphisms in African-American adults with a diagnosis of myocardial infarction or venous thromboembolism. Thromb Res 2000; 99: 223-30.

[27] Mikkelsson J, Perola M, Wartiovaara U, Peltonen L, Palotie A, Penttila A, Lehto S, Laakso M. Plasminogen activator inhibitor-1 (PAI-1) 4G/5G polymorphism, coronary thrombosis, and myocardial infarction in middle-aged Finnish men who died suddenly. Thromb Haemost 2000; 84: 78-82.

[28] Song J, Yoon YM, Jung HJ, Hong SH, Park H, Kim JQ. Plasminogen activator inhibitor-1 4G/5G promoter polymorphism and coagulation factor VII Arg353- >Gln polymorphism in Korean patients with coronary artery disease. J Korean Med Sci 2000; 15: 146-52.

[29] Fu L, Jin H, Song K, Zhang C, Shen J, Huang Y. Relationship between gene polymorphism of the PAI-1 promoter and myocardial infarction. Chin Med J (Engl) 2001; 114: 266-9.
[30] Viitanen L, Pihlajamäki J, Halonen P, Lehtonen M, Kareinen A, Lehto S, Laakso M. Association of angiotensin converting enzyme and plasminogen activator inhibitor-1 promoter gene polymorphisms with features of the insulin resistance syndrome in patients with premature coronary heart disease. Atherosclerosis 2001; 157: 57-64.
[31] Ortlepp JR, Lauscher J, Janssens U, Minkenberg R, Hanrath P, Hoffmann R. Analysis of several hundred genetic polymorphisms may improve assessment of the individual genetic burden for coronary artery disease. Eur J Intern Med 2002; 13: 485-92.
[32] Yamada Y, Izawa H, Ichihara S, Takatsu F, Ishihara H, Hirayama H, Sone T, Tanaka M, Yokota M. Prediction of the risk of myocardial infarction from polymorphisms in candidate genes. N Engl J Med 2002; 347: 1916-23.
[33] Atherosclerosis, Thrombosis; Vascular Biology Italian Study Group. No evidence of association between prothrombotic gene polymorphisms and the development of acute myocardial infarction at a young age. Circulation 2003; 107: 1117-22.
[34] Crainich P, Jenny NS, Tang Z, Arnold AM, Kuller LH, Manolio T, Sharrett AR, Tracy RP. Lack of association of the plasminogen activator inhibitor-1 4G/5G promoter polymorphism with cardiovascular disease in the elderly. J Thromb Haemost 2003; 1: 1799-804.
[35] Juhan-Vague I, Morange PE, Frere C, Aillaud MF, Alessi MC, Hawe E, Boquist S, Tornvall P, Yudkin JS, Tremoli E, Margaglione M, Di Minno G, Hamsten A, Humphries SE; HIFMECH Study Group. The plasminogen activator inhibitor-1-675 4G/5G genotype influences the risk of myocardial infarction associated with elevated plasma proinsulin and insulin concentrations in men from Europe: the HIFMECH study. J Thromb Haemost 2003; 1: 2322-9.
[36] Leander K, Wiman B, Hallqvist J, Sten-Linder M, de Faire U. PAI-1 level and the PAI-1 4G/5G polymorphism in relation to risk of non-fatal myocardial infarction: results from the Stockholm Heart Epidemiology Program (SHEEP). Thromb Haemost 2003; 89: 1064-71.
[37] Petrovic D, Globocnik-Petrovic M, Peterlin B. 4G4G genotype of PAI-1 gene promoter polymorphism is not associated with myocardial infarction in Caucasians with type-2 diabetes. Cardiology 2003; 100: 157-8.
[38] Zhan M, Zhou Y, Han Z. Plasminogen activator inhibitor-1 4G/5G gene polymorphism in patients with myocardial or cerebrovascular infarction in Tianjin, China. Chin Med J (Engl) 2003; 116: 1707-10.
[39] Tobin MD, Braund PS, Burton PR, Thompson JR, Steeds R, Channer K, Cheng S, Lindpaintner K, Samani NJ. Genotypes and haplotypes predisposing to myocardial infarction: a multilocus case–control study. Eur Heart J 2004; 25: 459-67.
[40] Pegoraro RJ, Ranjith N. Plasminogen activator inhibitor type 1 (PAI-1) and platelet glycoprotein IIIa (PGIIIa) polymorphisms in young Asian Indians with acute myocardial infarction. Cardiovasc J S Afr 2005; 16: 266-70.
[41] Whiting BM, Anderson JL, Muhlestein JB; Intermountain Heart Collaborative (IHC) Study Group. Candidate gene susceptibility variants predict intermediate end points but not angiographic coronary artery disease. Am Heart J 2005; 150: 243-50.
[42] Su S, Chen S, Zhao J, Huang J, Wang X, Chen R, Gu D. Plasminogen activator inhibitor-1 gene: selection of tagging single nucleotide polymorphisms and association with coronary heart disease. Arterioscler Thromb Vasc Biol 2006; 26: 948-54.
[43] Morange PE, Saut N, Alessi MC, Yudkin JS, Margaglione M, Di Minno G. Association of plasminogen activator inhibitor (PAI)-1 (SERPINE1) SNPs with myocardial infarction, plasma PAI-1, and metabolic parameters: the HIFMECH study. Arterioscler Thromb Vasc Biol 2007; 27: 2250-7.
[44] Sampaio MF, Hirata MH, Hirata RD, Santos FC, Picciotti R, Luchessi AD, de Quateli Doi S, Armaganijan D, Batlouni M. AMI is associated with polymorphisms in the NOS3 and FGB but not in PAI-1 genes in young adults. Clin Chim Acta 2007; 377: 154-62.
[45] Taymaz H, Erarslan S, Oner ET, Alkan T, Ağirbaşli M, Kirdar B. Sequence variations within the genes related to hemostatic imbalance and their impact on coronary artery disease in Turkish population. Thromb Res 2007; 119: 55-62.
[46] Onalan O, Balta G, Oto A, Kabakci G, Tokgozoglu L, Aytemir K. Plasminogen activator inhibitor-1 4G4G genotype is associated with myocardial infarction but not with stable coronary artery disease. J Thromb Thrombolysis 2008; 26: 211-7.
[47] Sarecka B, Zak I, Krauze J. Synergistic effects of the polymorphisms in the PAI-1 and IL-6 genes with smoking in determining their associated risk with coronary artery disease. Clin Biochem 2008; 41: 467-73.
[48] Isordia-Salas I, Leanos-Miranda A, Sainz IM, Reyes-Maldonado E, Borrayo-Sanchez G. Association of the plasminogen activator inhibitor-1 gene 4G/5G polymorphism with ST elevation

