Association of TFPI polymorphisms rs8176592, rs10931292, and rs10153820 with venous thrombosis
A meta-analysis
Yunhong Zhang, MDab, Aimei Pang, MD, Lin Zhao, MD, Qiang Guo, PhD, Zhen Zhang, PhD, Xiaoxiao Zhu, MDb, Ran Wei, PhD, Xunqiang Yin, MDab, Bin Wang, PhDac, Xia Li, PhD.

Abstract
Background: Tissue factor pathway inhibitor (TFPI) polymorphisms are known to be involved in venous thrombosis; however, any correlation between the TFPI polymorphisms rs8176592, rs10931292, and rs10153820 and venous thrombosis remains controversial. This meta-analysis aimed to elucidate the relationship between these TFPI polymorphisms and the susceptibility to venous thrombosis.

Methods: A literature search for relevant studies was conducted in PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure (CNKI), and Wanfang Med Online databases. Odds ratios (ORs) and their corresponding 95% confidence intervals (95% CIs) were calculated using fixed-effect/random-effect models by the STATA 12.0 software. Sources of heterogeneity were analyzed by subgroup analysis.

Results: Eleven case-control studies involving 3740 subjects (1362 venous thrombosis patients and 2378 healthy controls) were included. The TFPI rs8176592 polymorphism was associated with increased risk of venous thrombosis in the whole population, while no significant association was found between rs10931292/rs10153820 and venous thrombosis. In subgroup analysis based on ethnicity, an increased risk was observed with rs8176592 polymorphism in Asians (Recessive model, OR = 1.48, 95% CI = 1.06–2.07, P = .023). An increased risk associated with rs10931292 was identified in non-Asians (Recessive model, OR = 1.42, 95% CI = 1.03–1.97, P = .033). No significant risk was found in either Asians or non-Asians with the rs10153820 polymorphism. In subgroup analysis based on the source of controls, increased risks were identified in the hospital-based group with rs8176592 polymorphism and in the population-based group with rs10931292 polymorphism, whereas decreased risk was identified in the hospital-based group with the rs10931292 and rs10153820 polymorphisms.

Conclusion: Meta-analysis suggested that different TFPI polymorphisms may have different associations with venous thrombosis. TFPI rs8176592 polymorphism may increase the risk of venous thrombosis, especially in Asians and hospital-based patients. The TFPI rs10931292 polymorphism may increase the venous thrombosis risk for both non-Asians and population-based patients. Moreover, rs10931292 and rs10153820 polymorphisms of TFPI may decrease the risk of venous thrombosis for hospital-based patients.

Abbreviations: CIs = confidence intervals, CNKI = China National Knowledge Infrastructure, CVT = cerebral venous thrombosis, DVT = deep vein thrombosis, HWE = Hardy–Weinberg equilibrium, NOS = Newcastle–Ottawa quality assessment scale, ORs = odds ratios.
1. Introduction

Venous thrombosis is a widespread and serious disorder that occurs in the blood coagulation process in the venous system and leads to venous obstruction; deep vein thrombosis (DVT) and pulmonary embolism (PE) are the most commonly encountered manifestations. Venous thrombosis is estimated to vary between 1 and 2 per 1000 annually in the adult population. Venous thrombosis is associated with many types of risk factors, such as genetics, weight, age, sex, region, ethnicity, lifestyle, and environmental exposure.

Tissue factor pathway inhibitor (TFPI) encodes TFPI, a Kunitz-type serine protease inhibitor. The TFPI downregulates the tissue factor (TF)-dependent pathway by inhibiting both tissue factor-activated factor VII and activation of factor X, thereby limiting clot growth and preventing prothrombin to thrombin conversion. Low TFPI plasma level is associated with increases risk of venous thrombosis. The TFPI is localized on human chromosome 2q and contains 10 exons and 9 introns.

The search terms were as follows: "tissue factor pathway inhibitor" or "TFPI" and ("polymorphism" or "mutation" or "variant" or "allele" or "genotype" or "SNP") and ("venous thromboembolism" or "VTE" or "deep venous thrombosis" or "deep vein thrombosis" or "DVT" or "venous thrombosis" or "pulmonary thromboembolism" or "PTE" or "pulmonary embolism" or "PE" or "cerebral venous thrombosis" or "CVT"). Moreover, potentially related studies were also collected from the reference lists of the screened full-text articles above.

2. Methods

2.1. Search strategy

Relevant studies were identified in the following databases: PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure (CNKI), and Wanfang Med Online databases by searching up to October 23, 2018 without language restrictions. The search terms were as follows: ("tissue factor pathway inhibitor" or "TFPI") and ("polymorphism" or "mutation" or "variant" or "allele" or "genotype" or "SNP") and ("venous thromboembolism" or "VTE" or "deep venous thrombosis" or "deep vein thrombosis" or "DVT" or "venous thrombosis" or "pulmonary thromboembolism" or "PTE" or "pulmonary embolism" or "PE" or "cerebral venous thrombosis" or "CVT"). Moreover, potentially related studies were also collected from the reference lists of the screened full-text articles above.

