Original article

The Relationship between TAFI gene polymorphism and ACS in Chinese Han Population

Chengwei Xu[1], Yimeng Du[2] , Xiaoben Wu[3], Lili Wang[4], Jingjie Zhao[1], Zejun Wang[1]

1 Department of laboratory medicine, 2Department of Cardiology, Second Hospital of Shandong University, Jinan, 250033, P.R. China

3 Department of laboratory medicine, Shandong Provincial Hospital, Jinan, 250100, P.R. China

4 Department of laboratory medicine, Zhejiang Hangzhou Red Cross Hospital, Hangzhou, 310000, P.R. China

Abstract **Objective:** To investigate the relationship of the Thr147Ala and Thr325Ile polymorphisms of TAFI gene with acute coronary syndrome (ACS) in a Chinese Han population. **Methods:** A total of 210 consecutive ACS patients and 190 controls were enrolled. Thr147Ala and Thr325Ile polymorphisms of TAFI gene were detected with PCR-RFLP in all of the study subjects. The plasma TAFI activity (Act) and antigen (Ag) levels were determined by ELISA and chromogenic assay respectively. **Results:** Plasma TAFI Act and Ag levels were significantly higher in the ACS group than that in the control group. Although there was no significant correlation between the TAFI Act levels and gene polymorphisms (Thr325Ile) at position 325, the TAFI Ag concentrations of the Thr325Thr genotype were higher than that of other genotypes ($P < 0.05$). There was no statistical significance in TAFI Ag levels of the Thr325Ile and Ile325Ile genotypes ($P > 0.05$). **Conclusions:** Thr147Ala and Thr325Ile polymorphisms of the TAFI gene were not associated with ACS in a Chinese Han population.

KeyWords: TAFI; Polymorphism; Thr147Ala; Thr325Ile; ACS

Acute coronary syndrome (ACS), including unstable angina pectoris (UAP), acute myocardial infarction (AMI) and ischemic sudden death, results from the rupture of vulnerable plaques and the occlusion of the coronary artery secondary to platelet aggregation and thrombosis. Thrombosis is an important mechanism and key factor for the onset of ACS. Some study [1] demonstrated that one of the main factors for thromboses in patients with ACS is the imbalance between the coagulation and fibrinolysis system which is enhanced by blood coagulation and decreased by fibrinolysis. One of the main inhibitors of fibrinolysis is thrombin-activatable fibrinolysis inhibitor (TAFI), which generates an important complement to the classical coagulation and fibrinolysis pathways[2,3]. TAFI , a protein enzymogen secreted from liver and transported to plasma, is once activated by the thrombin-thrombomodulin complex, TAFIa is formed. TAFIa has been demonstrated to attenuate plasminogen activation by removing partially degraded fibrin and carboxyl-terminal lysine residues that mediate positive feedback in the fibrinolytic cascade.

The gene that encodes TAFI is located on chromosome 13q14.11, spanning approximately 48kb and consisting of 11exons [4]. Earlier research proved that the level of the TAFI protein is abundance in plasma and it is apparently genetically controlled [5,6]. Numerous single nucleotide polymorphisms (SNPs) of TAFI gene, such as Thr147Ala and Thr325Ile, have been reported to be strongly associated with plasma TAFI antigen (Ag) levels [5-11]. An increased plasma TAFI Ag concentration could be a risk factor for stable angina pectoris [12], coronary artery disease [13,14], myocardial infarction (MI) [15], and venous thrombosis [16-18]. Hence, TAFI is closely related to the cardiovascular diseases which may be hampered by inhibiting the plasma TAFI level. The TAFI gene polymorphisms encoding the protein that may affect its structure, concentration, or function, might have an influence in the balance between coagulation and fibrinolysis, and should be investigated to help identify a subset of patients at higher risk [19].

