The prevalence and clinical manifestation of hereditary thrombophilia in Korean patients with unprovoked venous thromboembolisms

Su Yeon Lee1*, Eun Kyoug Kim2*, Min Sun Kim1, Sun Hye Shin3, Haseong Chang1, Shin Yi Jang2, Hee-Jin Kim4*, Duk-Kyung Kim2*

1 Division of Cardiology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, 2 Division of Cardiology, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, 3 Division of Pulmonary and Critical Care Medicine, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, 4 Department of Laboratory Medicine & Genetics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

* These authors contributed equally to this work.
* dukkyung.kim@gmail.com (DKK); hee_jin.kim@samsung.com (HJK)

Abstract

Background

Hereditary thrombophilia (HT) is a genetic predisposition to thrombosis. Asian mutation spectrum of HT is different from Western ones. We investigated the incidence and clinical characteristics of HT in Korean patients with unprovoked venous thromboembolism (VTE).

Methods

Among 369 consecutive patients with thromboembolic event who underwent thrombophilia tests, we enrolled 222 patients diagnosed with unprovoked VTE. The presence of HT was confirmed by DNA sequencing of the genes that cause deficits in natural anticoagulants (NAs). Median follow-up duration was 40±38 months.

Results

Among the 222 patients with unprovoked VTE, 66 (29.7%) demonstrated decreased NA level, and 33 (14.9%) were finally confirmed to have HT in a genetic molecular test. Anti-thrombin III deficiency (6.3%) was most frequently detected, followed by protein C deficiency (5.4%), protein S deficiency (1.8%), and dysplasminogenemia (1.4%). The HT group was significantly younger (37 [32–50] vs. 52 [43–65] years; P < 0.001) and had a higher proportion of male (69.7% vs. 47%; P = 0.013), more previous VTE events (57.6% vs. 31.7%; P = 0.004), and a greater family history of VTE (43.8% vs. 1.9%; P < 0.001) than the non-HT group. Age <45 years and a family history of VTE were independent predictors for unprovoked VTE with HT (odds ratio, 9.435 [2.45–36.35]; P = 0.001 and 92.667 [14.95–574.29]; P < 0.001).
Conclusions

About 15% of patients with unprovoked VTE had HT. A positive family history of VTE and age <45 years were independent predictors for unprovoked VTE caused by HT.

Introduction

Venous thromboembolism (VTE) is increasingly recognized as a significant source of morbidity and mortality [1]. It occurs in about one in 1000 people each year in Western countries; however, in Asian populations, VTE incidence is lower [2–4]. Although various factors such as immobilization, surgery, pregnancy, and malignancies increase the risk of VTE, in 25 to 50 percent of cases, no predisposing factor is present, and that is called unprovoked VTE [1,5,6].

Compared with patients with provoked VTE, those with unprovoked VTE tend to have higher recurrence rate, which means they must be treated for a long time. One of the main causes of this clinical difference is a genetic variant, hereditary thrombophilia (HT), associated with a predisposition to thrombosis [7,8]. The mutation spectrum of HT and the subsequent clinical manifestations vary among ethnic groups. Activated protein C (APC) resistance, caused by factor V Leiden mutation and prothrombin G20210A mutation, increases pro-coagulant activity and occurs only in Western populations [9–11]. A deficiency of natural anticoagulants (NAs), including antithrombin (AT), protein C (PC), protein S (PS), and plasminogen, is more likely to occur in Asian populations [11–13]. However, few data are available on the prevalence and clinical characteristics of Asian HT patients with unprovoked VTE. Furthermore, previous studies mostly defined HT not as a genetic abnormality, but as a deficiency of coagulation factors, which caused varied prevalence results [14–18]. Therefore, we aimed to identify the actual incidence and clinical manifestations of HT confirmed by genetic testing in Korean patients diagnosed with unprovoked VTE.