2.2. Inclusion and exclusion criteria

All studies included in the meta-analysis met the following criteria: First, the design was a cohort or case-control study. Second, evaluated the association between TFPI polymorphisms and venous thrombosis. Third, sufficient genotype data for calculating the odds ratios (ORs) with 95% confidence intervals (95% CIs). Exclusion criteria were: First, duplicate publication. Second, animal models. Third, obviously irrelevant studies. Fourth, comment, review, or meta-analysis. Fifth, the genotype frequencies were unavailable.

2.3. Data extraction

The bibliography search and data extraction were conducted independently by 2 investigators. The following information from each study was extracted: the 1st author’s name, year of publication, country, ethnicity (Asian or non-Asian), genotyping method, source of controls, venous thrombosis type, numbers of cases and controls with the TFPI genotypes, and Hardy–Weinberg equilibrium (HWE) in controls. Source of controls was categorized as hospital-based or population-based population.

2.4. Quality assessment

A quality assessment was independently performed for all of the included studies by 2 authors using the Newcastle-Ottawa quality assessment scale (NOS), and any disagreement was resolved by discussion and consensus. The NOS comprises the following three parameters of quality: selection, comparability, and exposure. The range of the scores is from 0 to 9, and studies with scores of 6 to 9 points are considered to be high quality.

2.5. Statistical analysis

The possible associations between the TFPI polymorphisms and venous thrombosis were evaluated by ORs and 95% CIs. Pooled ORs were obtained from combination of individual studies according to the codominant model (T vs C for rs8176592 and rs10931292; C vs T for rs10153820), homoyzous model (TT for rs8176592 and rs10931292; CC vs TT for rs10153820), heterozygous model (TC vs CC for rs8176592 and rs10931292; CT vs TT for rs10153820), dominant model (TT+TC vs CC for rs8176592 and rs10931292; CC+CT vs TT for rs10153820), and recessive model (TT vs TC+CC for rs8176592 and rs10931292; CC vs TT for rs10153820). For each genetic comparison model, subgroup analysis according to ethnicity was investigated to estimate ethnic-specific ORs for Asians and non-Asians. Z-test was used to assess the significance of the pooled OR, with $P < .05$ considered statistically significant. Heterogeneity was assessed by Cochrane’s Q test and the I-square statistic. Significant heterogeneity was considered when $P < .05$, or $I^2 > 50\%$. In case of no or moderate heterogeneity ($P > .05$ or $I^2 < 50\%$), the fixed-effect model (Mantel-Haenszel test) was applied; otherwise, the random-effects model (Der Siminlon and Laird method) was used. Subgroup analysis based on ethnicity and source of control was carried out to further explore possible explanations for heterogeneity. Sensitivity analysis was performed to confirm whether the results were considerably affected by any single study. Potential publication bias was explored using Begg’s test. Associations were considered statistically significant when $P > .05$. Meta-analysis was conducted using STATA version 12.0 (Stata Corporation, College Station, TX).

3. Results

3.1. Search results and study characteristics

The detailed process of study selection is summarized in Figure 1. A total of 234 potentially relevant publications were initially identified; 214 were excluded after the titles and abstracts were screened. The 20 candidate articles were subjected to further evaluation and nine were excluded for the following reasons: 1...
Figure 1. Flow diagram of literature search and study selection.