Previous studies on the relationship between the TAFI gene polymorphisms and cardiovascular disease bring forth intriguing possibilities. Some different and even contradictory conclusions are drawn from the various ethnical populations. Previous studies conducted in Europe have shown that the Thr/Ala-147 polymorphism is a risk factor for MI [5, 20] and angina pectoris [21], and that TAFI polymorphisms C+1542G and Thr325Ile are related to the type of ACS [19] and thrombotic microangiopathies [22]. On the contrary, the HIFMECH study, a large European multicentric case-control study, found that Thr325Ile polymorphism of the TAFI gene does not influence the risk of MI [23]. Another single-centric prospective study focused on Canadian patients with stable angina pectoris, indicating that the T/T Thr325Ile polymorphism of the TAFI gene is associated with lower re-stenosis rates after percutaneous coronary interventions [6]. However, no study

Corresponding author: Dr. ChengWei Xu
Department of laboratory medicine of the Second Hospital of Shandong University
No.247 Beiyuan Street, Jinan 250033, China
Tel: 86-531-85875539; Fax: 86-531-85803361
E-mail: xuchengwei-jyk@163.com

ISSN: 1538-5124/$ - see front matter

has reported on the association of the TAFI gene polymorphisms with coronary artery disease from the Asian population, especially the Chinese. Therefore, the present study aimed to investigate the correlation of the Thr325Ile and Thr147Ala polymorphisms of the TAFI gene with ACS in a Chinese Han population.

Subject and Methods

Study population

The study population included 210 patients (154 men and 56 women; mean age 58.4 ± 8.6 years) with ACS who had been hospitalized between November 2006 and October 2008 at the Department of Cardiology, Second Hospital of Shandong University. All patients were divided into two subgroups: 110 in the AMI group and 100 in the UAP group. The diagnoses for AMI and UAP were in accordance with earlier established criteria[24]. The 210 patients were performed with coronary angiography, in which the left anterior descending artery, left circumflex artery, and right coronary artery or the main branch with a stenosis degree ≥ 50% were recognized as positive. In addition, 190 subjects (142 men and 48 women; mean age 57.8 ± 8.9 years old) who complained of chest pain and underwent coronary angiography in the outpatient department were included as the control group. Exclusion criteria for the study subjects were cancer, surgery, hepatic and renal insufficiency, a history of other thrombotic diseases, platelet suppressant drug and oral anticoagulants during blood sample collection. All participants were of the Han population from the Shandong province of P.R.China and were not related to any other participants in the study. Informed written consent was obtained from each individual according to a protocol approved by the Genome Ethical Committee of the second hospital, Shandong University.

Biochemical analysis

Before coronary angiography, blood sampling was performed in all subjects within 24 hours of admission. A total of 7.0 ml of elbow vein blood was collected from patients in a single session. Of the 7.0 ml, 2.0 ml was anti-coagulated by EDTA for DNA extraction, 2.0 ml was self-clotted to measure blood lipids (including triglyceride, cholesterol, high density lipoprotein and low density lipoprotein), plasma glucose, hepatic and renal function, etc. The remaining 2.7 ml of collected blood was anti-coagulated by adding 0.3 ml sodium citrate (in a 9:1 ratio), followed by mixing and centrifugating at 3000 rpm for 15 min. Platelet-scarce plasma was then obtained, aliquoted and stored at -70℃ for further detection of TAFI concentration. Both TAFI Act and Ag kits were purchased from American Diagnostica Inc. (Stamford, CT, USA). TAFI Act was determined by chromogenic assay [25], while TAFI Ag levels were detected by ELISA according to the manufacturer's protocols.

Genotyping of polymorphisms of the TAFI gene

Genomic DNA was extracted from 2.0 ml EDTA anti-coagulated blood by using a UNIQ-10 column (Shanghai Sangon Bioengineering Technology Service Corp. Ltd., Shanghai, China). The extracted whole genomic DNA was used to amplify DNA fragments with TAFI C1040T and G505A polymorphisms. The PCR primers were synthesized by Shanghai Sangon Bioengineering Technology Service Corp. Ltd. and the sequences were TAFI325-F (5'-CACAAAGAAAAACAGATCACACAG-3'), TAFI325-R (5'

Table 1
Baseline characteristics of the study population

	ACS(n=210)	Control (n=190)	P Value
Gender(M/F)	154/56	142/48	0.75
Age(years)	58.4± 8.6	57.8± 8.9	0.69
Smoking(%)	111(52.8)	92(48.4)	0.38
BMI(kg/m2)	26.7± 3.3	26.4± 2.9	0.34
Hypertension(%)	101(48.1)	89(46.8)	0.80
Diabetes(%)	29(13.8)	21(11.1)	0.41
Lipid abnormality(%)	62(29.5)	54(28.4)	0.81
TAFI Act(μ g/ml)	48.7± 9.1	26.4± 6.5	＜0.001
TAFI Ag(%)	139.4± 29.2	79.2± 25.8	＜0.001

ACS = acute coronary syndrome; BMI = body mass index;
TAFI Act = thrombin-activatable fibrinolysis inhibitor activity;
TAFI Ag = TAFI antigen.