Methods

Study design and patients

We reviewed 369 consecutive patients with thromboembolic event who underwent coagulation testing at our VTE clinic between February 2005 and December 2015. The diagnosis of VTE was based on multi-detectable computed tomography (CT) scans and duplex sonography of the suspicious site. VTE included pulmonary embolism (PE), chronic thromboembolic pulmonary hypertension, deep vein thrombosis (DVT) of extremities, portal vein thrombosis, splanchnic vein thrombosis, and cerebral vein thrombosis. Among those patients, we included only adults (≥ 20 years old) confirmed to have unprovoked VTE, defined as a thrombotic event that occurred in the absence of predisposing factors such as immobilization for more than three days, surgery under anesthesia lasting for more than 30 minutes, pregnancy, connective tissue disease, malignancies and thrombogenic condition which was central venous line or pacemaker. We excluded patients diagnosed with arterial thromboembolism and those with underlying liver disease or acquired thrombophilia (e.g., antiphospholipid syndrome, JAK2 mutation, or myeloproliferative neoplasm) [1,5,6].

We recorded each patient’s previous history of VTE, family members who experienced VTE, site of thromboembolism, initially presented symptoms, and comorbidities (diabetes, hypertension, and obesity). Hypertension was defined as systolic blood pressure > 140 mmHg or self-reported hypertension irrespective of pharmacologic treatment. Diabetes mellitus was
defined as a history of type 1 or type 2 diabetes mellitus treated either pharmacologically or by
diet. Obesity was defined as a body mass index greater than 25 kg/m\(^2\) based on Asian criteria.
During the follow-up period, we investigated the duration of anticoagulation therapy and
recurrence of VTE at any location. The protocol of this study was approved by the Institutional
Review Board of the Samsung Medical Center, Seoul, Korea.

Coagulation tests for thrombophilia
The coagulation tests used to screen for HT were PC activity (Stachrom\(^\text{®}\) Protein C, Diagnos-
tica Stago, Asnières, France), PS free Ag (Liatest\(^\text{®}\) Free Protein S, Diagnostica Stago), AT
activity (Stachrom\(^\text{®}\) AT III, Diagnostica Stago), and plasminogen activity (Stachrom\(^\text{®}\) Plas-
minogen, Diagnostica Stago), per the international guidelines [19]. All coagulation tests were
performed on the STA\(^\text{®}\)-Evolution Coagulation Analyzer. Reference ranges were determined
according to our institutional data. Whenever possible, coagulation tests were repeated 2
weeks after the discontinuation of anticoagulation therapy if results at the time of diagnosis
showed low levels of multiple NAs or if tests with abnormal results were performed under anti-
coagulant use.

Molecular genetic tests
Patients who had low levels of NAs underwent molecular genetic tests to confirm HT. Geno-
mic DNA was extracted from peripheral blood leukocytes using the Wizard Genomic DNA
Purification kit (Promega, Madison, WI, USA). All exons of the \(PROC\), \(PROS1\), \(SERPINC1\), and
\(PLG\) genes and their flanking intron regions were amplified using polymerase chain reac-
tion for PC, PS, AT, and PLG deficiencies, respectively, using the BigDye Terminator Cycle
Sequencing Ready Reaction kit (Applied Biosystems, Foster City, CA, USA). When no point
mutations were detected, multiple ligation-dependent probe amplification experiments were
additionally performed to detect large dosage mutations.

Statistical analyses
Categorical data are presented as number and percentage (%) and were compared using Chi-
square test or Fisher exact test. Continuous variables are expressed as mean ± SD or median
with interquartile range and were compared using the Student’s t test or Mann-Whitney U
test, as appropriate. To adjust for confounding factors, we used a multivariate logistic regres-
sion analysis with backward stepwise method using parameters with a P value <0.10 in univar-
iate analysis. A P-value less than 0.05 was considered statistically significant. All analyses were
performed using SPSS statistical software version 23 (Chicago, IL, USA).

Results
Prevalence of HT
Among 222 patients who presented with unprovoked VTE, 66 (29.7%) had low NA level on
coaulation tests, and 62 underwent genetic confirmation testing (3 did not have a follow up
evaluation, and 1 declined to participate in the genetic test). Only 33 (53%) of those who
showed NA deficiencies in coagulation testing were confirmed to have HT (15% of subjects
with unprovoked VTE). The most common types of HT was AT III deficiency (14 of 222,
6.3%) and PC deficiency (12, 5.4%), followed by PS deficiency (4, 1.8%), and dysplasminogen-
emia (3, 1.4%) (Fig 1).
Clinical characteristics of HT patients presented with unprovoked VTE

The clinical and laboratory findings of unprovoked VTE patients with or without HT are shown in Table 1. The HT group was significantly younger (37 [32–50] years vs. 52 [43–65] years, P < 0.001) and more frequently male (69.7% vs. 47.0%, P = 0.013) than the non-HT group. More than half of HT patients with unprovoked VTE had a history of previous VTE events, which is significantly higher than in the non-HT group (57.6% vs. 31.7%, P = 0.004). A family history of VTE was also more frequent in the HT group (43.8% vs. 1.9%, P < 0.001).