| Gene polymorphisms | Study | Year | Country | Ethnicity | Genotyping methods | Source of controls | Venous thrombosis type | Genotype | Quality score | Cases | Controls | P* |
|--------------------|-------|------|---------|-----------|-------------------|-------------------|----------------------|-----------|--------------|-------|----------|----|
| rs8176592          | Ameziane et al [27] | 2002 | France | non-Asian | PCR               | HB                | VTE                  | 167/142/21 | 384/358/84 | .967  | 8        |
|                    | Lincz et al [28]  | 2007 | Australia | non-Asian | PCR-RFLP          | HB                | VTE                  | 7/18/1    | 29/25/2   | .222  | 7        |
|                    | Sidelmann et al [29] | 2008 | Denmark | non-Asian | PCR               | HB                | DVT                  | 24/28/5   | 62/23/8   | .238  | 7        |
|                    | Opstad et al [30] | 2010 | Norway | non-Asian | Real-time PCR     | PB                | VT                   | 71/87/0   | 196/213/0 | .000  | 8        |
|                    | Pshukov et al [31] | 2012 | India | Asian    | PCR-RFLP          | HB                | DVT                  | 32/183/3  | 20/174/8  | .000  | 7        |
|                    | Sidelmann et al [32] | 2015 | Denmark | non-Asian | PCR-SSCP, PCR-RFLP | HB                | DVT                  | 33/77/7   | 34/6/0    | .608  | 8        |
|                    | Kamal et al [33]  | 2017 | India  | Asian    | PCR-RFLP          | HB                | DVT                  | 7/18/1    | 75/23/2   | .879  | 7        |
| rs10931292         | Lincz et al [28]  | 2007 | Australia | non-Asian | PCR-RFLP          | HB                | VTE                  | 20/6/0    | 39/15/2   | .713  | 7        |
|                    | Antirii et al [34] | 2008 | England | non-Asian | PCR               | HB                | DVT                  | 133/23/9  | 173/32/2  | .372  | 7        |
|                    | Liu et al [35]    | 2009 | China  | Asian    | PCR-RFLP          | HB                | VTE                  | 56/42/16  | 72/36/8   | .246  | 7        |
|                    | Opstad et al [32] | 2010 | Norway | non-Asian | Real-time PCR     | PB                | VT                   | 119/26/2  | 296/190/7 | .398  | 8        |
|                    | Kwon et al [36]   | 2014 | Korea  | Asian    | Real-time PCR     | PB                | VTE                  | 15/23/2   | 11/23/4   | .287  | 7        |
| rs10153820         | Miyata et al [37] | 1998 | Japan  | Asian    | PCR               | PB                | DVT                  | 54/46/11  | 130/66/29 | .068  | 8        |
|                    | Lincz et al [28]  | 2007 | Australia | non-Asian | PCR-RFLP          | HB                | VTE                  | 15/10/1   | 43/31/0   | .326  | 7        |
|                    | Liu et al [35]    | 2009 | China  | Asian    | PCR-RFLP          | HB                | VTE                  | 43/41/26  | 52/50/14  | .712  | 7        |
|                    | Opstad et al [32] | 2010 | Norway | non-Asian | Real-time PCR     | PB                | VT                   | 106/32/0  | 324/84/6  | .835  | 8        |
|                    | Kamal et al [33]  | 2017 | India  | Asian    | ASP               | HB                | DVT                  | 65/29/7   | 88/10/2   | .020  | 7        |

* Genotype for TFPI rs8176592, TT/TC/CC; TFPI rs10931292, TT/TC/CC; TFPI rs10153820, CC/CT/TT.
† Hardy–Weinberg equilibrium in the control group.
‡ Assessed by the Newcastle–Ottawa Assessment Scale for case-control studies.
ASP = allele specific PCR, DVT = deep venous thrombosis, HB = hospital-based, PB = population-based, PCR-RFLP = PCR-restriction fragment length polymorphism, PCR-SSCP = PCR-single strand conformation polymorphism, VT = venous thrombosis, VTE = venous thromboembolism.
was not control; 8 were not usable genotype frequency data. Finally, 11 articles shown in Table 1 met the inclusion criteria and were included in the final meta-analysis.\cite{26-36} These studies included 3740 subjects (1362 cases and 2378 controls). The TFPI genotypic frequencies in all the subjects of control groups were consistent with HWE except three studies for rs8176592, and one study for rs10153820 (Table 1). Study quality was assessed by NOS, and the scores ranged from 7 to 8, so the studies were considered to be high quality.

3.2. Meta-analysis results

The main results of this meta-analysis and heterogeneity assessment are presented in Table 2. The intron 7 rs8176592, promoter rs10931292 and rs10153820 polymorphisms of TFPI were studied.\cite{27} There were 8 studies with 976 cases and 1780 controls for TFPI rs8176592 polymorphism. All were case-control studies, including 3 venous thromboembolism (VTE) studies,\cite{27,28,34} 3 DVT studies,\cite{29,35,36} 1 venous thrombosis study,\cite{32} and 1 cerebral venous thrombosis (CVT) study.\cite{33}

![Forest plots for the associations between TFPI rs8176592 polymorphism and venous thrombosis. (A) codominant genetic model, (B) homozygous genetic model, (C) heterozygous genetic model, (D) dominant genetic model, (E) recessive genetic model. CI = confidence interval, OR = odds ratio, TFPI = tissue factor pathway inhibitor.](image-url)
Subjects were sampled from France, Australia, Denmark, Norway, India, Korea, and China. Significant associations between TFPI rs8176592 polymorphism and elevated risk of venous thrombosis was found in 3 models (homozygous: OR = 1.61, 95% CI = 1.08–2.40, P = .020; heterozygous model: OR = 1.53, 95% CI = 1.02–2.28, P = .039; dominant model: OR = 1.55, 95% CI = 1.05–2.28, P = .028) (Table 2 and Fig. 2). In the subgroup analysis based on ethnicity, TFPI rs8176592 polymorphism significantly increased the risk of venous thrombosis in Asians (recessive model: OR = 1.48, 95% CI = 1.06–2.07, P = .023), but not in non-Asians (recessive: OR = 0.81, 95% CI = 0.51–1.30, P = .387) (Table 3). Moreover, subgroup analysis

Table 2
Meta-analysis results for the TFPI polymorphisms and venous thrombosis.