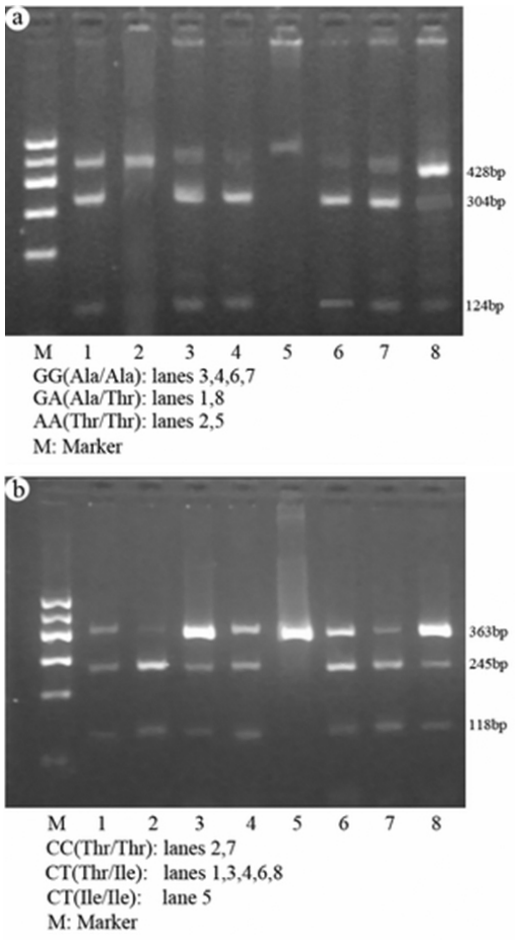

Fig.1 Demonstration of the existence of Thr/Ala-147(a) Thr/Ile-325 (b) polymorphisms in the Chinese Han population. Each genomic DNA extracted from venous blood was subjected to polymerase chain reaction (PCR) to amplify a fragment encompassing the codon for the amino acids at positions 147 and 325. PCR products were digested with BbvI (147) and SpeI (325). The TAFI-147 PCR product was 456 bp in size; the G (Ala) allele was digested into 28 + 124 + 304 bp, but the A (Thr) allele gave 28 + 428 bp. The TAFI-325 PCR product size was 363 bp; the C (Thr) allele was digested to 118 + 245 bp, but the T (Ile) allele was not digested by SpeI.

-AAAGCCACCCAATTGTGATT-3'), TAFI147-F (5'-TTGAAACTTCCACATGCAGC-3'), TAFI147-R (5'-TCTTGGGCACCATTTTGAG-3'). Genotyping of the two selected TAFI polymorphisms was performed by the modification of previously published procedures [26].

Statistical analysis

The frequencies of genotype and alleles were determined by direct counting. The fitness of participants and the Hardy-Weinberg equilibrium, and the comparison between genotype and allelic frequency were analyzed either by the Chi-square test or the 2× 2

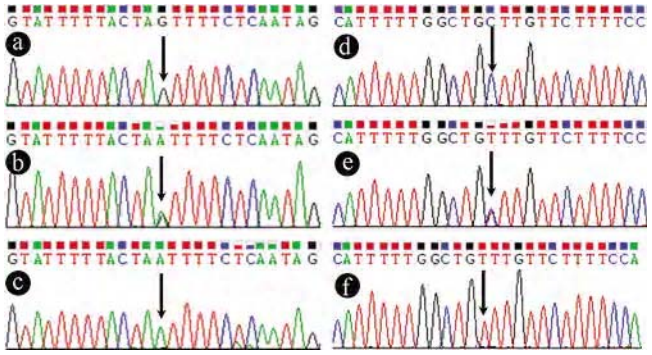

Fig.2 Sequencing analyses of 505A/G (Thr147Ala) (a-c) and 1040C/T (Thr325Ile)(d-f) of TAFI gene. Figures a, b and c were the sequences of TAFI 505A/G wide-type variant (GG), heterozygote (GA) and homozygote (AA), respectively, while Figures d, e and f were the sequences of TAFI 1040C/T wide-type variant (CC), heterozygote (CT) and homozygote (TT), respectively.

