The association between the Val34Leu polymorphism in the factor XIII gene and brain infarction

Alexis Elbaz, Odette Poirier, Sandrine Canaple, François Chédru, François Cambien, and Pierre Amarenco, on behalf of the GÉNIC investigators

Factor XIII catalyzes the formation of covalent bounds between fibrin monomers, thus stabilizing the fibrin clot and increasing its resistance to fibrinolysis. The frequency of a frequent Val34Leu polymorphism in the FXIII A-subunit gene has been shown to be lower in patients with myocardial infarction or venous thrombosis than in controls, whereas it was higher in patients with hemorrhagic stroke than in controls. Our aim was to study the relation between brain infarction (BI) and the FXIII Val34Leu polymorphism in 456 patients consecutively recruited with a BI confirmed by MRI, and 456 matched controls. The distribution of genotypes was different in cases (63.2% Val/Val; 30.9% Val/Leu; 5.9% Leu/Leu) compared with controls (49.8% Val/Val; 42.8% Val/Leu; 7.4% Leu/Leu; P < .001). Carrying the Leu allele was associated with an OR of 0.58 (95% CI = 0.44-0.75). A similar association was observed in cases and controls free of previous cardiovascular or cerebrovascular history (OR = 0.51; 95% CI = 0.36-0.73). No heterogeneity of this association was observed after stratification on the main BI subtypes. Adjustment for traditional vascular risk factors did not modify these findings. In addition, the effect of smoking was modified by the polymorphism (P = .05); the effect of smoking was weaker among Leu carriers than among noncarriers. In conclusion, there was a negative association of the FXIII Val34Leu polymorphism with BI, thus suggesting a protective effect of the Leu allele against thrombotic cerebral artery occlusion. In addition, our results suggest that among Leu carriers, the protective effect of the polymorphism outweighed the effect of smoking. (Blood. 2000;95:586-591)

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Introduction

Prospective and case-control studies suggest that factors involved in the coagulation and fibrinolytic pathways, such as fibrinogen, tissue plasminogen activator, factor VII, or plasminogen activator inhibitor-1, may contribute to the cause of thrombotic diseases. The role of factor XIII (FXIII) has been more recently investigated.

FXIII is a transglutaminase consisting of 2 catalytic A-subunits and 2 carrier protein B-subunits. When activated by thrombin, FXIIIa catalyzes the formation of covalent e-(γ-glutamyl)-lysyl bounds between fibrin monomers, thus stabilizing the fibrin clot and increasing its resistance to fibrinolysis. FXIIIa is also implicated in the cross-linking of several other proteins, such as α-2 antiplasmin, fibronectin, and collagen. Mutations of the FXIII A-subunit have been related to FXIII deficiency, a rare autosomal recessive disorder characterized by a tendency for spontaneous bleeding (including intracranial hemorrhages at a young age) and impaired wound healing.

Recently, a common G→T polymorphism, leading to a valine (Val) to leucine (Leu) substitution 3 amino acids from the thrombin activation site, was described in exon 2 of the FXIII A-subunit gene. The frequency of the Leu allele has been shown to be lower in subjects with myocardial infarction or deep venous thrombosis than in controls. Because the mutant allele is associated with a higher activity of the enzyme, this protective effect is not well understood, although it has been hypothesized that increased rates of FXIII activation could lead to ineffective cross-linking, or that the kinetics of the cross-linking reactions may be disrupted because of the effects of FXIIIa on other proteins.

Catto et al. investigated the relation between stroke and the Val34Leu polymorphism and found that the mutant allele was more frequent in cases with hemorrhagic stroke than in controls, although no significant difference was observed between cases with brain infarction (BI) and controls. These results support the view that determinants, including genetic susceptibility, of ischemic and hemorrhagic strokes should be investigated separately.

