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Significant genetic association of a functional *TFPI* variant with circulating fibrinogen levels and coronary artery disease

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Abstract

The tissue factor pathway inhibitor (*TFPI*) gene encodes a protease inhibitor with a critical role in regulation of blood coagulation. Some genomic variants in *TFPI* were previously associated with plasma TFPI levels, however, it remains to be further determined whether *TFPI* variants are associated with other coagulation factors. In this study, we carried out a large population-based study with 2,313 study subjects for blood coagulation data, including fibrinogen levels, prothrombin time (PT), activated partial thromboplastin time (APTT), and thrombin time (TT). We identified significant association of *TFPI* variant rs10931292 (a functional promoter variant with reduced transactivation) with increased plasma fibrinogen levels (P=0.017 under a recessive

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Author Contributions:

D. H. N., C.C.T., F.H. and Y.Z. contributed equally to this study. Study concept and design: Q. K. W., C. X. and D.H.N. Acquisition of data: D.H.N., C.C.T., F.H., Y.Z., D.W., J.F., S.L. and S.C. Analysis and interpretation of data: D.H.N., C.C.T., Q.C., C.X. and Q. K. W. Drafting of the manuscript: D.H.N., C.C.T. and Q. K. W. Critical revision of the manuscript for important intellectual content: C.C.T., C.X. and Q.C. Statistical analysis: D.H.N. and C.C.T. Obtained funding: Q. K. W and C.X. Study supervision: Q. K. W., Q.C. and C.X.

Compliance with Ethical Standards

Conflict of Interest

All authors have no conflict of interest.

Ethical approval:

All procedures performed in studies involving human participants were in accordance with the ethical standards of College of Life Science and Technology, Huazhong University of Science and Technology and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent:

Informed consent was obtained from all individual participants included in the study.

model), but not with PT, APTT or TT (P>0.05). Using a large case control association study population with 4,479 CAD patients and 3,628 controls, we identified significant association between rs10931292 and CAD under a recessive model (OR = 1.23, P = 0.005). For the first time, we show that a *TFPI* variant is found to be significantly associated with fibrinogen levels and risk of CAD. Our finding contributes significantly to the elucidation of the genetic basis and biological pathways responsible for fibrinogen levels and development of CAD.

Keywords

Tissue factor pathway inhibitor (TFPI); Coagulation Factors; Fibrinogen; Coronary Artery Disease (CAD); Association

Introduction

The *TFPI* gene encodes the tissue factor pathway inhibitor, which is a protease inhibitor regulating the tissue factor (TF)-dependent pathway of blood coagulation, a major factor for thrombosis and risk of cardiovascular disease (Maroney and Mast, 2015; Mast, 2016). The major goal of this study is to determine whether genomic variation in the *TFPI* gene is associated with the levels of key blood coagulation parameters such as the fibrinogen levels (FIB or Fg) and risk of cardiovascular disease. The *TFPI* gene is located on chromosome 2q32.1 and spans 101,531 base pairs (http://www.genecards.org/cgi-bin/carddisp.pl?gene=TFPI). TFPI is an anticoagulant protein that is expressed primarily in the vascular endothelium, megakaryocytes, platelets and plasma (Maroney and Mast, 2015; Mast, 2016). There are at least three alternatively spliced isoforms of TFPI in humans, TFPIα, TFPIβ and TFPIγ, which are produced from alternatively spliced mRNAs from a single gene (Maroney and Mast, 2015; Mast, 2016). TFPIα and TFPIβ are the two well-characterized, primary isoforms responsible for inhibiting coagulation (Maroney and Mast, 2015; Mast, 2016). TFPIα is a secreted protein that contains an acidic N- terminal domain, a basic C-terminal domain and 3 tandem Kunitz-type serine protease inhibitor domains, K1, K2 and K3(Maroney and Mast, 2015; Mast, 2016). The K1 domain interacts with FVIIa, the K2 domain with Xa and the K3 domain with protein S (Maroney and Mast, 2015; Mast, 2016). TFPIβ is shorter than TFPIα and contains only two tandem Kunitz-type serine protease inhibitor domains K1 and K2 followed by a GPI-anchor attachment sequence, which anchors TFPIβ to the cell membrane to execute its function (Maroney et al., 2013). The interaction of TFPI with the FVIIa-TF complex potently inhibits the initiation of blood coagulation (Maroney and Mast, 2015; Mast, 2016). The C-terminus of TFPIα interacts with factor V, which activates factor V and inhibits prothrombinase during the initiation of blood coagulation (Maroney and Mast, 2015; Mast, 2016; Wood et al., 2013).

