Double-Homozygosity for Factor V Leiden and the Prothrombin Gene G20210A Variant in a Young Patient With Idiopathic Venous Thrombosis

To the Editor:

There is growing evidence that environmental and genetic risk factors often interact to induce clinically manifest venous thromboembolism (VTE). The role of gene-gene interactions, although much rarer, is supported by cosegregation of genetic defects observed in patients with familial thrombophilia. In this context, factor V (FV) Leiden and the prothrombin G20210A gene (FII) mutation are of particular interest because of their high prevalence in the normal population; about 5% of FII mutation has been reported in because of their high prevalence in the normal population; about 5% of FII mutation are of particular interest with familial thrombophilia. In this context, factor V (FV) Leiden and 0.014% for the FII mutation.1,2 We present here a case of double-homozygosity for these defects.

A 34-year-old man presented with a first episode of idiopathic deep-vein thrombosis. He had never been exposed to environmental risk factors for thrombosis. Treatment consisted of subcutaneous low-molecular-weight heparin for 1 week followed by acenocoumarol for 3 months. At 18 months follow-up, he had experienced no recurrence.

Laboratory studies for thrombophilic disorders showed double-homozygosity for FV Leiden and the FII mutation, detected by polymerase chain reaction. None of his 15 relatives had a history of VTE. Four were double-heterozygous carriers, 4 were single carriers of the FII mutation, and 3 were noncarriers (Fig 1). Four relatives, 2 of whom had died, were not tested but they were obligate carriers of at least 1 (N = 1) or both (N = 3) mutations. The patient’s father, who had a history of smoking and hypercholesterolemia, died of myocardial infarction at 57 years of age and a son died from crib death. His mother experienced a myocardial infarction when she was 61 years old; she had a history of hypertension and diabetes mellitus. Fetal loss had occurred only in 1 noncarrier. Table 1 summarizes characteristics of this family.

Double-homozygosity for FV Leiden and the FII mutation is extremely rare. Theoretically, it is expected in 3 per 100 million whites. The thrombotic risk of this combined abnormality is unknown. Homozygosity for FV Leiden increases the risk of VTE approximately 80-fold compared with noncarriers. The risk in homozygous carriers of the FII mutation has not yet been estimated; only case reports have been published.

Remarkably, only our double-homozygous patient has developed
venous thrombosis, while none of his single- or double-heterozygous carrier relatives have experienced VTE thus far, despite their exposure to several environmental risk factors (Table 1). The compound carrier-ship in this family is apparently not associated with a high risk of VTE. This finding agrees with a recent observation that the thrombotic risk in FII mutants is hardly influenced by the simultaneous presence of FV Leiden. Others, however, reported a high risk of recurrence in double-heterozygous carriers. Concomitant protective genetic factors in families with a hardly increased risk of VTE may explain this discrepancy.

Both mutations have also been associated with myocardial infarction. Their contribution to this event in 2 double-heterozygous carriers, who already exhibited several established risk factors, remains speculative. None of the carriers showed fetal loss, another possible expression of thrombophilia.

Elevated plasma levels of prothrombin in carriers of the FII mutation have been correlated with the thrombotic risk. In our double-homozygous patient, prothrombin activity was shown to be clearly higher than in noncarriers, while heterozygous carriers had values that fell in between.

This family illustrates that expression of the supposed high risk of thrombosis, due to gene-gene interaction and exposure to environmental risk factors, is not a matter of course in compound carriers of FV Leiden and the FII mutation. Our findings emphasize the need for further studies to assess the implications of these common mutations in compound carriers.

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Sensitivity of CD4⁺ Peripheral Blood T Cells Toward Spontaneous and CD95 (APO-1/Fas)-Induced Apoptosis in Pediatric Human Immunodeficiency Virus Infection

To the Editor:

McCloskey et al recently reported that spontaneous apoptosis of T cells from human immunodeficiency virus (HIV)-infected individuals occurred only in previously activated cells independent of CD95 receptor (R) expression or CD95 sensitivity. Using fluorescein isothio-

**Table 1. Clinical Characteristics and Prothrombin Activity Levels of the Propositus and His Family Members**

<table>
<thead>
<tr>
<th></th>
<th>Homozygous FVL + FII (n = 1)</th>
<th>Heterozygous FVL + FII (n = 4)</th>
<th>Heterozygous FII (n = 4)</th>
<th>Noncarriers (n = 3)</th>
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</thead>
<tbody>
<tr>
<td>Pedigree code</td>
<td>II.9</td>
<td>1.1, II.4, III.3, III.5</td>
<td>II.2, II.8, III.1, III.6</td>
<td>II.1, III.2, III.4</td>
</tr>
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<td>Men/women</td>
<td>0/1</td>
<td>1/3</td>
<td>2/2</td>
<td>0/3</td>
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<tr>
<td>Age, yr</td>
<td>34</td>
<td>67, 43, 24, 18</td>
<td>44, 38, 22, 14</td>
<td>45, 19, 19</td>
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<tr>
<td>Thrombotic episodes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VTE, n</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial infarction, n</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fetal loss, n</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Exposure to environmental risk factors for VTE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Episodic of surgery, trauma, or immobilization, n</td>
<td>0</td>
<td>18</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Pregnancies, n</td>
<td>—</td>
<td>10</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Use of oral contraceptives, yr</td>
<td>—</td>
<td>18</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Prothrombin activity (%)</td>
<td>160</td>
<td>134, 143, 106, 114</td>
<td>134, 124, 154, 122</td>
<td>99, 93,* 118*</td>
</tr>
</tbody>
</table>

Abbreviations: FVL, factor V Leiden; FII, prothrombin G20210A gene mutation; VTE, venous thromboembolism.

*Measurement during use of oral contraceptives.

REFERENCES


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