Fourfold Table Exact Probabilities method. Quantitative data were represented as mean ± SD, while comparisons of two means were performed with a Student t test, comparisons of multiple means were performed with an F test, and comparisons of every two means in multiple groups were performed with a Newman-Keuls test. Significant differences were determined by P-values (P<0.05). All the data were processed using SPSS 13.0 software (SPSS, Chicago, IL, USA).

Results

There were no significant differences in the gender, age, body mass index (BMI), smoking history, diabetes, hypertension and a lipid abnormality between the ACS and the control groups (P>0.05) (Table 1).

In contrast to the control group, the plasma TAFI Act and Ag levels in the ACS group were significantly increased (48.7 ± 9.1μ g/ml vs. 26.4 ± 6.5μ g/ml and 139.4 ± 29.2% vs. 79.2 ± 25.8%, respectively, P<0.0001) (Table 1). In ACS group, the patients with AMI had a higher TAFI Act than the patients with UAP (51.4 ± 9.3μ g/ml vs. 44.6 ± 8.4μ g/ml, P<0.01), although the TAFI Ag plasma level remained unchanged (145.6± 33.5% vs. 128.3± 28.7%, P>0.05).

The isoform mutated from G to A at amino acid 147 (TAFI147) had a PCR product of 456bp. Following digestion by the Bbv Ⅰ enzyme, the Thr147 homozygote produced two fragments (28+428bp), the Ala147 homozygote produced three fragments (28+124+304bp) and the Thr325Ile heterozygote produced four fragments (28+124+304+428bp), as shown in Fig.1a. The isoform mutated from C to T at amino acid 325 (TAFI325) had a PCR product of 363bp. Following digestion with the Spe Ⅰ enzyme, the

Table 2
Relationship between Thr147Ala and Thr325Ile polymorphisms of the TAFI gene and plasma TAFI levels in the ACS and control groups

	ACS(n=210)			Control (n=190)		
		TAFI Act (μ g/ml)	TAFI Ag (%)		TAFI Act (μ g/ml)	TAFI Ag (%)
Thr147Ala	23	48.4± 5.7	139.8± 22.6	22	25.8± 3.6	78.5± 19.4
	112	47.3± 5.6	137.2± 23.8	96	26.3± 4.8	79.8± 18.3
	75	49.2± 6.4	136.4± 24.7	72	27.1± 4.1	83.6± 18.5
Thr325Ile	67	47.8± 7.2	145.2 ± 27.6*	64	26.5± 4.2	89.6± 19.2*
	109	48.1± 6.4	126.1± 23.4	92	25.8± 3.8	77.8± 18.4
	34	49.4± 5.8	119.2± 22.6	34	26.2± 3.7	72.5± 17.6

* $P<0.05$ vs. Thr/Ile and Ile/Ile genotypes. Abbreviations as in Table 1.

Ile325 homozygote produced a 363bp fragment, the Thr325 homozygote produced two fragments (118+245bp), and the Thr325Ile heterozygote produced three fragments (118+245+363bp), as given in Fig.1b. Each digestion result was confirmed by sequencing of the PCR amplicon, which uncovered the existence of this polymorphism site (Fig. 2).

There were no significant differences that arose from the genotype and allelic distribution for Thr147Ala and Thr325Ile between the ACS and control groups. These frequencies of genotype and allelic distribution were consistent with the Hardy-Weinberg equilibrium and were representative of the population ($P>0.05$) (Table 2). In the ACS group, there was no statistical difference in the genotype and allelic distribution of Thr147Ala and Thr325Ile between the AMI and UAP patients (data not shown).

In contrast to the other two genotypes in the ACS and control groups, the plasma TAFI Ag level of the Thr325Thr homozygote showed a statistically significant increase ($P<0.05$). However, no difference surfaced in the TAFI Ag plasma level between Thr325Ile and Ile325Ile ($P>0.05$). The Thr325Ile polymorphism was not associated with the plasma TAFI Act level in the ACS group ($P>0.05$). Also, no correlation existed of Thr147Ala polymorphism and TAFI Act and Ag levels in the ACS group ($P>0.05$) (Table 2) and subgroup (data not shown).

Discussion

The chief finding of this study was that the Thr147Ala and Thr325Ile polymorphisms of the TAFI gene were not associated with ACS in a Chinese Han population. Regarding the association between the TAFI gene polymorphism and the cardiocerebrovascular diseases, all published studies focused on the European [5,19-22], the Canadian[6] and the Japanese[26] and Indian[8]. To our knowledge, this is the first study conducted on the Asian Chinese population to elucidate the correlation between the TAFI gene polymorphism and coronary artery disease.