Blood coagulation is initiated with the formation of the FVIIa-TF complex at a site of blood vessel injury (Hoffman and Monroe, 2007). This proteolytically activates FX protease (Hoffman and Monroe, 2007). Activated FX (FXa) mediates the formation of thrombin from prothrombin (FII) together with FVa, calcium and phospholipid (prothrombinase complex) (Hoffman and Monroe, 2007). Thrombin mediates the formation of fibrin (FIa) from fibrinogen (FI) (Hoffman and Monroe, 2007). Cross-linking of the fibrin monomers by

FXIIIa results in the formation of a fibrin clot (Hoffman and Monroe, 2007). TFPI inactivates the TF–FVIIa complex in concert with FXa, thereby inhibiting coagulation (Maroney and Mast, 2015; Mast, 2016).

Increased coagulation may increase risk of thrombosis and thromboembolism, whereas decreased coagulation may be associated with bleeding (Hayward et al., 2012). A person's coagulation activity can be measured by a blood coagulation test, which is usually ordered if there is a problem of bleeding or an unexplained blood clot (thrombosis) (Chee, 2014; Hayward et al., 2012). Blood coagulation panels typically include the fibrinogen level, prothrombin time (PT), activated partial thromboplastin time (APTT)and thrombin time (TT) (Chee, 2014; Hayward et al., 2012).

Genetic factors play an important role in a person's coagulation activity (Souto et al., 2000). For example, the heritability of plasma fibrinogen levels was estimated to be from 24% to 50% (de Lange et al., 2001; de Lange et al., 2006; Souto et al., 2000; Yang et al., 2003). In 2009, a genome-wide association study (GWAS) with 22,096 study subjects of European ancestry identified 4 genetic loci for circulating fibrinogen levels, including a single nucleotide polymorphism (SNP) in the *FGB* gene encoding the fibrinogen β-chain and SNPs in *IRF1* (interferon regulatory factor 1), *PCCB* (propionyl coenzyme A carboxylase), and *NLRP3* (NLR family pyrin domain containing 3 isoform) (Dehghan et al., 2009). In 2011, a large-scale candidate gene association study with 23,634 European Americans (EA) and 6,657 African Americans (AA) revealed that EA and AA populations share risk SNPs associated with fibrinogen levels, such as *FGB* rs1800787 and *FGG* rs2066861 and variants in *IL6R*, *IL1RN*, and *NLRP3* (Wassel et al., 2011). In 2013, a multiethnic meta-GWAS with >100,000 subjects identified 23 fibrinogen loci and 15 of them are new loci (Sabater-Lleal et al., 2013). The most recent meta-GWAS involved 120,246 study subjects and identified 18 new loci for fibrinogen levels (de Vries et al., 2016). However, all fibrinogen loci identified to date can explain only 3% of the heritability of circulating fibrinogen levels (de Vries et al., 2016). The majority of heritability remains missing, a phenomenon referred to as "missing heritability". Identification of new SNPs associated with fibrinogen levels will further our understanding of the heritability and genetic architecture of plasma fibrinogen levels.

Due to the important role of TFPI in blood coagulation, we studied association of a functional variant, the T-287C variant in the *TFPI* promoter/regulatory region (SNP rs10931292) (Amini and Iles, 2008) with coagulation parameters, including fibrinogen levels, PT, APTT, and TT. We identified significant association with fibrinogen levels only. We further studied the association between SNP rs10931292 and coronary artery disease (CAD) because plasma fibrinogen levels were significantly associated with risk of CAD (Danesh et al., 2005). We found that SNP rs10931292 conferred a significant risk of CAD.

Materials and Methods

Study subjects

All study subjects for this study were selected from the Gene ID database, which is one of the largest databases with clinical data and DNA samples for cardiovascular diseases in

China. Both cardiovascular patients and controls without cardiovascular diseases were enrolled. All subjects belong to the ethnic group of Han by self-description. This study was approved by the Ethics Committee on Human Subject Research at Huazhong University of Science and Technology and local Institutional Review Boards (IRB) on Human Subject Research at participating hospitals. Written informed consent was obtained from the study participants. This study conformed to the guidelines set forth by the Declaration of Helsinki.

