Brief report

Marburg I polymorphism of factor VII–activating protease is associated with idiopathic venous thromboembolism

Berthold Hoppe, Farzaneh Tolou, Hartmut Radtke, Holger Kiesewetter, Thomas Dörner, and Abdulgabar Salama

The factor VII–activating protease (FSAP) variant Marburg I is known to attenuate the profibrinolytic system in vitro and was recently shown to be a significant predictor for the evolution and progression of carotid stenosis. The objective of this case-control study was to assess FSAP Marburg I’s role in the occurrence of venous thromboembolism (VTE). The frequency of FSAP Marburg I was significantly increased in patients with a history of VTE (17 of 213 patients, 8.0%, \( P = .014 \)) or idiopathic VTE (12 of 103 patients, 11.7%, \( P = .002 \)) compared to healthy controls (5 of 213 controls, 2.3%). Logistic regression analysis confirmed FSAP Marburg I to be an independent risk factor for VTE (odds ratio, 3.5; 95% confidence interval [CI], 1.2-10.0) and idiopathic VTE (odds ratio, 6.2; 95% CI, 2.0-18.9). (Blood. 2005;105:1549-1551)

Study design

During the initial examination the following parameters were determined\(^5\): Factor V 1691G → A (factor V Leiden) and prothrombin (PT) 20210G → A; activity of antithrombin (n = 205), protein S (n = 129), and protein C (n = 128); anticardiolipin IgG/IgM (n = 211), and lupus anticoagulants (n = 206). FSAP Marburg I (1601G → A) was analyzed retrospectively using the same protocol\(^6\) and the following primer pairs: FSAP 1601G/wild-type: forward primer: 5’ tggggcctggagtgtga 3’; reverse primer: 5’ ggttgctcagttggcgc 3’; FSAP 1601A/Marburg I: forward primer: 5’ tgggctcagttggcgc 3’; reverse primer: 5’ ggttgctcagttggcgc 3’. Blood donors (n = 213, controls) from the same geographical area as the patients were recruited by sex/age-stratified sampling (age strata [y]: < 20, 20-29, 30-39, 40-49, 50-59, and ≥60) according to the distribution of cases. Consecutive donors with no history of VTE were enrolled until the respective sex/age groups reached the number of cases. Controls were tested for factor V 1691G → A, PT 20210G → A, and FSAP 1601G → A. The study was approved by the local ethics committee. All participants gave informed consent.

Statistical analyses included univariate analysis (Fisher exact test) and logistic regression analysis with factor V Leiden, PT 20210G → A, and FSAP Marburg I as independent variables. Statistical analyses were performed using SPSS statistics package V.11 (SPSS, Chicago, IL) and GraphPad Prism 4 (GraphPad Software, San Diego, CA).

Results and discussion

The laboratory characteristics of patients and controls are shown in Table 2. The overall frequencies of FSAP Marburg I in cases and controls were 8.0% (n = 17) and 2.3% (n = 5), respectively. FSAP Marburg I was independently associated with VTE (odds ratio, 3.5; 95% CI, 1.2-10.0). All carriers of FSAP Marburg I were heterozygous for this variant. Regarding patients with idiopathic VTE, the independent association with FSAP Marburg I was even stronger than that identified for all patients (odds ratio, 6.2; 95% CI, 2.0-18.9). After exclusion of patients who developed idiopathic venous thromboembolism, the frequency of FSAP Marburg I was significantly increased in patients with a history of VTE (17 of 213 patients, 8.0%, \( P = .014 \)) or idiopathic VTE (12 of 103 patients, 11.7%, \( P = .002 \)) compared to healthy controls (5 of 213 controls, 2.3%).

From the Institute of Transfusion Medicine, Campus Virchow-Klinikum, Charité—Universitätsmedizin Berlin, Berlin, Germany.


Reprints: Berthold Hoppe; Institute of Transfusion Medicine, Campus Virchow-Klinikum, Charité—Universitätsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin, Germany; e-mail: berthold.hoppe@charite.de.

The publication costs of this article were defrayed in part by page charge payment. Therefore, and solely to indicate this fact, this article is hereby marked “advertisement” in accordance with 18 U.S.C. section 1734.

