Genetics

Risk of Recurrent Venous Thrombosis in Homozygous Carriers and Double Heterozygous Carriers of Factor V Leiden and Prothrombin G20210A

Willem M. Lijfering, MD, PhD; Saskia Middeldorp, MD, PhD; Nic J.G.M. Veeger, MSc; Karly Hamulyak, MD, PhD; Martin H. Prins, MD, PhD; Harry R. Büller, MD, PhD; Jan van der Meer, MD, PhD†

Background—Homozygous or double heterozygous factor V Leiden and/or prothrombin G20210A is a rare inherited thrombophilic trait. Whether individuals with this genetic background have an increased risk of recurrent venous thrombosis is uncertain.

Methods and Results—A case-control design within a large cohort of families with thrombophilia was chosen to calculate the risk of recurrent venous thrombosis in individuals with homozygosity or double heterozygosity of factor V Leiden and/or prothrombin G20210A. Cases were individuals with recurrent venous thrombosis, and controls were those with only 1 venous thrombosis. The cohort consisted of 788 individuals with venous thrombosis; 357 had factor V Leiden, 137 had prothrombin G20210A, 27 had factor V Leiden and/or prothrombin G20210A homozygosity, and 49 had double heterozygosity for both mutations. We identified 325 cases with recurrent venous thrombosis and 463 controls with only 1 venous thrombosis. Compared with noncarriers, crude odds ratio for recurrence was 1.2 (95% confidence interval, 0.9 to 1.6) for heterozygous carriers of factor V Leiden, 0.7 (95% confidence interval, 0.4 to 1.2) for prothrombin G20210A, 1.2 (95% confidence interval, 0.5 to 2.6) for homozygous carriers of factor V Leiden and/or prothrombin G20210A, and 1.0 (95% confidence interval, 0.6 to 1.9) for double heterozygotes of both mutations. Adjustments for age, sex, family status, first event type, and concomitance of natural anticoagulant deficiencies did not alter the risk estimates.

Conclusions—In this study, individuals with homozygous factor V Leiden and/or homozygous prothrombin G20210A or double heterozygous carriers of factor V Leiden and prothrombin G20210A did not have a high risk of recurrent venous thrombosis. (Circulation. 2010;121:1706-1712.)

Key Words: epidemiology ■ genes ■ risk factors ■ thrombosis

Factor V Leiden and the prothrombin G20210A gene mutation have a prevalence within white populations of approximately 5% and 2%, respectively.1,2 The prevalence of carriers who are double heterozygotes for factor V Leiden and the prothrombin mutation is much lower (0.1%).3 Homozygosity for these mutations is even more rare, with a prevalence of 0.02% for factor V Leiden and 0.014% for prothrombin G20210A.4,5 Heterozygous carriers of factor V Leiden and prothrombin G20210A are at an approximately 5- and 3-fold higher risk, respectively, for first venous thrombosis compared with individuals without these mutations.6,7 This risk is 20-fold higher in subjects who are heterozygous carriers of both factor V Leiden and prothrombin G20210A and 18-fold higher in homozygous factor V Leiden carriers.3,8 Some guidelines recommend treatment of homozygous carriers of factor V Leiden or double heterozygous carriers of factor V Leiden and prothrombin G20210A with anticoagulant treatment for an indefinite time after a first episode of venous thrombosis, probably because patients with this genetic background have such a high risk for first venous thrombosis.9 Testing for factor V Leiden and/or prothrombin G20210A in patients with first venous thrombosis is, however, only indicated if the risk of recurrence is increased compared with noncarriers with venous thrombosis. Previous studies showed that this is not the case in heterozygous factor V Leiden carriers and in heterozygous prothrombin G20210A carriers, and the authors concluded that testing for these genetic defects is therefore not clinically relevant.10,11 Others argued

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From the Division of Hemostasis and Thrombosis, Department of Hematology, University Medical Center Groningen, Groningen (W.M.L., N.J.G.M.V., J.v.d.M.); Department of Vascular Medicine, Academic Medical Center, Amsterdam (S.M., H.R.B.); Departments of Hematology (K.H.) and Clinical Epidemiology and Medical Technology Assessment (M.H.P.), Maastricht University Medical Center, Maastricht; and Department of Clinical Epidemiology, University Medical Center, Leiden (W.M.L., S.M.), the Netherlands.