For the association study between *TFPI* SNP rs10931292 and coagulation parameters, clinical diagnostic data on fibrinogen levels, PT, APTT, and TT were extracted from the GeneID database.

For the case control association study between *TFPI* SNP rs10931292 and CAD, each study subject was carefully evaluated by at least two independent cardiologists using the American College of Cardiology/American Heart Association criteria for a diagnosis of CAD and myocardial infarction (MI) as described previously by us(Chen et al., 2016; Li et al., 2013; Shen et al., 2007; Shen et al., 2008a; Shen et al., 2008b; Shen et al., 2012; Shen et al., 2013; Shen et al., 2014; Tu et al., 2013; Wang et al., 2011; Wang et al., 2004; Xu et al., 2014). We classified individuals with ≥70% luminal stenosis in at least 1 main vessel, percutaneous coronary angioplasty (PCA), coronary artery bypass graft (CABG), and MI as CAD cases. We classified individuals with typical chest pain sustained for at least 30 min, characteristic electrocardiographic patterns of acute MI, and elevation of troponin I or T and cardiac enzymes such as creatine kinase-MB and lactate dehydrogenase as being affected with MI. The control subjects are those individuals without a history CAD or MI or detectable stenosis of a coronary artery by coronary angiography. We excluded study subjects with congenital heart disease, type I diabetes mellitus, myocardial spasm, and myocardial bridge identified by angiography. We extracted demographic and other relevant clinical information, if present, from the medical records from the selected study subjects.

Isolation of human genomic DNA and SNP genotyping

Human genomic DNA was purified from whole blood samples using the Wizard Genomic DNA Purification kit (Promega, USA). Each DNA sample was analyzed for quantity and quality by spectrophotometry (Nanodrop 1000, Thermo Fisher Scientific, Wilmington, DE, USA) and agarose gel electrophoresis.

For association studies, we selected SNP rs10931292 in the *TFPI* promoter and regulatory region because this variant was shown to be a functional variant that affects the transcriptional activation of the *TFPI* promoter in a luciferase reporter assay (Amini and Iles, 2008). *TFPI* SNP rs10931292 was genotyped by the TaqMan assay using a Roche 480 Light Cycler (Roche, Germany) as described previously by us (Chen et al., 2015; Chen et al., 2016; Huang et al., 2015b; Li et al., 2013; Shen et al., 2009; Tu et al., 2013; Wang et al., 2011; Xiong et al., 2013). Twenty-four samples were randomly selected for Sanger sequencing analysis. The sequencing results were compared to the TaqMan genotyping data, and 100% matching was found between the two genotyping platforms.

Statistical analysis

Genotyping data were analyzed for Hardy-Weinberg equilibrium using PLINK version 1.07 (http://pngu.mgh.harvard.edu/~purcell/plink/archive.shtml). For analysis of the association between *TFPI*SNP rs10931292 and coagulation parameters (Fg/FIB, PT APPT, and TT), we performed linear modeling by incorporating covariates of age and gender using statistical program SPSS (version 17.0). The linear regression analysis was carried out under three different genetic models, including an additive model, an autosomal dominant model or an autosomal recessive model.

For the association analysis between *TFPI* SNP rs10931292 and CAD, we used the X^2 test. The analysis of allelic association was carried out using 2×2 Pearson χ^2 contingence tables, whereas genotypic association analysis was performed using 2×3 Pearson χ^2 contingence tables under three different genetic models, including an additive model, an autosomal dominant model or an autosomal recessive model. *P* values and corresponding odds ratios (ORs) with 95% confidential intervals were also calculated. The statistical analysis was performed using PLINK version 1.07 or SPSS version.17.0. For case control association analysis, multiple logistic regression analysis was performed to adjust significant covariates of age and gender for CAD using SPSS version.17.0.

We used PS software 3.0.12 to calculate the statistical power and sample sizes (http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize) as described (Chen et al., 2015; Chen et al., 2016; Huang et al., 2015b; Li et al., 2013; Xu et al., 2014; Yin et al., 2017). The statistical power can be calculated with special parameters, including the minor allele frequency (MAF), OR or effect size, the numbers of cases and controls, and the Type I error of 0.05.