There were no significant differences between the two groups in clinical comorbidities or laboratory findings, except level of hemoglobin (15 [13–15] vs. 13 [12–15] g/dL, P = 0.025). VTE was more frequently located in the lower extremities in patients with HT than in those without HT (87.9% vs. 67.2%, P = 0.011).

Detailed characteristics of the HT group are given in Table 2. Patients with dysplasminogenemia tended to be older than those with other types of HT. In all types of HT, males were predominant. The first presentation of unprovoked VTE was mainly DVT rather than PE. Patients with AT-III deficiency or PC deficiency tended to have a higher previous history of VTE and family history of VTE. The details of genetic mutations are shown in Supplemental Table 1. (S1 Table)

In multivariate analysis, age < 45 years (odds ratio [OR] 9.435, 95% confidence interval [95% CI] 2.45–36.35, P = 0.001) and a family history of VTE (OR 92.667, 95% CI 14.95–574.29, P < 0.001) were independent predictors for HT (Table 3).

Anticoagulant therapy and recurrence of VTE

Median follow up duration was 40±38 months. Mean treatment duration of anticoagulation was much longer in the HT group than in the non-HT group (47±42 vs. 24±28 months, P < 0.001). Vitamin K antagonist (warfarin) was preferred in both groups (90.0% in HT group and 70.5% in non-HT group). Among 11 patients who experienced a recurrence of VTE, only 2 had HT (18%). About half of the recurrences were PE, followed by DVT (27%) and thrombosis in the cerebral vein, portal vein, and suprapelvic vein (9% each). Noticeably, recurrent VTE in the HT group occurred under anticoagulation, whereas all cases of recurrence in the non-HT group occurred after the end of treatment or follow-up (Fig 2).
In this retrospective study, we investigated the prevalence of HT and its subtypes in Korean patients with unprovoked VTE, comparing clinical manifestations and recurrences between unprovoked VTE patients with or without HT. About 15% of patients with unprovoked VTE had genetically proven HT, and AT-III deficiency and PC deficiency were most frequent subtypes. Patients with HT who developed unprovoked VTE were younger and more frequently had a family history of VTE than those without HT. However, recurrence of VTE did not differ between patients with or without HT.

The prevalence of HT varies among ethnic groups. APC resistance caused by factor V Leiden and G20210A mutations are restricted to Caucasian populations [9–11], while deficiencies

### Table 1. Baseline characteristics of the study population.

|                        | HT (-)   | HT (+)  | Total | P value |
|------------------------|----------|---------|-------|---------|
| Age, years             | 52 (43–65) | 37 (32–50) | 50 (41–63) | < 0.001 |
| BMI, kg/m²             | 24 (22–26) | 24 (22–27) | 24 (22–26) | 0.459   |
| Males, %               | 86 (47.0) | 23 (69.7) | 109 (50.5) | 0.013   |
| Diabetes mellitus, %   | 18 (9.8)  | 1 (3.0)  | 19 (8.8)  | 0.177   |
| Hypertension, %        | 55 (30.1) | 7 (21.2)  | 62 (28.7) | 0.207   |
| Previous history of VTE, % | 58 (31.7) | 19 (57.6) | 77 (35.6) | 0.004   |
| Age at first attack, years | 46 (37–56) | 37 (27–49) | 43 (35–55) | 0.054   |
| Family history of VTE, % | 3 (1.9)    | 14 (43.8) | 17 (8.8)  | < 0.001 |