| Gene polymorphisms | Inherited model | Heterogeneity-test | P for Q test | I² (%) | Analysis model | Pooled OR (95% CI) | P |
|---------------------|-----------------|-------------------|-------------|--------|----------------|-------------------|---|
| rs8176592           | Codominant (T vs C) | .064 | 47.5 | FEM | 1.12 (0.99,1.27) | .076 |
|                     | Homozygous (TT vs CC) | .147 | 38.8 | FEM | 1.61 (1.08,2.40) | .020 |
|                     | Heterozygous (CT vs CC) | .695 | 0.0 | FEM | 1.53 (1.02,2.28) | .039 |
|                     | Dominant (TT+TC vs CC) | .506 | 0.0 | FEM | 1.55 (1.05,2.28) | .028 |
|                     | Recessive (TT vs TC+CC) | .015 | 59.7 | REM | 1.05 (0.77,1.44) | .752 |
| rs10031292          | Codominant (T vs C) | .080 | 52.1 | REM | 1.11 (0.79,1.56) | .558 |
|                     | Homozygous (TT vs CC) | .071 | 53.6 | REM | 0.84 (0.29,2.44) | .754 |
|                     | Heterozygous (CT vs CC) | .059 | 55.9 | REM | 0.73 (0.24,2.22) | .583 |
|                     | Dominant (TT+TC vs CC) | .865 | 51.2 | REM | 0.82 (0.30,2.52) | .697 |
|                     | Recessive (TT vs TC+CC) | .126 | 44.4 | REM | 1.17 (0.01,1.53) | .240 |
| rs10153820          | Codominant (C vs T) | .006 | 72.6 | REM | 0.66 (0.44,1.00) | .050 |
|                     | Homozygous (CC vs TT) | .121 | 45.2 | FEM | 0.63 (0.38,1.04) | .070 |
|                     | Heterozygous (CT vs TT) | .233 | 28.2 | FEM | 0.77 (0.47,1.28) | .320 |
|                     | Dominant (CC+CT vs TT) | .127 | 44.3 | FEM | 0.66 (0.41,1.06) | .088 |
|                     | Recessive (CC vs CT+TT) | .023 | 64.8 | REM | 0.64 (0.41,1.00) | .051 |

CI = confidence interval, FEM = fixed-effects model, OR = odds ratio, P = P-value of overall effect, REM = random-effects model, TFPI = tissue factor pathway inhibitor.

Table 3
The results of ethnicity subgroup analysis for TFPI polymorphisms and venous thrombosis.

| Gene polymorphisms | Inherited model | Subgroup | Heterogeneity-test | P for Q test | I² (%) | Analysis model | Pooled OR (95% CI) | P |
|---------------------|-----------------|----------|-------------------|-------------|--------|----------------|-------------------|---|
| rs8176592           | Codominant (T vs C) | Non-Asian | .027 | 67.2 | REM | 0.92 (0.66,1.28) | .605 |
|                     | Homozygous (TT vs CC) | Non-Asian | .368 | 5.1 | REM | 1.22 (0.98,1.52) | .074 |
|                     | Heterozygous (CT vs CC) | Asian | .213 | 35.4 | REM | 1.15 (0.52,2.57) | .729 |
|                     | Heterozygous (CT vs CC) | Non-Asian | .972 | 0.0 | FEM | 1.55 (0.97,2.47) | .068 |
|                     | Dominant (TT+TC vs CC) | Asian | .227 | 32.6 | REM | 1.48 (0.67,3.23) | .330 |
|                     | Dominant (TT+TC vs CC) | Non-Asian | .567 | 0.0 | FEM | 1.49 (0.95,2.33) | .084 |
|                     | Recessive (TT vs TC+CC) | Asian | .217 | 34.5 | FEM | 1.74 (0.81,3.74) | .158 |
|                     | Recessive (TT vs TC+CC) | Non-Asian | .011 | 72.9 | REM | 0.81 (0.51,1.30) | .387 |
|                     | Recessive (TT vs TC+CC) | Asian | .391 | 0.2 | REM | 1.49 (1.06,2.07) | .023 |
|                     | Recessive (TT vs TC+CC) | Non-Asian | .424 | 0.0 | REM | 1.25 (0.92,1.64) | .168 |
|                     | Codominant (T vs C) | Asian | .037 | 77.1 | REM | 0.98 (0.44,2.17) | .956 |
|                     | Homozygous (TT vs CC) | Non-Asian | .117 | 53.4 | REM | 0.65 (0.13,3.35) | .610 |
|                     | Homozygous (TT vs CC) | Asian | .045 | 75.1 | REM | 1.26 (0.17,9.30) | .819 |
|                     | Heterozygous (CT vs CC) | Non-Asian | .095 | 57.5 | REM | 0.43 (0.07,2.53) | .349 |
|                     | Heterozygous (CT vs CC) | Asian | .160 | 44.4 | REM | 1.27 (0.36,4.59) | .711 |
|                     | Dominant (TT+TC vs CC) | Non-Asian | .113 | 54.2 | REM | 0.60 (0.11,3.09) | .336 |
|                     | Dominant (TT+TC vs CC) | Asian | .079 | 67.6 | REM | 1.23 (0.24,4.65) | .804 |
|                     | Recessive (TT vs TC+CC) | Non-Asian | .884 | 0.0 | REM | 1.42 (1.03,1.97) | .033 |
|                     | Recessive (TT vs TC+CC) | Asian | .098 | 63.5 | REM | 0.92 (0.38,2.21) | .849 |
| rs10031292          | Codominant (C vs T) | Non-Asian | .093 | 64.5 | REM | 0.72 (0.33,1.60) | .423 |
|                     | Codominant (C vs T) | Asian | .004 | 82.3 | REM | 0.61 (0.34,1.11) | .107 |
|                     | Homozygous (CC vs TT) | Non-Asian | .106 | 61.6 | REM | 0.77 (0.02,25.74) | .885 |
|                     | Homozygous (CC vs TT) | Asian | .101 | 56.4 | REM | 0.56 (0.24,1.29) | .172 |
|                     | Heterozygous (CT vs TT) | Non-Asian | .187 | 42.5 | FEM | 1.27 (0.16,12.16) | .775 |
|                     | Heterozygous (CT vs TT) | Asian | .169 | 43.7 | FEM | 0.75 (0.44,1.26) | .275 |
|                     | Dominant (CC+CT vs TT) | Non-Asian | .127 | 57.2 | REM | 0.88 (0.03,24.13) | .942 |
|                     | Dominant (CC+CT vs TT) | Asian | .095 | 57.5 | REM | 0.60 (0.27,1.36) | .219 |
|                     | Recessive (CC vs CT+TT) | Non-Asian | .151 | 51.5 | REM | 0.70 (0.33,1.47) | .347 |
|                     | Recessive (CC vs CT+TT) | Asian | .011 | 77.7 | REM | 0.60 (0.30,1.18) | .140 |