Results

Significant association of *TFPI* SNP rs10931292 with circulating fibrinogen levels

TFPI plays an important role in regulation of blood coagulation (Maroney and Mast, 2015; Mast, 2016), therefore, we hypothesized that genomic variants of *TFPI* may be associated with some coagulation parameters. To test the hypothesis, we performed a population-based study to analyze the association between *TFPI* SNP rs10931292 and quantitative traits of fibrinogen levels, PT, APTT and TT. We searched our GeneID database for all individuals with available data on fibrinogen levels, PT, APTT and TT. A total of 2,313 subjects were found to have data on coagulation parameters (Table 1) and used for association analysis with *TFPI* SNP rs10931292. The clinical and demographic characteristics of the 2,313 study subjects are shown in Table 1. For the association of *TFPI* SNP rs10931292 with levels of fibrinogen, PT, APTT and TT, our study population can provide 70%, 74%, 80%, and 78% of statistical power, respectively, with the effect size (β) of 0.5, MAF of 0.31 and a type I error of 0.05.

All 2,313 study subjects were genotyped for a functional SNP in the promoter/regulatory region of the *TFPI* gene, rs10931292. No deviation from the Hardy-Weinberg equilibrium was observed for SNP rs10931292 ($P > 0.01$). Linear regression analysis revealed significant association between rs10931292 and fibrinogen levels under an additive model ($P = 0.026$)

and an autosomal recessive model ($P = 0.017$) (Table 2). Individuals with the GG genotype showed a significantly higher fibrinogen levels than those with other genotypes (Fig. 1A). The study population included 1,871 CAD patients and 442 non-CAD individuals (Table 1), however, the association between *TFPI* SNP rs10931292 and fibrinogen levels remain significant after adjusting for CAD (Table 2).

No significant association was detected between *TFPI* SNP rs10931292 and PT, APTT or TT under any genetic model (Table 2 and Fig. 1A–D).

Significant association between *TFPI* SNP rs10931292 and CAD

Fibrinogen levels play an important role in coagulation and hemostasis as well as inflammation and are a well-established risk factor for cardiovascular disease (Danesh et al., 2005; Lowe and Rumley, 2014). Moreover, the fibrinogen level was shown to be increased in atherosclerosis and CAD (Koenig, 1999). As shown above, there is a significant association between *TFPI* SNP rs10931292 and fibrinogen levels (Fig. 1A and Table 2). Therefore, we hypothesized that *TFPI* SNP rs10931292 is associated with risk of CAD. To test the hypothesis, we performed a large-scale case control association study to analyze the association between *TFPI* SNP rs10931292 and the binary trait of CAD. Our study involved a case population with 4,479 CAD patients and a control population with 3,628 non-CAD controls (Table 3). The clinical and demographical features of the case group and the control group are shown in Table 3. Under the population parameter setting of OR of 1.2 for CAD, and the MAF of 0.31 for SNP rs10931292 (HapMap CHB Dataset), our samples (4,479 CAD cases and 3,628 controls) can provide a statistical power of 100% to detect an association between rs10931292 and CAD with a type I error of 0.05.

SNP rs10931292 was genotyped in the case control population. Hardy-Weinberg disequilibrium tests showed that the genotyping data for SNP rs10931292 did not deviate from a randomly mated population ($P > 0.01$). The allelic association analysis did not identify significant association between rs10931292 and CAD ($P = 0.08$) (Table 4). However, significant association was identified between rs10931292 and CAD under a recessive genetic model ($P = 0.001$ before adjustment; $P = 0.005$ after adjustment for gender and age) (Table 5). This may be due to the possibility that the effect of two copies of the risk allele under a recessive model may be stronger than that of a single copy under a study of allelic association. When the study population was divided into different groups, the association between rs10931292 and CAD remained significant for early onset CAD and male CAD under a recessive model, with adjusted *P* values of 0.049 and 0.016, respectively (Table 5).