Our aim was to investigate the association between BI and the Val34Leu polymorphism of the factor XIII gene in patients with BI and matched controls, as part of the GÉNIC study. This relation was studied overall, and among the main BI subtypes. In addition, because FXIII level has been shown to be modified by smoking among pregnant women and healthy subjects, we investigated whether the polymorphism and smoking interacted in determining the risk of BI.
Subjects and methods

Cases

Cases were consecutively recruited among all patients admitted in 12 French neurologic centers, if they fulfilled the following criteria: (1) clinical symptoms suggestive of stroke, (2) no brain hemorrhage on computed tomographic (CT) scan, (3) infarct proven by MRI, (4) 18 to 85 years old, and (5) both parents of Caucasian origin. Cases were included in the week-interval after the event. Patients reporting previous cardiovascular or cerebrovascular history were eligible.

Controls

Controls without history of stroke were recruited among individuals hospitalized at the same institutions, for any other reason than neurologic diseases; these consisted of orthopedic (46%), ophthalmologic (12%), rheumatologic (11%), surgical (6%), and other (25%) causes. One control was matched by sex, age (± 5 years), and center to each case. Subjects reporting a positive cardiovascular history other than stroke were eligible. Their parents had to be of Caucasian origin.

Data collection and risk factors definition

Information on demographic characteristics and risk factors was collected using a structured questionnaire. Hypertension was defined by a history of treated hypertension. Smoking history was coded as never, ex (stopped smoking at least 1 year before inclusion in the study), and current smoking; number of cigarettes smoked per day and duration of smoking were recorded, and the number of pack-years (PY) was computed as the number of packs smoked per day times the number of years. Subjects were classified as diabetics when treated for insulin dependent or noninsulin dependent diabetes. Use of lipid-lowering drugs was assessed. History of MI, angioplasty, coronary artery by-pass surgery, or lower-limb arterial disease was recorded; positive cardiovascular history was defined by the presence of any of these diseases. History of stroke or transient ischemic attacks was obtained in cases.

Investigations

Electrocardiogram (ECG), extracranial duplex, and transcranial Doppler were performed on all cases and controls. Presence of plaques, arterial stenoses, and occlusions were assessed. Two-dimensional echocardiography and transcranial Doppler were performed on all cases and controls. Presence of plaques, arterial stenoses, and occlusions were assessed. Two-dimensional echocardiography results were available for 464 patients (91%) and transesophageal echocardiography was performed in 358 (77%). MRI could not be performed or was of poor quality in only 38 cases (7.5%); nevertheless, these patients were included in the study because the CT scan clearly showed a recent BI. Conventional or magnetic resonance cerebral angiogram was performed on 208 patients (41%); Blood was drawn in the morning from fasting subjects for DNA extraction and lipid profile determinations in 1 central laboratory.

Brain infarction subtypes classification

Patients were classified into etiologic subtypes by 2 neurologists (P.A., F.Ch.) according to prespecified criteria, after review of clinical files, discharge summaries, follow-up visit reports, and results of investigations.

Atherothrombotic stroke: Defined by (1) an ipsilateral internal carotid stenosis ≥ 50%, or (2) an ipsilateral stenosis ≥ 50% of another intra-/extra-cranial artery, or (3) plaques > 4 mm in the aortic arch with a mobile component.

Cardioembolic stroke: When a cardiac source was recognized (MI within the prior 3 weeks, atrial fibrillation, mitral stenosis, cardiac thrombus, valvular vegetations, atrial myxoma, prosthetic mitral or aortic valve, left ventricular aneurysm, dilated cardiomyopathy).

Lacunar stroke: Defined by a small deep infarct measuring < 15 mm size (MRI), in a patient with a clinical syndrome compatible with the diagnosis of lacune, without any finding in favor of an atherothrombotic or cardioembolic stroke.

Arterial dissections: Diagnosed in patients with typical clinical angiographic patterns of carotid or vertebral arteries dissection.

Other causes: Rare causes such as polycythemia vera, cerebral arteritis, or thrombocytopenia.