Pooled OR = odds ratio; CI = confidence interval; REM = random-effects model; TFPI = tissue factor pathway inhibitor.
based on source of controls demonstrated that TFPI rs8176592 polymorphism was related to increased venous thrombosis risk in the hospital-based group (homozygous: OR = 1.61, 95% CI = 1.08–2.40, P = .020; heterozygous: OR = 1.53, 95% CI = 1.02–2.28, P = .039; dominant: OR = 1.55, 95% CI = 1.05–2.28, P = .028) (Table 4), while no statistical correlation was found in the population-based group.

There were 5 studies with 453 cases and 795 controls for TFPI rs10153820 polymorphism. All were case-control studies, including 2 VTE studies,[26,31] 2 DVT studies,[28,34] and 1 venous thrombosis study.[32] Subjects were sampled from Japan, Australia, China, Norway, and India. No obvious associations were found in any of the genetic models (Table 2). In the ethnicity subgroup analysis, the TFPI rs10153820 polymorphism had no significant association with the risk of venous thrombosis in Asians or non-Asians (Table 3).

However, subgroup analysis based on source of controls demonstrated that TFPI rs10153820 polymorphism was related to decreased venous thrombosis risk in hospital-based group (codominant: OR = 0.46, 95% CI = 0.25–0.84, P = .011; homozygous: OR = 0.37, 95% CI = 0.19–0.72, P = .004; heterozygous: OR = 0.47, 95% CI = 0.24–0.94, P = .033; dominant: OR = 0.39, 95% CI = 0.21–0.74, P = .039; recessive: OR = 0.45, 95% CI = 0.21–0.96, P = .039) (Table 4).

3.3. Publication bias

The publication bias of the selected articles was detected by Begg’s test. No publication bias was detected for rs8176592 polymorphism in any of the genetic comparison models (codominant: t = 1.60, P = .160; homozygous: t = 0.71, P = .479; heterozygous: t = 0.63, P = .563; dominant: t = 0.84, P = .448; recessive: t = 1.02, P = .349) (Fig. 3). In addition, no publication bias was detected for rs10153820 polymorphism in any of the genetic comparison models (codominant: t = 0.46, P = .650; homozygous: t = 0.71, P = .479; heterozygous: t = 0.63, P = .563; dominant: t = 0.84, P = .448; recessive: t = 1.02, P = .349) (Fig. 3).
Bias was detected for rs10931292 and rs10153820 polymorphisms in any of the genetic comparison models (all results: $P > .05$).

### 3.4 Sensitivity analysis

Sensitivity analysis was conducted to detect the influence of each individual study on the pooled ORs by sequentially removing one study each time. The data demonstrated that the pooled ORs were stable with the removal of any study in any of the models (Fig. 4).

### 4. Discussion

Venous thrombosis is the 3rd most common cardiovascular disease that seriously endangers human health,[7] While its...
pathogenesis is still unclear, accumulating evidence has demonstrated that gene polymorphisms are involved. The TFPI is an important natural anticoagulant between the blood and the vascular cells which inhibits the earliest steps in activation of the extrinsic coagulation pathway. Any changes that occur in TFPI have the potential to impact the ability of the coagulation pathway, which may affect the occurrence and the development of venous thrombosis.