### Laboratory exam

|                        | HT (-)   | HT (+)  | Total | P value |
|------------------------|----------|---------|-------|---------|
| Hemoglobin, g/dL       | 13 (12–15) | 15 (13–15) | 13 (12–15) | 0.025   |
| Total bilirubin, mg/dL | 0.7 (0.4–1.0) | 0.7 (0.5–1.1) | 0.7 (0.4–1.0) | 0.627   |
| AST, U/L               | 23 (18–33) | 22 (19–29) | 23 (18–32) | 0.782   |
| ALT, U/L               | 21 (15–35) | 22 (15–32) | 21 (15–33) | 0.755   |
| PT, INR                | 1.1 (1.0–1.5) | 1.1 (1.0–1.6) | 1.1 (1.0–1.5) | 0.344   |
| Fibrinogen, mg/dL      | 307 (258–386) | 292 (248–328) | 303 (256–375) | 0.115   |
| D-dimer, μg/mL         | 1.0 (0.3–2.9) | 0.4 (0.3–1.5) | 0.8 (0.3–2.4) | 0.077   |

### Location of VTE

|                        | HT (-)   | HT (+)  | Total | P value |
|------------------------|----------|---------|-------|---------|
| PE, %                  | 89 (48.6) | 13 (39.4) | 102 (47.2) | 0.215   |
| with DVT, %            | 61 (68.5) | 12 (92.3) | 73 (71.6) | 0.066   |
| DVT, %                 | 123 (67.2) | 29 (87.9) | 152 (70.4) | 0.011   |
| Lower extremity, both  | 36 (29.5) | 9 (31.0)  | 45 (29.8)  | 0.449   |
| Lower extremity, proximal, % | 99 (82.5) | 27 (93.1) | 126 (84.6) | 0.126   |
| PVT, %                 | 13 (7.1)  | 3 (9.1)  | 16 (7.4)  | 0.454   |
| SVT, %                 | 13 (7.1)  | 1 (3.0)  | 14 (6.5)  | 0.337   |
| CTEPH, %               | 29 (15.8) | 2 (6.1)  | 31 (14.4) | 0.108   |

### Clinical manifestation

|                        | HT (-)   | HT (+)  | Total | P value |
|------------------------|----------|---------|-------|---------|
| Hypoxia                | 29 (15.8) | 1 (3.0)  | 30 (13.9) | 0.034   |
| Shock a                | 11 (6.0)  | 0 (-)   | 11 (5.1)  | 0.154   |
| Tachycardia            | 22 (12)  | 3 (9.1)  | 25 (11.6) | 0.446   |

Values are median, interquartile range or n (%).

a This row includes one cardiac death caused by pulmonary embolism.

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; BMI = Body mass index; CTEPH = Chronic thromboembolic pulmonary hypertension; DVT = Deep vein thrombosis; HT = Hereditary thrombophilia; VTE = Venous thromboembolism; PE = Pulmonary embolism; PT = Prothrombin time; PVT = Portal vein thrombosis; RV = Right ventricle; SVT = Splanchnic vein thrombosis.

https://doi.org/10.1371/journal.pone.0185785.t001

**Discussion**

In this retrospective study, we investigated the prevalence of HT and its subtypes in Korean patients with unprovoked VTE, comparing clinical manifestations and recurrences between unprovoked VTE patients with or without HT. About 15% of patients with unprovoked VTE had genetically proven HT, and AT-III deficiency and PC deficiency were most frequent subtypes. Patients with HT who developed unprovoked VTE were younger and more frequently had a family history of VTE than those without HT. However, recurrence of VTE did not differ between patients with or without HT.

The prevalence of HT varies among ethnic groups. APC resistance caused by factor V Leiden and G20210A mutations are restricted to Caucasian populations [9–11], while deficiencies
of NAs have greater implications in Asian populations [11–13]. The frequency of HT has been reported heterogeneously according to the diagnostic strategy in Asian populations. Studies from other Asian countries have indicated that the prevalence of HT in VTE was 28.3% to 34% [17,18]. In Korean data, it was also reported that the prevalence of NA deficiencies with VTE was 24.3% [15]. These previous data were relied upon not the genetic abnormalities but NAs deficiency itself. Our data also showed that the prevalence of NAs deficiency in patients with unprovoked VTE was 29.7%, which was quite similar to the previous data. But, in this study, we strictly classified the patients with genetically proved HT as the HT group to investigate clinical manifestations of VTE in ‘real’ HT patients. The homogeneity of HT patients by accurate diagnosis using genetic tests resulted in those clinical manifestations being more reliable and conclusive than previous studies.