However, there were some different conclusions that were drawn from all of the experiments conducted. Investigations from the Europe indicated that Thr/Ala-147 polymorphism is a risk factor for MI[5,20] and angina pectoris[21], and that TAFI polymorphism C+1542G and Thr325Ile are related to ACS[19] and thrombotic microangiopathies[22]. On the contrary, a study from Canada showed that T/T Thr325Ile polymorphism of the TAFI gene in the patients with stable angina pectoris is associated with a lower restenosis rate after percutaneous coronary interventions [6]. The HIFMECH study from Europe found that Thr325Ile polymorphism of the TAFI gene does not influence the risk of myocardial infarction[23]. Similarly, the result was observed in a Spanish population by Tassies et al [19] that the Ala147Thr polymorphism was not associated with ACS type. A French study indicated that Ala147Thr and C+1542G polymorphisms in the TAFI gene are not correlated with a higher risk of venous thrombosis in FV Leiden carriers[27]. The investigation on the Japanese population demonstrated that TAFI polymorphisms at amino groups 147 and 325 are not risk factors for cerebral infarction [26]. Even so, Morange et al [11] found no definite relationship between TAFI gene haplotypes and the incidence of coronary heart disease.

In agreement with the above mentioned studies [6,23,26,27], the present study found that there was no relationship between the

Thr147Ala and Thr325Ile polymorphisms of the TAFI gene and ACS. The discrepancies of the results could be due to differences in the patient races from different geographic regions. There may be differing genetic frequencies and variation in the correlation of the TAFI gene polymorphisms and the cardiocerebrovascular diseases.

Previous publications suggested that plasma TAFI Ag levels are strongly genetically controlled [5-11]. The SNPs of TAFI gene include 505A/G (Thr147Ala), 1040C/T(Thr325Ile), C+1542G, etc. The combination of C+1542G associated with 505A/G of the TAFI gene was shown to explain about 62% of the TAFI plasma levels [28]. The 1040C/C(Thr/Thr) and T/T(Ile/Ile) genotypes are related to the highest and lowest TAFI Ag plasma levels, respectively [6,10,23], so are the 505A/A (Thr/Thr) and G/G (Ala/Ala) genotypes[10]. Similar to previous studies[6,10,23], we have found that all of the subjects, especially the ACS patients with the 1040C/C TAFI genotype, had the highest plasma levels of TAFI Ag compared with those with the C/T and T/T genotypes, C/T and T/T genotypes had lower but not statistically significant levels between them. However, no difference was recorded in the plasma TAFI Act levels of the 1040C/T TAFI gene in the ACS and control groups. In disagreement with the study by Brouwers et al [10], all populations with 505 A/A, A/G and G/G TAFI genotypes in the current study did not show any significant differences in TAFI Ag and Act levels in the ACS and control groups. Several possible reasons for the inconsistencies include: First, the race in our study is different from the others; secondary, the possibility that other genes may regulate TAFI level cannot be excluded; finally, the methods for measuring TAFI varied in the above studies. Recent findings suggested that some commercially used antibodies are genotype-specific and that some artifacts may arise when measuring TAFI Ag by different ELISA assays [29].

Results regarding the recent findings on the association between the TAFI levels and the cardiovascular diseases are conflicting. On the one hand, an elevated plasma TAFI Ag levels could be a risk marker for coronary artery disease[12-15] and venous thrombosis [16-18]. On the other hand, increased TAFI levels have been related to a decreased risk for MI[20] and refractory unstable angina [30]. With resemblance to the results [12-15], the present study showed that the plasma TAFI Ag and Act levels in the ACS group were significantly higher than those in the control group. The finding was not the same as the result by Zorio et al[15] that high TAFI Ag decreased, but high TAFI Act increased the risk for MI in young patients. Different patients, the time of blood sampling and diverse methods for measuring TAFI concentrations may account for the difference.

In conclusion, the present study demonstrated that the Thr147Ala and Thr325Ile polymorphisms of the TAFI gene were not associated with ACS in a Chinese Han population, although the Thr325Ile polymorphism has an effect on TAFI Ag level. Further investigation should be focused on the multicenter and larger samples and follow up the study population.