†Deceased.

Reprint requests to Willem M. Lijfering, MD, PhD, Division of Hemostasis and Thrombosis, Department of Hematology, University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, the Netherlands. E-mail w.lijfering@int.umcg.nl

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1706
that screening for these genetic defects is important because double heterozygous carriers of factor V Leiden and prothrombin G20210A had a 2.6-fold higher risk for recurrence compared with heterozygous factor V Leiden carriers, and for that reason they should receive anticoagulant treatment for an indefinite period after first venous thrombosis. However, the studied population was very small (n=17) in the latter study. Recurrence rates of venous thrombosis in homozygous factor V Leiden carriers have been estimated in small numbers as well. One subgroup analysis of a prospective cohort study showed only 1 recurrence in 8 consecutive patients with homozygous factor V Leiden at a median follow-up of 8 years, whereas another study showed that 4 of 11 consecutive patients with homozygous factor V Leiden had a recurrence within 2 years after the end of initial anticoagulant treatment. The largest (retrospective) study on this issue (n=32; median follow-up, 4.5 years) reported a 1.8-fold (95% confidence interval [CI], 1.0 to 6.2) increased risk for recurrence in patients with homozygous factor V Leiden compared with heterozygotes.

Definitions

Clinical Perspective on p 1712

Given the large ranges of these risk estimates, we performed a case-control study within a large thrombophilic family cohort study to assess the risk of recurrent venous thrombosis in individuals with homozygosity or double heterozygosity of factor V Leiden and/or prothrombin G20210A compared with heterozygotes and noncarriers. Because we sampled individuals from a thrombophilic cohort, we were able to collect a large number of carriers of factor V Leiden and/or prothrombin G20210A with single, combined, and homozygous factor V Leiden or prothrombin G20210A, as well as (their) related noncarriers.

Methods

Data Retrieval

A description of this family cohort has been reported previously. It contains pooled data of 6079 individuals from 5 large retrospective family cohort studies with various thrombophilic defects. These studies were performed by 3 university hospitals in the Netherlands (Groningen, Amsterdam, Maastricht). Consecutive patients (probands) with venous thrombosis or premature atherosclerosis and a thrombophilic defect (including antithrombin, protein C, or protein S deficiency; factor V Leiden; prothrombin G20210A; high factor VIII levels; or hyperhomocysteinemia) and their first-degree relatives were identified. Because the number of antithrombin-deficient probands was small, second-degree relatives (ie, grandparents and/or blood-related uncles or aunts) with a deficient parent were also identified. Physicians at the thrombosis outpatient clinics of the participating centers collected detailed information about previous episodes of venous thrombosis, exposure to exogenous risk factors for venous thrombosis (surgery, immobilization or trauma, pregnancy, postpartum period until 6 weeks, and use of oral contraceptives or hormone replacement therapy), and anticoagulant treatment using a validated questionnaire and by reviewing medical records. Clinical data were collected before laboratory tests were performed. The study started in May 1995 and was completed in July 2004.

Definitions

As described previously, in this cohort absolute risk estimates of recurrent venous thrombosis in relatives who are homozygous or double heterozygous for factor V Leiden and/or prothrombin G20210A could not be obtained because of the small numbers of subjects. For this reason, we included both probands and relatives in the present study who had a history of venous thrombosis (n=601 and n=187, respectively). Individuals on anticoagulant treatment for an indefinite time (n=206) were not included in the study. A case-control study design was chosen. Cases were individuals who had had recurrent venous thrombosis; controls were individuals with only first venous thrombosis. Because of the retrospective study design, anticoagulant treatment of first and eventual recurrent venous thrombosis was not influenced by the presence or absence of thrombophilic defects.