Undetermined cause: When 2 or more causes defined above coexisted in the same individual.

Unknown cause: When no cause was identified. Patients with an isolated elevation of antiphospholipid antibodies, patent foramen ovale, atrial septal aneurysm, valvular straits, mitral valve prolapse, or mitral annulus calcifications, belonged to this group.

Val34Leu polymorphism of the factor XIII A subunit gene

The genotyping protocol is available on our Internet site: http://ifr69.vjf.inserm.fr/~canaus/. Among 510 cases and 510 controls included in the study, DNA was obtained, extracted, and amplified for 474 (93%) cases and 488 (96%) controls, corresponding to 456 matched pairs.

Data analysis

Allelic frequencies were calculated by gene-counting. Hardy-Weinberg equilibrium was tested using the $\chi^2$ statistic. We compared genotype distributions in cases and controls using conditional logistic regression analysis for matched sets.3 Odds-ratios (ORs) were computed with multivariate conditional logistic regression analysis and first-order multiplicative terms were introduced in the models to test for interaction. The ORs associated with the Val/Leu and the Leu/Leu genotypes were very similar; we therefore carried a collapsibility test,13 and because the test did not reject collapsibility of these genotypes ($P = .95$), ORs were computed assuming a dominant model, by comparing the frequency of the Val/Leu and Leu/Leu genotypes pooled together with the frequency of the Val/Val genotype in cases and controls, using conditional logistic regression analysis. Our analyses concerned the whole study group, and were subsequently stratified according to the 4 main BI subtypes (atherothrombotic, lacunar, cardioembolic strokes, and strokes of unknown cause; analyses concerning strokes of undetermined cause are not reported, because it is by definition a highly heterogeneous group); in each strata, cases were compared with their matched controls. The homogeneity of the association between the polymorphism and the disease across the main subtypes was tested using the Breslow-Day heterogeneity test.14 Analyses restricted to pairs of cases and controls both free of previous cardiovascular or cerebrovascular history are also reported. Statistical testing was performed at the 2-tailed 0.05 level. Data were analyzed with the SAS package.16

The research protocol was approved by the ethics committee of Hôpital Cochin and all subjects signed informed consents.

Results

The characteristics of the study subjects (456 matched pairs of cases and controls) are shown in Table 1. The frequencies ($n$) of BI subtypes were atherothrombotic, 23.0% (105); lacunar, 20.6% (94); cardioembolic, 16.0% (73); undetermined cause, 12.7% (58); dissections, 2.4% (11); rare causes, 2.0 (9); unknown cause, 23.3% (106).

Distributions of genotypes of the Val34Leu polymorphism in cases and controls for each BI subtypes are shown in Table 2, overall and according to etiologic subtypes. The distribution of genotypes was significantly different between cases and controls ($P < .001$). The proportion of individuals heterozygous or homozygous for the Leu allele and the frequency of this allele were higher in controls than in cases. Similar results were observed among etiologic subtypes, with the difference being significant for the lacunar group. Among controls, there were no differences in the frequency of genotypes according to the main hospitalization departments ($P = .98$, data not shown). The allele frequencies were similar to previously reported frequencies.
The number of matched pairs). Analyses restricted to cases and controls free of cardiovascular or cerebrovascular history yielded similar results (OR = 0.51; 95% CI = 0.36-0.73). No heterogeneity in this relation was observed according to sex (P for interaction = .4) or BI subtype (Breslow-Day test, P = .60). Among subtypes, the strongest effect of the Leu allele was observed in lacunar strokes. The relation between BI and FXIII Val34Leu was not modified by age (P for interaction = .7); after stratification according to median age (68 years), similar ORs were observed for subjects younger (OR = 0.52; 95% CI = 0.34-0.78), or older (OR = 0.55; 95% CI = 0.37-0.81) than 68 years.