Discussion

In this large-scale population study with 2,313 study subjects, we assessed potential genetic association between the *TFPI* gene and coagulation, specifically focusing on the data from a coagulation test panel (fibrinogen levels, PT, APTT and TT). We identified significant association between *TFPI* SNP rs10931292 and plasma fibrinogen levels (Table 2). The minor allele G/C of SNP rs10931292 was associated with a significant increase of fibrinogen levels (Fig. 1). The association of *TFPI* SNP rs10931292 with coagulation parameters was

found to be specific to fibrinogen levels because no significant association was detected for PT, APTT or TT (Table 2). To the best of our knowledge, this is the first time that a *TFPI* variant is found to be significantly associated with fibrinogen levels. Because all genetic variants identified to date account for only 3% of heritability of fibrinogen levels (de Vries et al., 2016; Sabater-Lleal et al., 2013), our finding of a novel fibrinogen-associated variant in *TFPI* contributes to the elucidation of the genetic basis and biological pathways of fibrinogen levels.

An increased plasma fibrinogen level is a well-established risk factor for cardiovascular disease (Danesh et al., 2005; Lowe and Rumley, 2014). Therefore, we assessed whether *TFPI* SNP rs10931292 was associated with risk of CAD. Using a large case control association study population with 4,479 CAD patients and 3,628 controls, we identified significant association between *TFPI* SNP rs10931292 and CAD under a recessive genetic model (Table 5). Individuals with the GG/CC genotype had a significantly increased risk of CAD (OR = 1.23, $P = 0.005$) (Table 5). The minor allele G/C is the risk allele. To the best of our knowledge, this is the first report showing significant association between a *TFPI* variant and CAD. Together, our data suggest that *TFPI* SNP rs10931292 is associated with increased fibrinogen levels and increased risk of CAD (Tables 2). Specifically, the GG genotype was associated with an increased fibrinogen levels, thereby conferring a significant risk of CAD.

TFPI SNP rs10931292 is a T/A to C/G substitution located 287 bp upstream of the transcriptional start site (T-287C). Luciferase assays with a reporter with the *TFPI* promoter/regulatory region (−1999/+229) fused to the luciferase gene showed that the C allele had a much lower transactivation activity than the T allele ($P = 0.009$) in human microvascular endothelial cells (Amini and Iles, 2008). A reduced expression of *TFPI* may increase coagulation, resulting in increased risk of thrombosis, CAD and MI. We previously reported the first GWAS for CAD in the Chinese population and identified a SNP in the *ADTRP* gene (rs6903956) that reduces expression of *ADTRP* and increases risk of CAD and MI (Wang et al., 2011). The finding was replicated by multiple independent studies (Guo et al., 2012; Huang et al., 2015a; Tayebi et al., 2013). Lupu et al (2011) showed that *ADTRP* regulated the *TFPI* expression level in endothelial cells. SNP rs6903956 reduces the expression level of *ADTRP*, which reduces expression of *TFPI*, and increases risk of coagulation, thrombosis, CAD and MI (Luo et al., 2016). Therefore, *TFPI* SNP rs10931292 may use the similar mechanism as *ADTRP* SNP rs6903956 in increasing risk of CAD.

Genomic variants in *TFPI* were previously studied for their association with TFPI plasma levels, and other important factors important for coagulation. Dennis et al (Dennis et al., 2015) performed a review of genetic risk variants for plasma levels of TFPI and meta-analysis. They showed that SNPs rs5940 and rs7586970 in *TFPI* were associated with the plasma levels of TFPI, but no association was found for *TFPI* SNPs rs10153820 and rs10931292 (the variant analyzed in the present study) (Dennis et al., 2015). *TFPI* variants were also studied for their association with venous thrombosis, but both significant and negative associations were reported (Bezemer and Rosendaal, 2007; Hessner and Luhm, 2000; Kleesiek et al., 1999). No association was reported for *TFPI* SNP rs10931292 and venous thrombosis yet (Bezemer and Rosendaal, 2007). Opstad et al (2010) previously

studied several SNPs in *TFPI* for their association using 1,001 CAD patients and 204 controls, but did not identify any significant association between *TFPI* SNPs and CAD. One reason for their failure to identify any significant association between *TFPI* SNPs and CAD may be due to the small sample size, in particular, the small group of controls. In this study, we performed a large-scale case control association study with 4,479 CAD patients and 3,628 non-CAD controls and identified significant association between *TFPI* SNP rs10931292 and CAD under a recessive model (Table 5). The same *TFPI* SNP rs10931292 was also significantly associated with plasma fibrinogen levels (Table 2). However, we acknowledge that these significant associations need to be further validated in other independent Chinese populations and populations from other ethnic background. Moreover, one other limitation of this study is that for logistic regression analysis for CAD, only age and sex were included as covariates because other data such as BMI, lipid levels, hypertension and diabetes were missing for most of the general population control subjects.