Several previous studies have considered the clinical characteristics of HT. Mateo et al. [20] reported that a family history of thrombosis and younger age (age < 45 years) were the main clinical factors that enhanced the risk of NA deficiencies. In a Japanese study of patients with DVT, the HT group was younger than the non-HT group (44.7 years vs. 52.6 years) [13]. In a recent study, Weingarz et al. [21] demonstrated an increase in the prevalence of HT with younger age (age < 40 years old) at first VTE episode, especially in cases of unprovoked VTE (OR 2.20, 95% CI 1.45–3.36, P < 0.001). In our study, the clinical features of the HT group of patients with unprovoked VTE were similar to those in previous studies. A family history of

Table 2. Baseline characteristics of the HT group.

| AT-III deficiency | PC deficiency | PS deficiency | Dysplasminogenemia |
|-------------------|---------------|---------------|-------------------|
| Patients, % a     | 14 (6.3)      | 12 (5.4)      | 4 (1.8)           | 3 (1.4)           |
| Age, years        | 35 (33–41)    | 46 (32–53)    | 34 (32–52)        | 61 (44–64)        |
| Males, %          | 8 (57.1)      | 9 (75.0)      | 4 (100)           | 2 (69.7)          |
| PE, %             | 2 (14.3)      | 7 (58.3)      | 3 (75.0)          | 1 (39.4)          |
| DVT, %            | 12 (85.7)     | 11 (91.7)     | 3 (75.0)          | 3 (100)           |
| Previous history of VTE, % | 9 (64.3) | 9 (75.0) | 0 (-) | 1 (33.3) |
| Family history of VTE, %  | 8 (57.1) | 5 (45.5) | 1 (25.0) | 0 (-)  |
| Level of NAs, % (Normal range) | 48 ± 11 (83–123) | 44 ± 19 (80–161) | 27 ± 17 (62–154) | 60 ± 20 (75–112) |

Values are n (%) or mean ± SD (median, interquartile range).

a Prevalence of HT among 222 subjects diagnosed as unprovoked VTE

NAs = natural anticoagulants.

Abbreviations as in Table 1.

https://doi.org/10.1371/journal.pone.0185785.t002

Table 3. Results of multivariate analysis of baseline-independent predictors of hereditary thrombophilia.

| Variable                  | OR (95% CI)     | P value |
|---------------------------|-----------------|---------|
| Age < 45 years            | 9.435 (2.45–36.35) | 0.001   |
| Male                      | 3.333 (0.85–13.04) | 0.084   |
| Previous history of VTE   | 2.059 (0.70–6.09)  | 0.192   |
| Family history of VTE     | 92.667 (14.95–574.29) | <0.001  |

Adjusted covariates include male sex, age, previous history of VTE, family history of VTE, DVT, hemoglobin, and D-dimer.

Abbreviations as in Table 1.

https://doi.org/10.1371/journal.pone.0185785.t003
VTE and young age at presentation (<45 years) were strong predictors of unprovoked VTE caused by HT.

Generally, unprovoked VTE itself is one of the most important risk factors of recurrence, whereas the presence of NA deficiencies did not appear to increase the risk of recurrence [8,22,23]. Guidelines recommend that patients diagnosed with unprovoked VTE, regardless of HT status, extend anticoagulation beyond 3 months of therapy unless they have a high bleeding risk [24]. Interestingly, in contrast to the non-HT group, all recurrences of VTE in the HT group developed under appropriate treatment with anticoagulation in present study. Therefore, it is important to closely monitor for recurrence of VTE in patients with HT, even when they are maintaining anticoagulation.

Study limitations

This study had some limitations. First, the study was performed retrospectively at a single center, and thus our series might not well represent the characteristics of VTE in the general population. However, our center is a tertiary referral center for thromboembolism, and we defined HT based on molecular genetic tests. Therefore, we believe that our study design had little effect on the results. Second, the test strategy of this study could have missed some recurrent mutations in Asian populations such as PC Lys192del and PS Lys196Glu, which do not result in a significant decrease of the amidolytic activity of PC and free PS Ag, respectively. [14, 25, 26].

Conclusion

The prevalence of genetically confirmed HT in patients with unprovoked VTE was about 15%. A positive family history of VTE and young age (age < 45 years) were independent predictors for development of unprovoked VTE due to HT.

Supporting information

S1 Data.
(XLSX)
S1 Table. Coagulaiton and genetic test results of 33 Korean patients with hereditary thrombophilia.

(DOCX)

Author Contributions

Conceptualization: Eun Kyoug Kim, Hee-Jin Kim, Duk-Kyung Kim.