acute myocardial infarction in young patients. Rev Esp Cardiol 2009; 62: 365-72.
[49] Tassies D, Roque M, Monteagudo J, Martorell T, Sionis A, Arzamendi D, Heras M, Reverter JC. Thrombin-activatable fibrinolysis inhibitor genetic polymorphisms as markers of the type of acute coronary syndrome. Thromb Res 2009; 124: 614-8.
[50] Var A, Utük O, Akçali S, Sanlidağ T, Uyanik BS, Dinç G. Impact of hemostatic gene single point mutations in patients with non-diabetic coronary artery disease. Mol Biol Rep 2009; 36: 2235-43.
[51] Abboud N, Ghazouani L, Saidi S, Ben-Hadj-Khalifa S, Addad F, Almawi WY. Association of PAI-1 4G/5G and -844G/A gene polymorphisms and changes in PAI-1/tissue plasminogen activator levels in myocardial infarction: a case-control study. Genet Test Mol Biomarkers 2010; 14: 23-7.
[52] Cao XL, ZC Y, Yin L, Wang SC, Jia XL, Huang H. Reactive protein, plasminogen activator inhibitor type-1 (PAI-1) levels, PAI-1 promoter 4G/5G polymorphism and acute myocardial infarction. J Geriatr Cardiol 2010; 7: 147-51.
[53] Koch W, Schrempf M, Erl A, Mueller JC, Hoppmann P, Schomig A. 4G/5G polymorphism and haplotypes of SERPINE1 in atherosclerotic diseases of coronary arteries. Thromb Haemost 2010; 103: 1170-80.
[54] Ahmed W, Malik M, Saeed I, Khan AA, Sadeque A, Kaleem U. Role of tissue plasminogen activator and plasminogen activator inhibitor polymorphism in myocardial infarction. Mol Biol Rep 2011; 38: 2541-8.
[55] Ashavaid TF, Todur SP, Kondkar AA, Nair KG, Shalia KK, Dalal JJ. Platelet polymorphisms: frequency distribution and association with coronary artery disease in an Indian population. Platelets 2011; 22: 85-91.
[56] Lima LM, Carvalho MD, Fonseca Neto CP, Garcia JC, Sousa MO. PAI-1 4G/5G polymorphism and plasma levels association in patients with coronary artery disease. Arq Bras Cardiol 2011; 97: 462-389.
[57] Egger M, Davey Smith G, Schneider M and Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-634.
[58] Schneiderman J, Sawdey MS, Keeton MR, Bordin GM, Bernstein EF, Dilley RB, Loskutoff DJ. Increased type 1 plasminogen activator inhibitor gene expression in atherosclerotic human arteries. Proc Natl Acad Sci U S A 1992; 89: 6998-7002.
[59] Raghunath PN, Tomaszewski JE, Brady ST, Caron RJ, Okada SS, Barnathan ES. Plasminogen activator system in human coronary atherosclerosis. Arterioscler Thromb Vasc Biol 1995; 15: 1432-43.
[60] Lupu F, Bergonzelli GE, Heim DA, Cousin E, Genton CY, Bachmann F, Kruithof EK. Localization and production of plasminogen activator inhibitor-1 in human healthy and atherosclerotic arteries. Arterioscler Thromb 1993; 13: 1090-100.
[61] Sobel BE, Woodcock-Mitchell J, Schneider DJ, Holt RE, Marutsuka K, Gold H. Increased plasminogen activator inhibitor type 1 in coronary artery atherectomy specimens from type 2 diabetic compared with nondiabetic patients: a potential factor predisposing to thrombosis and its persistence. Circulation 1998; 97: 2213-21.