Venous thrombosis (either first or recurrent) was defined as provoked if it had occurred at or within 3 months after exposure to exogenous risk factors including surgery, trauma, immobilization for >7 days, pregnancy, postdelivery period, the use of oral contraceptives or hormonal replacement therapy, or malignancy. In the absence of these risk factors, venous thrombosis was classified as unprovoked. Superficial phlebitis and isolated calf vein thrombosis were not classified as a thrombotic event. Recurrence was considered established if it was demonstrated by objective techniques (ie, compression ultrason or venography for proximal deep vein thrombosis and ventilation/perfusion lung scanning, spiral computed tomographic scanning, or pulmonary angiography for pulmonary embolism) at a site other than that of the first event or at the same site if previously repeated tests showed no residual venous thrombosis or when the patient had received full-dose heparin and a vitamin K antagonist for at least 3 months without objective testing at a time when these techniques were not yet available. If recurrence of deep vein thrombosis at the same site was suspected but objective tests were not conclusive, it was diagnosed when the patient revealed pronounced signs and symptoms of recurrence without preceding postthrombotic syndrome or when pulmonary embolism was objectively demonstrated.

Statistical Analysis

The prevalence of noncarriership of factor V Leiden and prothrombin G20210A in the studied population was investigated, as well as prevalence of single carriership of heterozygous factor V Leiden or prothrombin G20210A, homozygosity of factor V Leiden and/or prothrombin G20210A, and double heterozygosity of both mutations. We calculated odds ratios with 95% CIs for the risk of recurrence in individuals who were heterozygous carriers of either factor V Leiden or prothrombin G20210A, were homozygous carriers of factor V Leiden and/or prothrombin G20210A, or were double heterozygous carriers of both mutations compared with noncarriers of both factor V Leiden and prothrombin G20210A. Odds ratios were adjusted for age, sex, and anticoagulant treatment time with logistic regression methods. To account for clustering of events within families, odds ratios were also adjusted with the use of robust sandwich method logistic regression in Stata, version 10.0 (Stata Corp, College Station, Tex). Additional preplanned sensitivity analyses were performed for family status by excluding relatives (this also corrects the matching aspect of family members because probands are unrelated consecutive patients), by excluding individuals with natural anticoagulant deficiencies because a prior study of ours showed that these individuals were at high risk of recurrence, and by excluding individuals who had missing data of antithrombin, protein C, or protein S levels. Other preplanned sensitivity analyses included individuals whose first venous thrombotic event was unprovoked because a previous study suggested that double heterozygous carriers of factor V Leiden and prothrombin G20210A in particular were at high risk of recurrence, as well as individuals whose first event was deep vein thrombosis because different risk of deep vein thrombosis and pulmonary embolism has been assumed in carriers of factor V Leiden (so-called factor V Leiden paradox). Because total follow-up time between a first event and recurrence or date of sampling can differ between individuals, we subsequently used a concurrent sampling method to recalculate odds ratios. Concurrent odds ratios are obtained by calculating the incidence rate of recurrent venous thrombosis from the end of anticoagulant treatment...
after the first episode of venous thrombosis until either the date of first recurrence or the end of study. It is, strictly speaking, a rate ratio rather than an odds ratio. We stratified concurrent odds ratios over a 2-, 2- to 5-, and 5-year follow-up time to identify whether there were differences in risk between groups over time. Furthermore, concurrent odds ratios were adjusted for clustering of events within families by using a Cox regression model that used the robust sandwich method in Stata. No formal calculations for sample size were determined because we performed a post hoc analysis of data.

All participants provided written informed consent, and approval was obtained from the institutional review boards of the 3 participating university hospitals. Statistical analyses were performed with SPSS for Windows, release 16.0 (SPSS Inc, Chicago, Ill) and Stata, version 10.0 (Stata Corp, College Station, Tex). The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