In summary, we have identified a significant association between *TFPI* SNP rs10931292 and increased fibrinogen levels and risk of CAD. Our study, for the first time, implicates the *TFPI* genetic variation in the regulation of plasma fibrinogen levels and developmental of CAD.

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Abbreviations

TFPI	Tissue factor pathway inhibitor
CAD	Coronary artery disease
MI	Myocardial infarction
FIG or Fg	Fibrinogen levels
PT	Prothrombin time
APTT	Activated partial thromboplastin time
TT	Thrombin time
IRF1	Interferon regulatory factor 1

PCCB	Propionyl coenzyme A carboxylase
NLRP3	NLR family pyrin domain containing 3 isoform
OR	Odds ratio
95%CI	95% confidence interval

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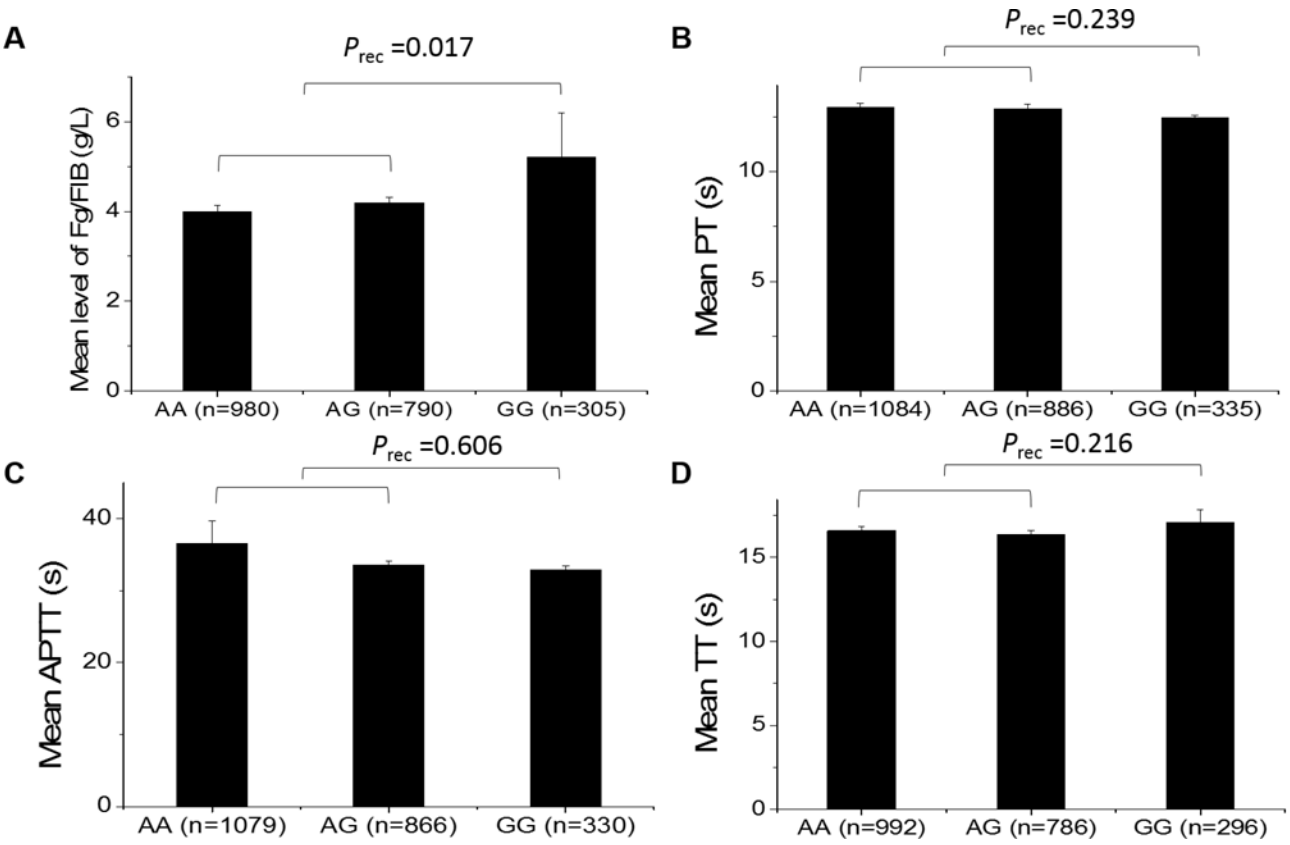