Data curation: Su Yeon Lee, Min Sun Kim, Sun Hye Shin, Haseong Chang, Shin Yi Jang.

Formal analysis: Su Yeon Lee, Eun Kyoug Kim, Min Sun Kim, Sun Hye Shin, Haseong Chang, Duk-Kyung Kim.

Investigation: Su Yeon Lee.

Methodology: Hee-Jin Kim.

Project administration: Shin Yi Jang.

Supervision: Hee-Jin Kim, Duk-Kyung Kim.

Validation: Eun Kyoug Kim, Hee-Jin Kim, Duk-Kyung Kim.

Writing – original draft: Su Yeon Lee, Eun Kyoug Kim, Duk-Kyung Kim.

Writing – review & editing: Su Yeon Lee, Eun Kyoug Kim, Duk-Kyung Kim.

References

1. White RH. The epidemiology of venous thromboembolism. Circulation. 2003; 107: I4–8. https://doi.org/10.1161/01.CIR.0000078468.11849.66 PMID: 12814979

2. Hirsh J, Hoak J. Management of deep vein thrombosis and pulmonary embolism. A statement for healthcare professionals. Council on Thrombosis (in consultation with the Council on Cardiovascular Radiology), American Heart Association. Circulation. 1996; 93: 2212–2245. https://doi.org/10.1161/01.CIR.93.12.2212 PMID: 8925592

3. Nordstrom M, Lindblad B, Bergqvist D, Kjellstrom T. A prospective study of the incidence of deep-vein thrombosis within a defined urban population. J Intern Med. 1992; 232: 155–160. PMID: 1506812

4. Liao S, Woulfe T, Hyder S, Merriman E, Simpson D, Chunilal S. Incidence of venous thromboembolism in different ethnic groups: a regional direct comparison study. J Thromb Haemost. 2014; 12: 214–219. https://doi.org/10.1111/jth.12446 PMID: 24283769

5. Rosendaal FR. Venous thrombosis: a multicausal disease. Lancet. 1999; 353: 1167–1173. https://doi.org/10.1016/S0140-6736(98)02647-0 PMID: 10209995

6. Heit JA, O'Fallon WM, Petterson TM, Lohse CM, Silverstein MD, Mohr DN, et al. Relative impact of risk factors for deep vein thrombosis and pulmonary embolism: a population-based study. Arch Intern Med. 2002; 162: 1245–1248. https://doi.org/10.1001/archinte.162.11.1245 PMID: 12038942

7. Couturaud F, Leroyer C, Julian JA, Kahn SR, Ginsberg JS, Wells PS, et al. Factors that predict risk of thrombosis in relatives of patients with unprovoked venous thromboembolism. Chest. 2008; 136: 1537–1545. https://doi.org/10.1378/chest.09-0757 PMID: 18592474

8. Christiansen SC, Canneugieter SC, Koster T, Vandenbroucke JP, Rosendaal FR. Thrombophilia, clinical factors, and recurrent venous thrombotic events. JAMA. 2005; 293: 2352–2361. https://doi.org/10.1001/jama.293.19.2352 PMID: 15900005

9. De Stefano V, Finazzi G, Mannucci PM. Inherited thrombophilia: pathogenesis, clinical syndromes, and management. Blood. 1996; 87: 3531–3544. PMID: 8611675

10. Ridker PM, Miletich JP, Hennekens CH, Buring JE. Ethnic distribution of factor V Leiden in 4047 men and women. Implications for venous thromboembolism screening. JAMA. 1997; 277: 1305–1307. PMID: 9109469

11. Khan S, Dickerman JD. Hereditary thrombophilia. Thromb J. 2006; 4: 15. https://doi.org/10.1186/1477-9560-4-15 PMID: 16986541
12. Shen MC, Lin JS, Tsay W. High prevalence of antithrombin III, protein C and protein S deficiency, but no factor V Leiden mutation in venous thrombophilic Chinese patients in Taiwan. Thromb Res. 1997; 87: 377–385. PMID: 9271815

13. Miyata T, Sato Y, Ishikawa J, Okada H, Takeshita S, Sakata T, et al. Prevalence of genetic mutations in protein S, protein C and antithrombin genes in Japanese patients with deep vein thrombosis. Thromb Res. 2009; 124: 14–18. https://doi.org/10.1016/j.thromres.2008.08.020 PMID: 18954896