A flow chart of the study with probands, relatives, and their genotypes is presented in the Figure. Clinical characteristics of 788 evaluable individuals are summarized in Table 1. Sixty-four percent were women. Mean age at onset of the first episode of venous thrombosis was 38 (SD 15) years. Of first events, 335 (43%) were unprovoked. A total of 325 individuals (41%) had recurrent venous thrombosis (ie, the cases), and 463 individuals had only 1 venous thrombosis (ie, the controls). Mean age at recurrence was 44 (SD 15) years, and 217 recurrent events (67%) were unprovoked. Mean time delay from interruption of anticoagulation to recurrent events was 6.9 years. Natural anticoagulant deficiencies (antithrombin, protein C, or protein S deficiency) were more often found in cases than in controls; the crude odds ratio was 2.8 (95% CI, 2.0 to 4.0) compared with individuals without these hereditary deficiencies. In noncarriers of both factor V Leiden and prothrombin G20210A, the percentage of deep vein thrombosis as initial first venous thrombotic event was 69% (n=240/347). In individuals who were heterozygous carriers of either factor V Leiden or prothrombin G20210A, who were homozygous carriers of factor V Leiden and/or prothrombin G20210A, or who were double heterozygous carriers of both mutations, these percentages were 80% (n=225/283), 71% (n=58/82), 70% (n=19/27), and 76% (n=37/49), respectively.

Odds ratios of recurrent venous thrombosis, adjusted for age and sex, in individuals who were heterozygous carriers of either factor V Leiden or prothrombin G20210A, who were homozygous carriers of factor V Leiden and/or prothrombin G20210A, or who were double heterozygous carriers of both mutations, these percentages were 80% (n=225/283), 71% (n=58/82), 70% (n=19/27), and 76% (n=37/49), respectively.

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lant deficiencies, or missing data of antithrombin, protein C, or protein S levels did not alter the risk estimates. Risks of recurrent venous thrombosis in individuals with a first unprovoked event or whose first event was deep vein thrombosis were similar between groups (Table 3). There were no differences in risk between groups over time (Table 4).

Not all events were confirmed by objective techniques because these were not available at time of onset, and therefore we excluded individuals with clinically diagnosed first venous thrombosis (n=195; 25%) from our cohort and repeated the analysis. Adjusted for age and sex, odds ratios for objectively confirmed recurrent venous thrombosis in individuals who were heterozygous carriers of factor V Leiden or prothrombin G20210A, who were homozygous carriers of factor V Leiden and/or prothrombin G20210A, or who were double heterozygous carriers of both mutations, compared with individuals who were noncarriers of both factor V Leiden and prothrombin G20210A, were 1.0 (95% CI, 0.7 to 1.5), 0.7 (95% CI, 0.4 to 1.2), 0.3 (95% CI, 0.1 to 1.2), and 0.7 (95% CI, 0.3 to 1.5). Because a fair number of

Table 2. Risk of Recurrent Venous Thrombosis in Individuals Derived From Thrombophilic Families

<table>
<thead>
<tr>
<th>Individuals With Recurrence, n</th>
<th>Individuals Without Recurrence, Controls, n</th>
<th>Mean Follow-Up Time, y</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR* (95% CI)</th>
<th>Adjusted OR† (95% CI)</th>
<th>Adjusted OR‡ (95% CI) Excluding Relatives</th>
<th>Natural Anticoagulant Deficiencies</th>
<th>Missing Data‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noncarrier factor V Leiden/noncarrier prothrombin mutation</td>
<td>140</td>
<td>207</td>
<td>6.9</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Heterozygous factor V Leiden/noncarrier prothrombin mutation</td>
<td>126</td>
<td>157</td>
<td>5.7</td>
<td>1.2 (0.9−1.6)</td>
<td>1.2 (0.9−1.7)</td>
<td>1.1 (0.8−1.6)</td>
<td>1.2 (0.8−1.7)</td>
<td>1.3 (0.9−2.0)</td>
</tr>
<tr>
<td>Noncarrier factor V Leiden/heterozygous prothrombin mutation</td>
<td>27</td>
<td>55</td>
<td>5.4</td>
<td>0.7 (0.4−1.2)</td>
<td>0.7 (0.4−1.2)</td>
<td>0.7 (0.4−1.2)</td>
<td>0.8 (0.4−1.4)</td>
<td>0.6 (0.3−1.2)</td>
</tr>
<tr>
<td>Homozygous factor V Leiden and/or homozygous prothrombin mutation</td>
<td>12</td>
<td>15</td>
<td>8.3</td>
<td>1.2 (0.5−2.6)</td>
<td>0.9 (0.4−2.1)</td>
<td>1.1 (0.5−2.5)</td>
<td>0.6 (0.2−1.9)</td>
<td>1.0 (0.3−2.9)</td>
</tr>
<tr>
<td>Heterozygous factor V Leiden/heterozygous prothrombin mutation</td>
<td>20</td>
<td>29</td>
<td>6.6</td>
<td>1.0 (0.6−1.9)</td>
<td>0.9 (0.5−1.8)</td>
<td>1.0 (0.5−1.8)</td>
<td>0.9 (0.5−1.9)</td>
<td>1.1 (0.6−2.3)</td>
</tr>
</tbody>
</table>