Despite recent attention paid to the association between the polymorphisms of TFPI (rs8176592, rs10931292, and rs10153820) and the risk of venous thrombosis in recent years, the opinions are still controversial. For example, 5 studies report

Figure 4. Sensitivity analysis for the associations between the TFPI rs8176592 polymorphism and venous thrombosis. (A) codominant genetic model, (B) homozygous genetic model, (C) heterozygous genetic model, (D) dominant genetic model, (E) recessive genetic model. CI = confidence interval, TFPI = tissue factor pathway inhibitor.
that \textit{TFPI} rs8176592 polymorphism was related to the risk of venous thrombosis, [27,28,32,33,36] while 3 studies report it was not [29,34,35]. Amini reported that the \textit{TFPI} rs10931292 polymorphism was related with venous thrombosis risk, [30] while 4 other studies reported that it was not related to the risk of venous thrombosis. [28,31,32,34] In addition, 4 studies reported that the \textit{TFPI} rs10153820 polymorphism was related to the risk of venous thrombosis, [28,31,32,34] while Miyata reported that it was not [28]. Therefore, we conducted the present meta-analysis to comprehensively evaluate the available data on the association between \textit{TFPI} rs8176592, rs10931292, and rs10153820 polymorphisms and venous thrombosis risk. According to the standards of NOS, all 11 studies were considered to be high quality research.

In this study, pooled analysis demonstrated that \textit{TFPI} rs8176592 polymorphism was significantly associated with increased risk of venous thrombosis, especially in Asians and hospital-based patients. A possible reason for the increased association among Asians is the linkage disequilibrium patterns in alleles in different ethnicities. The \textit{TFPI} rs8176592 polymorphism may play a more important role in the risk of venous thrombosis in Asians. No significant association was found in the population-based group, which may be due to the limited sample size of the available studies. However, no significant association was found between rs10931292, rs10153820 and venous thrombosis in any of the 5 models. Subgroup analysis based on ethnicity showed that \textit{TFPI} rs10931292 polymorphism was associated with increased risk of venous thrombosis in non-Asians, whereas no significant association was found in Asians, indicating that \textit{TFPI} rs10931292 polymorphism may be a potential biomarker of venous thrombosis for non-Asians. Interestingly, subgroup analysis based on source of controls demonstrated that \textit{TFPI} rs10931292 polymorphism might increase the risk of venous thrombosis in the population-based group while decrease the risk of venous thrombosis in the hospital-based group. The possible reason may be attributed to the differences in the patient selection criteria, as well as the number of subjects. Moreover, in subgroup analysis based on source of controls, it was found that \textit{TFPI} rs10153820 polymorphism might decrease the risk of venous thrombosis in the hospital-based group in all genetic models but not in the population-based group, suggesting a higher importance of \textit{TFPI} rs10153820 polymorphism for hospital-based patients.

In addition to ethnicity and source of controls, subgroup analysis was also considered from venous thrombosis type and genotyping methods, but the genetic frequency was not available and the subgroup analysis could not be carried out. Furthermore, even though the region was divided according to ethnicity, the ethnic origin of venous thrombosis patients and healthy controls could not be obtained because of the limited information in the included studies. Still, the sensitivity analysis showed that no individual study had a significant effect on the pooled results, and Begg’s test provided no evidence for funnel-plot asymmetry, indicating that there was no obvious publication bias in the present study.

To our knowledge, this is the meta-analysis that reveals the association between \textit{TFPI} polymorphism and the risk of venous thrombosis. Our findings contribute to the better understanding of genetic polymorphisms of \textit{TFPI} in venous thrombosis and pinpoint a novel biomarker and potential therapeutic target for venous thrombosis patients. Meanwhile, we are aware of several limitations in this study. Firstly, the sample size of the individual studies included in the current meta-analysis were relatively small and the information concerning the patients was not adequate to perform more thorough subgroup studies such as age, weight, sex, lifestyle, environmental exposures, and subtype of venous thrombosis to evaluate the heterogeneity among the included studies. Secondly, the polymorphisms of \textit{TFPI} rs8176592, rs10931292, and rs10153820 were detected by different methods, which might influence the accuracy of the results. Moreover, even though the geographical information could be obtained from the included studies, the information of the ethnic origin of patients was unavailable from the enrolled studies. Further evidence gathered through well-designed and well-conducted trials to better elucidate the relation between \textit{TFPI} polymorphism and venous thrombosis is needed to confirm our results.

5. Conclusion

Meta-analysis of the available data suggested that different \textit{TFPI} polymorphisms may have different associations with venous thrombosis risk. \textit{TFPI} rs8176592 associated with increased risk of venous thrombosis, especially in Asians and hospital-based patients. The \textit{TFPI} rs10931292 may increase the risk of venous thrombosis in non-Asians and population-based patients, while decrease that in hospital-based patients. \textit{TFPI} rs10153820 polymorphism may decrease the risk of venous thrombosis in hospital-based patients. These findings highlight the role of \textit{TFPI} polymorphism in venous thrombosis and offer potential biomarkers for the risk evaluation, diagnosis, and therapeutic strategy for the clinic.