14. Kim HJ, Seo JY, Lee KO, Bang SH, Lee ST, Ki CS, et al. Distinct frequencies and mutation spectrums of genetic thrombophilia in Korea in comparison with other Asian countries both in patients with thromboembolism and in the general population. Haematologica. 2014; 99: 561–569. https://doi.org/10.3324/haematol.2013.092023 PMID: 24162787

15. Kim S, Song I, Kim HK, Huh S. Thrombophilia in Korean patients with arterial or venous thromboembolisms. Ann Surg Treat Res. 2016; 90: 340–345. https://doi.org/10.4174/asstr.2016.90.6.340 PMID: 27274510

16. Lee M, No HJ, Jang SY, Kim N, Choi SH, Kim H, et al. Hereditary thrombophilia in Korean patients with idiopathic pulmonary embolism. Yonsei Med J. 2012; 53: 571–577. https://doi.org/10.3349/ymj.2012.53.3.571 PMID: 22477002

17. Suehisa E, Nomura T, Kawasaki T, Kanakura Y. Frequency of natural coagulation inhibitor (antithrombin III, protein C and protein S) deficiencies in Japanese patients with spontaneous deep vein thrombosis. Blood Coagul Fibrinolysis. 2001; 12: 95–99. PMID: 11302483

18. Chen TY, Su WC, Tsao CJ. Incidence of thrombophilia detected in southern Taiwanese patients with venous thrombosis. Ann Hematol. 2003; 82: 114–117. https://doi.org/10.1007/s00277-002-0603-z PMID: 12601491

19. Goodwin AJ, Rosendaal FR, Kottke-Marchant K, Bovill EG. A review of the technical, diagnostic, and epidemiologic consideration for protein S assays. Arch Pathol Lab Med. 2002; 126: 1349–1366. https://doi.org/10.1043/0003-9985(2002)126<1349:AROTTD>2.0.CO;2 PMID: 12421142

20. Mateo J, Oliver A, Borrell M, Sala N, Fontcuberta J. Laboratory evaluation and clinical characteristics of 2,132 consecutive unselected patients with venous thromboembolism—results of the Spanish Multicentric Study on Thrombophilia (EMET-Study). Thromb Haemost. 1997; 77: 445–451.

21. Weingarz L, Schwonberg J, Schindewolf M, Hecking C, Wolf Z, Erbe M, et al. Prevalence of thrombophilia according to age at the first manifestation of venous thromboembolism: results from the MAISTHRO registry. Br J Haematol. 2013; 163: 655–665. https://doi.org/10.1111/bjh.12575 PMID: 24219332

22. Baglin T, Luddington R, Brown K, Baglin C. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. Lancet. 2003; 362: 523–526. https://doi.org/10.1016/S0140-6736(03)14111-6 PMID: 12932383

23. Palareti G, Legnani C, Cosmi B, Valdore L, Lunghi B, Bernardi F, et al. Predictive value of D-dimer test for recurrent venous thromboembolism after anticoagulation withdrawal in subjects with a previous idiopathic event and in carriers of congenital thrombophilia. Circulation. 2003; 108: 313–318. https://doi.org/10.1161/01.CIR.0000079162.69615.0F PMID: 12847064

24. Kearon C, Akl EA, Omelas J, Blaisa V, Jimenez D, Bounameaux H, et al. Antithrombotic therapy for VTE disease: CHEST Guideline and Expert Panel Report. Chest. 2016; 149: 315–352 https://doi.org/10.1016/j.chest.2015.11.026 PMID: 26867832

25. Tang L, Lu X, Yu JM, Wang QY, Yang R, Guo T, et al. PROC c.574_576del polymorphism: a common genetic risk factor for venous thrombosis in the Chinese population. J Thromb Haemost. 2012; 10: 2019–2026. https://doi.org/10.1111/j.1538-7836.2012.04862.x PMID: 22817391

26. Kimura R, Sakata T, Kokubo Y, Okamoto A, Okayama A, Tomoike H, et al. Plasma protein S activity correlates with protein S genotype but is not sensitive to identify K196E mutant carriers. J Thromb Haemost. 2006; 4: 2010–2013. https://doi.org/10.1111/j.1538-7836.2006.02071.x PMID: 16961608