© 2005 by The American Society of Hematology
Table 1. Clinical characteristics of patients and controls

<table>
<thead>
<tr>
<th>Venous thromboembolism</th>
<th>Total</th>
<th>Idiopathic</th>
<th>Secondary</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>213</td>
<td>103</td>
<td>110</td>
<td>213</td>
</tr>
<tr>
<td>Female, %</td>
<td>71.8</td>
<td>72.8</td>
<td>70.9</td>
<td>71.8</td>
</tr>
<tr>
<td>Age, median, y (range)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>35 (15-80)</td>
<td>37 (15-80)</td>
<td>34 (15-78)</td>
<td>35 (18-66)</td>
</tr>
<tr>
<td>Male</td>
<td>46 (20-82)</td>
<td>49 (22-69)</td>
<td>42 (20-82)</td>
<td>43.5 (23-66)</td>
</tr>
</tbody>
</table>

No. clinical events

<table>
<thead>
<tr>
<th>No. with acquired risk factor*</th>
<th>Immobilization</th>
<th>Surgery/trauma</th>
<th>Pregnancy/puerperium</th>
<th>Malignancy/other diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT</td>
<td>42</td>
<td>43</td>
<td>18</td>
<td>13</td>
</tr>
<tr>
<td>DVT + PE</td>
<td>45</td>
<td>43</td>
<td>18</td>
<td>13</td>
</tr>
<tr>
<td>PE</td>
<td>17</td>
<td>43</td>
<td>18</td>
<td>13</td>
</tr>
</tbody>
</table>

DVT indicates deep vein thrombosis; PE, pulmonary embolism; NA, not applicable.
*Combinations of acquired risk factors were found in 6 cases.

VTE under hormonal contraception (n = 18), FSAP Marburg I remained independently associated with VTE (odds ratio, 5.7; 95% CI, 1.7-19.6). In patients with secondary VTE (n = 5, 4.5%) due to acquired risk factors, no association with FSAP Marburg I could be demonstrated.

Significant hereditary thrombophilic risk factors other than FSAP Marburg I, for instance, factor V Leiden (n = 54), PT 20210G → A (n = 13), factor V Leiden + PT 20210G → A (n = 3), factor V Leiden + protein S deficiency (n = 2), protein S deficiency (n = 1), and antithrombin deficiency (n = 1) were found in 74 patients. A history of VTE in relatives of patients with FSAP Marburg I and no other significant hereditary thrombophilic risk factors was found in 4 of 10 cases. The frequencies of carriers of factor V Leiden and PT 20210G → A in controls, patients with VTE, and idiopathic VTE (Table 2) are in agreement with previously published data, reflecting the comparable composition of our collectives.

Based on our data FSAP Marburg I appears to be a candidate for hereditary thrombophilia. However, some details of our study should be discussed. We analyzed prevalent and not incident cases. Thus, there might be a tendency for inadequate recall of past events. This will not influence the accuracy of the detection of FSAP Marburg I and VTE, because both were based on objective findings. However, the recall of circumstances of VTE might be in some cases incomplete, although the majority of patients presented within 1 year after VTE.

The association of FSAP Marburg I with VTE in prevalent cases could be due to a survival bias of this factor. Although this explanation does not seem likely, it cannot be completely ruled out. An additional potential source of bias is the used control group. Blood donors necessarily should have no known underlying diseases, for example, malignancies or autoimmune diseases. However, as these diseases are not likely to influence the genotype frequency of FSAP, our control group seems to be suitable for determining the frequency of FSAP Marburg I in our geographical area.

FSAP Marburg I is a prevalent variant that exhibits an independent association with VTE. Similar to the prevalence of factor V Leiden and PT 20210G → A, its frequency in the general population is about 2% to 4%. Its effect was especially pronounced in patients with idiopathic VTE, who are known to be prone for recurrence of disease. However, based on the presented data, no statement about the influence of FSAP Marburg I on the recurrence rate of VTE is possible. This should be the aim of further studies. The possible significance of FSAP Marburg I becomes obvious when one considers that many previously described thrombophilic risk factors were found to be associated with VTE only under certain circumstances, for example, in surgical patients or in combination with other thrombophilic risk factors.

Finally, our results might be helpful in understanding the findings of Prandoni et al., who described an association between atherosclerosis (carotid plaques) and idiopathic but not secondary VTE and who raised the question whether these 2 conditions might share common risk factors. Interestingly, FSAP Marburg I was initially described as a predictor for the evolution and progression of carotid stenosis, and in our study it could be demonstrated to be associated with idiopathic but not with secondary VTE (Table 2).

Larger studies are needed to conclusively determine the importance of FSAP Marburg I in VTE.

Acknowledgments

This work is dedicated to my father, Prof Dr Immo Hoppe.

We thank Gisela Diederich for excellent technical assistance.

References

7. Lindmarker P, Schulman S, Sten-Linder M, Wiman B, Egberg N, Johnsson H. The risk of


Marburg I polymorphism of factor VII–activating protease is associated with idiopathic venous thromboembolism

Berthold Hoppe, Farzaneh Tolou, Hartmut Radtke, Holger Kiesewetter, Thomas Dörner and Abdulgabar Salama