References

1. Jenid H, Bhatt DL, Corti R, Badimon JJ, Fuster V, Francis GS. Aspirin and Clopidogrel in Acute Coronary Syndromes: Therapeutic Insights From the CURE Study. Arch Intern Med, 2003;163:1145-53.
2. Bajzar L, Manuel R, Nesheim ME. Purification and characterization of TAFI, a thrombin-activable fibrinolysis inhibitor. J Biol Chem, 1995; 270:14477-84.
3. Bouma BN, Mosnier LO. Thrombin activatable fibrinolysis inhibitor (TAFI) at the interface between coagulation and fibrinolysis. Pathophysiol Haemost Thromb, 2003; 33:375-81.
4. Boffa MB, Reid TS, Joo E, Nesheim ME, Koschinsky ML. Characterization of the gene encoding human TAFI (thrombin-activable fibrinolysis inhibitor; plasma procarboxypeptidase B). Biochemistry, 1999; 38:6547-58.
5. Henry M, Aubert H, Morange PE, Nanni I, Alessi MC, Tiret L, Juhan-Vague I. Identification of polymorphisms in the promoter and the 3' region of the TAFI gene: evidence that plasma TAFI antigen levels are strongly genetically controlled. Blood, 2001; 97:2053-8.
6. Segev A, Hegele RA, Lau HK, Sparkes JD, Teitel JM, Chisholm RJ, Strauss BH. Thr325Ile polymorphism of the TAFI gene is related to TAFI antigen plasma levels and angiographic restenosis after percutaneous coronary interventions. Thromb Res, 2004; 114:137-41.
7. Franco RF, Fagundes MG, Meijers JC, Reitsma PH, Lourenco D, Morelli V, Maffei FH, Ferrari IC, Piccinato CE, Silva WA, Jr., Zago MA. Identification of polymorphisms in the 5'-untranslated region of the TAFI gene: relationship with plasma TAFI levels and risk of venous thrombosis. Haematologica, 2001;86:510-7.
8. Biswas A, Tiwari AK, Ranjan R, Meena A, Akhter MS, Yadav BK, Behari M, Saxena R. Thrombin activatable fibrinolysis inhibitor gene polymorphisms are associated with antigenic levels in the Asian-Indian population but may not be a risk for stroke. Br J Haematol, 2008; 143:581-8.
9. Meltzer ME, Doggen CJ, de Groot PG, Meijers JC, Rosendaal FR, Lisman T. Low thrombin activatable fibrinolysis inhibitor activity levels are associated with an increased risk of a first myocardial infarction in men. Haematologica, 2009; 94: 811-8.
10. Brouwers GJ, Vos HL, Leebeek FW, Bulk S, Schneider M, Boffa M, Koschinsky M, van Tilburg NH, Nesheim ME, Bertina RM, Gomez Garcia EB. A novel, possibly functional, single nucleotide polymorphism in the coding region of the thrombin-activatable fibrinolysis inhibitor (TAFI) gene is also associated with TAFI levels. Blood, 2001; 98:1992-3.
11. Morange PE, Tregouet DA, Frere C, Luc G, Arveiler D, Ferrieres J, Amouyel P, Evans A, Ducimetiere P, Cambien F, Tiret L, Juhan-Vague I. TAFI gene haplotypes, TAFI plasma levels and future risk of coronary heart disease: the PRIME Study. J Thromb Haemost, 2005; 3:1503-10.
12. Silveira A, Schatteman K, Goossens F, Moor E, Scharpe S, Stromqvist M, Hendriks D, Hamsten A. Plasma procarboxypeptidase U in men with symptomatic coronary artery disease. Thromb Haemost, 2000; 84:364-8.
13. Santamaria A, Martinez-Rubio A, Borrell M, Mateo J, Ortin R, Fontcuberta J. Risk of acute coronary artery disease associated with functional thrombin activatable fibrinolysis inhibitor plasma level. Haematologica, 2004; 89:880-1.
14. Schroeder V, Wilmer M, Buehler B, Kohler HP. TAFI activity in coronary artery disease: a contribution to the current discussion on TAFI assays. Thromb Haemost, 2006; 96:236-7.
15. Zorio E, Castello R, Falco C, Espana F, Osa A, Almenar L, Aznar J, Estelles A. Thrombin-activatable fibrinolysis inhibitor in young patients with myocardial infarction and its relationship with the fibrinolytic function and the protein C system. Br J Haematol, 2003; 122:958-65.
16. van Tilburg NH, Rosendaal FR, Bertina RM. Thrombin activatable fibrinolysis inhibitor and the risk for deep vein thrombosis. Blood, 2000; 95:2855-9.
17. Eichinger S, Schonauer V, Weltermann A, Minar E, Bialonczyk C, Hirschl M, Schneider B, Quehenberger P, Kyrle PA. Thrombin-activatable fibrinolysis inhibitor and the risk for recurrent venous thromboembolism. Blood, 2004; 103: 3773-6.