OR indicates odds ratio.
*Adjusted for age, sex, and clustering of events within families.
†Adjusted for anticoagulant treatment time and clustering of events within families.
‡Missing data for antithrombin, protein C, or protein S.

Table 3. Risk of Recurrent Venous Thrombosis Confined to Environmental Risk Factors or Event Type

<table>
<thead>
<tr>
<th>Idiopathic First Venous Thrombosis</th>
<th>First Event Deep Vein Thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals With Recurrence, n</td>
<td>Individuals Without Recurrence, n</td>
</tr>
<tr>
<td>Noncarrier factor V Leiden/noncarrier prothrombin mutation</td>
<td>64</td>
</tr>
<tr>
<td>Heterozygous factor V Leiden/noncarrier prothrombin mutation</td>
<td>62</td>
</tr>
<tr>
<td>Noncarrier factor V Leiden/heterozygous prothrombin mutation</td>
<td>14</td>
</tr>
<tr>
<td>Homozygous factor V Leiden and/or homozygous prothrombin mutation</td>
<td>3</td>
</tr>
<tr>
<td>Heterozygous factor V Leiden/heterozygous prothrombin mutation</td>
<td>7</td>
</tr>
</tbody>
</table>

OR indicates odds ratio.
*Adjusted for age, sex, and clustering of events within families.
subjects were single homozygous carriers of factor V Leiden (n=21), we calculated the odds ratio of recurrence in this group as well. Crude odds ratio was 1.1 (95% CI, 0.5 to 2.4) compared with noncarriers of both factor V Leiden and prothrombin G20210A.

Discussion

This study demonstrates no increased risk for recurrent venous thrombosis in subjects with single heterozygous prothrombin G20210A and only a mildly increased risk in single heterozygous factor V Leiden carriers compared with noncarriers derived from thrombophilic families. Homozygosity for factor V Leiden and/or prothrombin G20210A did not increase the risk for recurrence, which is in agreement with 1 study\(^{10}\) but in disagreement with another study.\(^{13}\)

Double heterozygosity of factor V Leiden and prothrombin G20210A was also not associated with an increased risk of recurrence, which is in disagreement with a previous report.\(^{12}\)

These inconsistencies may be due to small numbers of double heterozygous carriers of factor V Leiden and prothrombin G20210A in a prior study (n=17)\(^{12}\) and of homozygous carriers of factor V Leiden and/or prothrombin G20210A (n=27) and of double heterozygous carriers of factor V Leiden and prothrombin G20210A (n=49) were relatively small in our study as well. This might have led to a type II error. Moreover, events in our retrospective study were not always confirmed by objective techniques. However, odds ratios did not substantially change after we excluded individuals with clinically diagnosed first venous thrombosis from analyses. Furthermore, our cohort contained a relatively large proportion of individuals with antithrombin, protein C, or protein S deficiency, which increased the risk of recurrence 2.8-fold (95% CI, 2.0 to 4.0) compared with individuals without these hereditary deficiencies. Therefore, generalizability of our results is somewhat hampered. However, results were not influenced after we excluded individuals with natural anticoagulant deficiencies from analysis. From a methodological point of view, inclusion of probands in a study is problematic. Because the outcome of probands was either a first or recurrent venous thrombotic event, results would have been biased if we had calculated absolute risk estimates. Therefore, we decided to calculate only relative risk estimates. These estimates are not biased by the inclusion of probands because probands were consecutive patients with either first or recurrent venous thrombosis (ie, there is no bias toward including patients with recurrences preferentially within this study design). A biased result can, however, occur when the duration of follow-up in controls is much shorter than in cases (ie, controls would then have less time to develop a recurrence and consequently to become a case, which could explain our null findings). Although it seemed that heterozygous factor V Leiden/heterozygous prothrombin mutation cases had a longer mean follow-up time (6.6 years) versus controls (4.0 years), this result was not statistically significant. Furthermore, when we calculated a concurrent odds ratio, which analyzes time effects in closer detail than traditional odds ratios,\(^{25}\) risk of recurrence was slightly higher (odds ratio of 1.3 compared with 1.0, respectively), although this was not clinically relevant and was very similar to the