Figure 1. Analysis of association of TFPI SNP rs10931292 and coagulation indicators

(A) Fibrinogen levels (Fg/FIB). Mean fibrinogen levels for different genotypes: N_{AA}=980 subjects, 3.99 ± 0.15 g/L; N_{AG}=790 subjects, 4.18 ± 0.14 g/L; N_{GG}=305 subjects, 5.21 ± 0.97 g/L.(B) PPT. Mean PPT for different genotypes: N_{AA}=1084 subjects, 12.92 ± 0.20 s; N_{AG}=886 subjects, 12.86 ± 0.23 s; N_{GG}=335 subjects, 12.46 ± 0.10 s.(C) APTT. Mean APTT for different genotypes: N_{AA}=1079 subjects, 36.52 ± 3.14 s; N_{AG}=866 subjects, 33.59 ± 0.46 s; N_{GG}=330 subjects, 32.89 ± 0.49 s. (D) TT. Mean TT for different genotypes: N_{AA}=992 subjects, 16.58 ± 0.24 s; N_{AG}=786 subjects, 16.34 ± 0.28 s; N_{GG}=296 subjects, 17.08 ± 0.76 s. P_{rec}, *P* value after adjustment with age and gender under a recessive model.

Table 1

Characteristics of the study subjects for the association analysis between *TFPI* SNP rs10931292 and blood coagulation parameters.

Characteristics	N or %
Total number, n	2,313
Male number, n (%)	1,429 (61.78%)
Age, years (mean±SD)	64.93±11.97
CAD, n	1871 (80.9%)
Fg/FIB (Fibrinogen level) (mean±SEM)* (g/L)	4.07±0.08
PT (Prothrombin time) (Mean±SEM) (second)	12.83±0.13
APTT (Activated partial thromboplastin time) (mean±SEM) (second)	34.88±1.50
TT (Thrombin time)(mean± SEM) (second)	16.56±0.19

Table 2

Analysis of association of *TFPI* SNP rs10931292 with coagulation parameters.

Coagulation Indicator	Sample Size (AA/AG/GG)	P_{adj}			Effect [B (95% CI)]		
		Additive	Dominant	Recessive	Additive	Dominant	Recessive
Fibrinogen	980/790/305	[a]**0.026**	0.131	**0.017**	0.53 (0.06–1.00)	0.51 (−0.15–1.17)	1.14 (0.21–2.08)
		[b]0.027	0.136	0.018	0.52 (0.06–0.98)	0.51 (−0.16–1.17)	1.13 (0.20–2.07)
Prothrombin time	1,084/886/335	0.289	0.492	0.239	−0.19 (−0.55–0.17)	−0.18 (−0.69–0.33)	−0.44 (−1.17–0.29)
		0.283	0.487	0.232	−0.20 (−0.56–0.16)	−0.18 (−0.69–0.33)	−0.45 (−1.17–0.29)
Activated partial thromboplastin time	1,079/866/330	0.308	0.274	0.606	−2.16 (−6.32–2.00)	−3.32 (−9.27–2.63)	−2.23 (−10.68–6.23)
		0.353	0.300	0.679	−1.97 (−6.13–2.19)	−3.15 (−9.10–2.80)	−1.78 (−10.24–6.68)
Thrombin time	992/786/296	0.595	0.915	0.216	0.14 (−0.38–0.67)	−0.04 (−0.79–0.71)	0.67 (−0.40–1.74)
		0.595	0.915	0.216	0.14 (−0.38–0.67)	−0.04 (−0.79–0.71)	0.68 (−0.40–1.75)

P_{adj}, *P* value obtained from multiple linear modeling after adjustment for age and gender[a] or for age, gender and CAD[b].

Additive model = GG/AG/AA; Dominant model = GG+AG/AA; Recessive model = GG/AG+AA.

Table 3

Clinical and demographical characteristics of the case-control study population for testing association between *TFPI* SNP rs10931292 and CAD.