18. Verdu J, Marco P, Benlloch S, Sanchez J, Lucas J. Thrombin activatable fibrinolysis inhibitor (TAFI) polymorphisms and plasma TAFI levels measured with an ELISA insensitive to isoforms in patients with venous thromboembolic disease (VTD). Thromb Haemost, 2006; 95:585-6.
19. 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.
20. Juhan-Vague I, Morange PE, Aubert H, Henry M, Aillaud MF, Alessi MC, Samnegard A, Hawe E, Yudkin J, Margaglione M, Di Minno G, Hamsten A, Humphries SE. Plasma thrombin-activatable fibrinolysis inhibitor antigen concentration and genotype in relation to myocardial infarction in the north and south of Europe. Arterioscler Thromb Vasc Biol, 2002; 22:867-73.
21. Morange PE, Juhan-Vague I, Scarabin PY, Alessi MC, Luc G, Arveiler D, Ferrieres J, Amouyel P, Evans A, Ducimetiere P. Association between TAFI antigen and Ala147Thr polymorphism of the TAFI gene and the angina pectoris incidence. The PRIME Study (Prospective Epidemiological Study of MI). Thromb Haemost, 2003; 89:554-60.
22. Sucker C, Hetzel GR, Farokhzad F, Dahhan F, Schmitz M, Kurschat C, Grabensee B, Maruhn-Debowski B, Zotz R, Scharf R. Association of genotypes of thrombin-activatable fibrinolysis inhibitors with thrombotic microangiopathies--a pilot study. Nephrol Dial Transplant, 2007; 22:1347-50.
23. Morange PE, Henry M, Frere C, Juhan-Vague I. Thr325Ile polymorphism of the TAFI gene does not influence the risk of myocardial infarction. Blood, 2002; 99: 1878-9.
24. Ren MY, Sui SJ, Zhang Y, Xu FY, Xu XQ, Zhao JJ, Du YM, Liu WH. Increased plasma osteoprotegerin levels are associated with the presence and severity of acute coronary syndrome. Acta Cardiol, 2008;63:615-22.
25. Paola Cellai A, Antonucci E, Alessandrello Liotta A, Fedi S, Marcucci R, Falciani M, Giglioli C, Abbate R, Prisco D. TAFI activity and antigen plasma levels are not increased in acute coronary artery disease patients admitted to a coronary care unit. Thromb Res, 2006;118:495-500.
26. Akatsu H, Yamagata H, Chen Y, Miki T, Kamino K, Takeda M, Campbell W, Kondo I, Kosaka K, Yamamoto T, Okada H. TAFI polymorphisms at amino acids 147 and 325 are not risk factors for cerebral infarction. Br J Haematol, 2004; 127: 440-7.
27. Morange PE, Aillaud MF, Nicaud V, Henry M, Juhan-Vague I. Ala147Thr and C+1542G polymorphisms in the TAFI gene are not asssociated with a higher risk of venous thrombosis in FV Leiden carriers. Thromb Haemost, 2001; 86:1583-4.
28. Heit JA, Silverstein MD, Mohr DN, Petterson TM, Lohse CM, O'Fallon WM, Melton LJ, 3rd. The epidemiology of venous thromboembolism in the community. Thromb Haemost, 2001; 86:452-63.
29. Guimaraes AH, van Tilburg NH, Vos HL, Bertina RM, Rijken DC. Association between thrombin activatable fibrinolysis inhibitor genotype and levels in plasma: comparison of different assays. Br J Haematol, 2004;124:659-65.
30. Brouwers GJ, Leebeek FW, Tanck MW, Wouter Jukema J, Kluft C, de Maat MP. Association between thrombin-activatable fibrinolysis inhibitor (TAFI) and clinical outcome in patients with unstable angina pectoris. Thromb Haemost, 2003; 90: 92-100.