### Table 4. Concurrent Odds Ratios for Recurrent Venous Thrombosis in Individuals Derived From Thrombophilic Families*

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Follow-Up &lt;2 y</th>
<th>Follow-Up 2 to 5 y</th>
<th>Follow-Up &gt;5 y</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observation</td>
<td>No. of Events</td>
<td>Concurrent OR (95% CI)</td>
<td>Observation</td>
</tr>
<tr>
<td>Noncarrier factor V Leiden/noncarrier prothrombin mutation</td>
<td>2494 (347)</td>
<td>140</td>
<td>Reference</td>
<td>519 (347)</td>
</tr>
<tr>
<td>Homozygous factor V Leiden and/or homozygous prothrombin mutation</td>
<td>230 (27)</td>
<td>12</td>
<td>0.9 (0.5–1.6)</td>
<td>43 (27)</td>
</tr>
<tr>
<td>Heterozygous factor V Leiden/heterozygous prothrombin mutation</td>
<td>247 (48)</td>
<td>20</td>
<td>1.3 (0.8–2.1)</td>
<td>62 (48)</td>
</tr>
</tbody>
</table>

OR indicates odds ratio.

*Concurrent ORs adjusted for clustering of events within families.
risk of recurrence in single heterozygous factor V Leiden carriers both in our study and in others. In addition, concurrent odds ratios were stable over time and were comparable to traditional odds ratio calculations, which can be expected when risks are stable over time.

Given the rarity of individuals who are homozygous for factor V Leiden and/or prothrombin G20210A or who are double heterozygous for factor V Leiden and prothrombin G20210A, large multicenter studies are probably needed to provide a conclusive answer in regard to whether these individuals are at high risk of recurrence and, consequently, if patients with first venous thrombosis should be screened for factor V Leiden and prothrombin G20210A. In regard to this issue, a recent systematic review involved a literature search of individuals at risk of recurrence who were either homozygous factor V Leiden carriers or double heterozygous factor V Leiden and prothrombin G20210A carriers. Unfortunately, inclusion criteria in that study were very strict. For example, the authors could only include 10 double heterozygous individuals, which also indicates that there is a lack of evidence about the usefulness of testing for these genetic defects.

We conclude from our results that individuals with homozygous factor V Leiden and/or homozygous prothrombin G20210A or double heterozygous carriers of factor V Leiden and prothrombin G20210A do not have a high risk of recurrent venous thrombosis.

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Disclosures

None.

References


**CLINICAL PERSPECTIVE**

Homoyzogus or double heterozygous factor V Leiden and/or prothrombin G20210A is a rare inherited thrombophilic trait. Although individuals who have these mutations are at an ~20-fold increased risk of first venous thrombosis, it is uncertain whether the risk of recurrence in these individuals is also increased. The clinical implications for such individuals, such as receiving antiocoagulant treatment for an indefinite time after first venous thrombosis, depend on the risk of recurrence.

In this case-control study, performed in a large cohort of thrombophilic families, we assessed the risk of recurrence of venous thrombosis in individuals with homozygosity or double heterozygosity for factor V Leiden and prothrombin G20210A. The cohort consisted of 788 individuals with prior venous thrombosis, of whom 325 had recurrent events. A total of 494 mutations were identified. Compared with noncarriers, carriers of the mutations factor V Leiden (n=283), prothrombin G20210A (n=82), double heterozygous (n=49) or homozygous factor V Leiden, or homozygous prothrombin G20210A (n=27) did not display an increased risk of recurrent events. Testing for these genetic mutations in patients with first venous thrombosis seems therefore to be of limited use.

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