Characteristics	CAD Group	Control Group	*P*
Number (n)	4,479	3,628	–
MI, n (%)	1,083 (24.18%)	0	<0.001
Male, n (%)	2707 (60.44%)	2242 (61.80%)	0.22
Age, years (mean± SD) *	65.27±12.55	58.79±11.28	<0.001
Hypertension, n (%)	1982 (44.25%)	N/A	–
DM, n (%)	631 (14.09%)	N/A	–
Smoker, n (%)	1115 (24.89%)	N/A	–
Drinker, n (%)	773 (17.26%)	N/A	–
Total cholesterol (mmol/L) *	5.97 ± 1.33	N/A	–
LDL cholesterol (mmol/L) *	2.76 ±0.15	N/A	–
HDL cholesterol (mmol/L) *	1.55 ± 0.28	N/A	–
Triglyceride (mmol/L) *	1.74 ± 0.12	N/A	–

* Data were presented as mean ± SEM; N/A. data not available or not complete.

Table 4

Analysis of allelic association between *TFPI* SNP rs10931292 and CAD.

Population (n, case/control)	P_{hwe}	Risk Allele	Frequency (Case/Control)	Before adjustment		After adjustment	
				P_{obs}[a]	OR(95%CI)	P_{adj}[b]	OR(95%CI)
Overall CAD (4,479/3,628)	0.08	G	0.34/0.33	0.08	1.06 (0.99–1.14)	0.08	1.07 (0.99–1.15)
Early-onset CAD (1,541/3,628)	0.08	G	0.33/0.33	0.94	1.00 (0.89–1.14)	0.64	1.04 (0.89–1.20)
Female CAD (1,698/1,329)	0.33	G	0.35/0.33	0.51	1.04 (0.93–1.16)	0.62	1.03 (0.91–1.16)
Male CAD (2,707/2,242)	0.20	G	0.33/0.32	0.05	1.09 (1.00–1.19)	0.07	1.09 (0.99–1.19)

P_{hwe}, *P* value from Hardy-Weinberg disequilibrium tests; P_{obs}, observed *P* value; P_{adj}, *P* value after adjustment for covariates of age and gender; OR, odds ratio; 95% CI, 95% confidence interval; Early-onset CAD, males age 50 years or younger; females age 55 years or younger at the first diagnosis of the disease.

Table 5

Analysis of genotypic association between *TFPI* SNP rs10931292 and CAD under three different genetic models.

Population (n, case/control)	Genetic model	Before adjustment		After adjustment	
		P_{obs}[a]	OR (95%CI)	P_{adj}[b]	OR (95%CI)
Overall CAD (4479/3628)	Additive	0.089	1.06 (0.99–1.13)	0.088	1.06 (0.99–1.14)
	Dominant	0.826	1.01 (0.92–1.11)	0.618	1.03 (0.93–1.13)
	Recessive	**0.001**	1.25 (1.09–1.44)	**0.005**	1.23 (1.06–1.42)
Early-onset CAD (700/3628)	Additive	0.944	1.00 (0.89–1.14)	0.644	1.04 (0.90–1.20)
	Dominant	0.428	1.07 (0.91–1.26)	0.061	1.21 (0.99–1.46)
	Recessive	0.167	1.19 (0.93–1.53)	0.049	1.35 (1.00–1.81)
Female CAD (1698/1329)	Additive	0.524	1.04 (0.93–1.15)	0.634	1.03 (0.92–1.16)
	Dominant	0.625	1.04 (0.89–1.21)	0.804	1.02 (0.87–1.20)
	Recessive	0.038	1.27 (1.01–1.60)	0.169	1.19 (0.93–1.52)
Male CAD (2707/2242)	Additive	0.058	1.09 (1.00–1.18)	0.079	1.08 (0.99–1.18)
	Dominant	0.424	1.05 (0.93–1.18)	0.409	1.05 (0.93–1.19)
	Recessive	**0.006**	1.28 (1.07–1.53)	**0.016**	1.25 (1.04–1.50)

P_{obs}, observed *P* value (X^2 test); P_{adj}, *P* value after adjustment for covariates (logistic regression analysis by adjusting for gender and age); OR, odds ratio; 95% CI, 95% confidence interval; Early-onset CAD, males age 50 years or younger; females age 55 years or younger at the first diagnosis of the disease; Additive model = GG/AG/AA; Dominant model = GG+AG/AA; Recessive model = GG/AG+AA.