Author contributions

Conceptualization: Qiang Guo.
Data curation: Yunhong Zhang.
Formal analysis: Aimei Pang.
Investigation: Aimei Pang, Xiaoxiao Zhu, Xunqiang Yin.
Methodology: Yunhong Zhang.
Project administration: Ran Wei, Xia Li.
Resources: Lin Zhao, Bin Wang, Xia Li.
Software: Zhen Zhang.
Supervision: Xia Li.
Validation: Bin Wang.
Writing – original draft: Yunhong Zhang.
Writing – review & editing: Xia Li.
Xia Li orcid: 0000-0001-8938-1206.

References

[1] Bafunno V, Margaglione M. Genetic basis of thrombosis. Clin Chem Lab Med 2010;48(Suppl 1):S41–51.
[2] Hong J, Lee JH, Yim HY, et al. Incidence of venous thromboembolism in Korea from 2009 to 2013. PLoS One 2018;13:e0191897.
[3] Tait C, Baglin T, Watson H, et al. Guidelines on the investigation and management of venous thrombosis at unusual sites. Br J Haematol 2012;159:28–38.
[4] Sekere\'er\'eg F, Johansen AM, Abildgaard U. Venous thromboembolism–incidence and risk factors in Oslo. Tidsskr Nor Laegeforen 2000;120: 1240.
[5] Hert JA, Spencer FA, White RH. The epidemiology of venous thromboembolism. J Thromb Haemost 2016;14:1–14.
[6] Huang W, Goldberg RJ, Anderson FA, et al. Secular trends in occurrence of acute venous thromboembolism: the Worcester VTE study (1985–2009). Am J Med 2014;127:829–39.
[7] Niesz IA, Christiansen SC, Romundstad P, et al. Incidence and mortality of venous thrombosis: a population-based study. J Thromb Haemost 2007;5:692–9.
[8] Stubbs MJ, Mouys M, Thomas M. Deep vein thrombosis. BMJ 2018;360:k351.
[9] Souto JC, Almasy L, Borrell M, et al. Genetic susceptibility to thrombosis and its relationship to physiological risk factors: the GAIT study. Genetic analysis of idiopathic thrombophlebitis. Am J Hum Genet 2002;70:1452–9.
[10] Larsen TB, Sørensen HT, Snythe A, et al. Major genetic susceptibility for venous thromboembolism in men: a study of Danish twins. Epidemiology 2003;14:328–32.
[11] Abdollahi M, Cushman M, Rosendaal FR. Obesity: risk of venous thrombosis and the interaction with coagulation factor levels and oral contraceptive use. Thrombo Haemost 2003;89:493–8.
[12] Cushman M. Epidemiology and risk factors for venous thrombosis. Curr Opin Cardiol 2003;18:331–7.
[13] Zhao XP, He SW, Yue B, et al. Molecular characterization, expression analysis, and bactericidal activity of the derivative peptides of TFPI-1 and TFPI-2 in half-smooth tongue sole, Cynoglossus semilaevis. Res Pract Thromb Haemost 2016;58:563–71.
[14] Augustsson C, Svensson A, Kjaer B, et al. Factor Xa and VIIa inhibition by Tissue Factor Pathway Inhibitor is prevented by a monoclonal antibody to its Kunitz-1 domain. J Thromb Haemost 2018.
[15] Ellery PE, Adams MJ. Tissue factor pathway inhibitor: then and now. Semin Thromb Hemost 2014;40:881–6.
[16] Wood JP, Ellery PE, Maroney SA, et al. Biology of tissue factor pathway inhibitor. Blood 2014;123:2943–43.
[17] Thomassen S, Mastenbroek TG, Swieringa F, et al. Suppressive role of factor Xa and VIIa inhibition in thrombin generation under flow is restricted to low procoagulant strength. Thromb Haemost 2018;118:502–13.
[18] Dennis J, Kassam I, Morange PE, et al. Genetic determinants of tissue factor pathway inhibitor plasma levels. Thromb Haemost 2015;114:245–57.
[19] Almasy L, Soria JM, Souto JC, et al. A locus on chromosome 2 influences levels of tissue factor pathway inhibitor: results from the GAIT study. Arterioscler Thromb Vasc Biol 2005;25:1489–92.
[20] Segera O, van Oerle R, ten Cate H, et al. Thrombin generation as an intermediate phenotype for venous thrombosis. Thromb Haemost 2010;103:114–22.
[21] Moatii D, Seknadjie P, Galand C, et al. Polymorphisms of the tissue factor pathway inhibitor (TFPI) gene in patients with acute coronary syndromes and in healthy subjects: impact of the V264M substitution on plasma levels of TFPI. Arterioscler Thromb Vasc Biol 1999;19:862–9.
[22] Stang A. Critical evaluation of the Newcastle–Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603–5.
[23] DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: an update. Contemp Clin Trials 2007;28:105–14.
[24] Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959;22:719–48.
[25] Fan FY, Liu NP. Meta-analysis of association between K469E polymorphism of the ICAM-1 gene and retinopathy in type 2 diabetes. Int J Ophthalmol 2015;8:603–7.
[26] Miyata T, Sakata T, Kumeda K, et al. C-399T polymorphism in the promoter region of human tissue factor pathway inhibitor (TFPI) gene does not change the plasma TFPI antigen level and does not cause venous thrombosis. Thromb Haemost 1998;80:346–6.
[27] Amezcune N, Seguin C, Borgel D, et al. The -33T→C polymorphism in intron 7 of the TFPI gene influences the risk of venous thromboembolism, independently of the factor V Leiden and prothrombin mutations. Thromb Haemost 2002;88:195–9.
[28] Lincz LF, Adams MJ, Scorgie FE, et al. Polymorphisms of the tissue factor pathway inhibitor gene are associated with venous thromboembolism in the antiphospholipid syndrome and carriers of factor V Leiden. Blood Coagul Fibrinolysis 2007;18:559–64.
[29] Sidelnikov JJ, Bladbjerg EM, Gram J, et al. Tissue factor pathway inhibitor relates to fibrin degradation in patients with acute deep venous thrombosis. Blood Coagul Fibrinolysis 2008;19:405–9.
[30] Amini Nekoo A, Illes D. Analysis of a T-287C polymorphism in the tissue factor pathway inhibitor gene and identification of a repressor element in the promoter. Thromb Res 2008;121:813–9.
[31] Liu YE, Yang LH, Hui LH, et al. Polymorphisms of tissue factor pathway inhibitors C-399T and T-287C in venous thromboembolism. J Shanxi Med Univ 2009;40:
[32] Opstad TB, Eilertsen AL, Holbraaten E, et al. Tissue factor pathway inhibitor polymorphisms in women with and without a history of venous thrombosis and the effects of postmenopausal hormone therapy. Blood Coagul Fibrinolysis 2010;21:516–21.
[33] Prabhakar P, De T, Nagaraja D, et al. The intron 7 -33T→C polymorphism in TFPI gene and cerebral venous thrombosis: evidence for a protective role. Thromb Res 2012;130:687–9.
[34] Kwon A, Jo SH, Jo YA, et al. Genetic polymorphisms and plasma levels of tissue factor and tissue factor pathway inhibitor in venous thromboembolism. Blood Coagul Fibrinolysis 2014;25:416–21.
[35] Jiang J, Jiao Y, Ding X, et al. Association between genetic polymorphisms and deep vein thrombosis in a Chinese population. Thromb Res 2015;136:687–9.
[36] Kamal K, Amit S, Kanwaljeet S, et al. Association of genetic polymorphisms with plasma TFPI level: boon or curse for DVT patients - study from India. Blood Cells Mol Dis 2017;66:31–6.
[37] Tinholt M, Sandset PM, Iversen N. Polymorphisms of the coagulation pathway inhibitors C-399T and T-287C in venous thromboembolism. Thromb Haemost 2005;25:1489–92.
[38] Sandset PM. Tissue factor pathway inhibitor (TFPI) and the regulation of tissue factor-dependent blood coagulation. Blood Coagul Fibrinolysis 2010;21:516–21.
[39] Prabhakar P, De T, Nagaraja D, et al. The intron 7 -33T→C polymorphism in TFPI gene and cerebral venous thrombosis: evidence for a protective role. Thromb Res 2012;130:687–9.
[40] Kwon A, Jo SH, Jo YA, et al. Genetic polymorphisms and plasma levels of tissue factor and tissue factor pathway inhibitor in venous thromboembolism. Blood Coagul Fibrinolysis 2014;25:416–21.
[41] Jiang J, Jiao Y, Ding X, et al. Association between genetic polymorphisms and deep vein thrombosis in a Chinese population. Thromb Res 2015;136:687–9.
[42] Kamal K, Amit S, Kanwaljeet S, et al. Association of genetic polymorphisms with plasma TFPI level: boon or curse for DVT patients - study from India. Blood Cells Mol Dis 2017;66:31–6.
[43] Tinholt M, Sandset PM, Iversen N. Polymorphisms of the coagulation system and risk of cancer. Thromb Res 2016;140(Suppl 1):S49–54.
[44] Sandset PM. Tissue factor pathway inhibitor (TFPI): an update. Haemostasis 1996;26(Suppl 4):154–65.
[45] Walker FJ, Fay PJ. Regulation of blood coagulation by the protein C system. FASEB J 1992;6:2561–7.
[46] Golino P, Ragni M, Cimmino G, et al. Role of tissue factor pathway inhibitor in the regulation of tissue factor-dependent blood coagulation. Cardiovasc Drug Rev 2002;20:67–80.
[47] Harris GM, Stendt CL, Vollenhoven BJ, et al. Decreased plasma tissue factor pathway inhibitor in women taking combined oral contraceptives. Am J Hematol 1999;60:173–80.
[48] Kaiser B, Hoppensteadt DA, Farred J. Tissue factor pathway inhibitor: an update of potential implications in the treatment of cardiovascular disorders. Expert Opin Investig Drugs 2001;10:1925–35.