Associations between several variables and the polymorphism were studied separately in cases and controls. No significant associations between the genotype and hypertension, smoking, and diabetes, or total cholesterol levels, were detected either in cases or in controls (data not shown). HDL-cholesterol level was higher in Val homozygotes compared with Leu carriers, both among cases (P = .02) and controls (P = .06). After adjustment for these risk factors, the association between BI and the Val34Leu polymorphism was not modified either overall (OR = 0.50; 95% CI = 0.36-0.71) or when analyses were restricted to subjects free of cardiovascular or cerebrovascular history (OR = 0.49; 95% CI = 0.32-0.76).

In this study, current smokers were at increased risk of BI (OR = 1.80; 95% CI = 1.21-2.68), with a significant trend according to the number of PY (P < .001), whereas ex-smokers were not (Table 1; OR = 1.05; 95% CI = 0.74-1.50); in the following analyses, never and ex-smokers were therefore pooled together and compared with current smokers. We observed an interaction between the Val34Leu polymorphism and current smoking (P = .05). As shown in Table 3, although the risk of BI increased gradually with the number of pack-years smoked among Val homozygotes (P for trend = .003), the trend was not significant among carriers of the Leu allele (P = .43). When analyses were restricted to cases and controls free of cardiovascular or cerebrovascular history, the modification by the polymorphism of the risk of

### Table 2. The Val34Leu polymorphism in the A-subunit of the factor XIII gene in cases with brain infarction and controls

<table>
<thead>
<tr>
<th>N (%)</th>
<th>Val/Val</th>
<th>Val/Leu</th>
<th>Leu/Leu</th>
<th>P</th>
<th>Leu%</th>
<th>OR (95% CI)‡</th>
<th>OR (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls§</td>
<td>227 (49.8)</td>
<td>195 (42.8)</td>
<td>34 (7.4)</td>
<td>&lt;10⁻³</td>
<td>28.8</td>
<td>0.58 (0.44-0.75)</td>
<td>0.53 (0.40-0.70)</td>
</tr>
<tr>
<td>Cases</td>
<td>288 (63.2)</td>
<td>141 (30.9)</td>
<td>27 (5.9)</td>
<td>21.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atherothrombotic strokes</td>
<td>54 (51.4)</td>
<td>44 (41.9)</td>
<td>7 (6.7)</td>
<td>.12</td>
<td>27.6</td>
<td>0.63 (0.37-1.10)</td>
<td>0.57 (0.32-1.03)</td>
</tr>
<tr>
<td>Controls</td>
<td>68 (62.9)</td>
<td>29 (27.6)</td>
<td>10 (9.5)</td>
<td>23.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>37 (39.4)</td>
<td>49 (52.1)</td>
<td>8 (8.5)</td>
<td>.004</td>
<td>34.6</td>
<td>0.32 (0.16-0.65)</td>
<td>0.29 (0.14-0.63)</td>
</tr>
<tr>
<td>Lacunar strokes</td>
<td>58 (61.7)</td>
<td>29 (30.8)</td>
<td>7 (7.5)</td>
<td>22.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>36 (49.3)</td>
<td>31 (42.5)</td>
<td>6 (8.2)</td>
<td>.06</td>
<td>29.5</td>
<td>0.47 (0.23-0.94)</td>
<td>0.38 (0.18-0.82)</td>
</tr>
<tr>
<td>Cases</td>
<td>49 (67.1)</td>
<td>22 (30.1)</td>
<td>2 (2.7)</td>
<td>17.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardioembolic strokes</td>
<td>58 (54.7)</td>
<td>43 (40.6)</td>
<td>5 (4.7)</td>
<td>.68</td>
<td>25.0</td>
<td>0.85 (0.49-1.46)</td>
<td>0.77 (0.44-1.35)</td>
</tr>
<tr>
<td>Strokes of unknown cause</td>
<td>63 (59.4)</td>
<td>37 (34.9)</td>
<td>6 (5.7)</td>
<td>23.1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Using conditional logistic regression for matched sets. ORs are computed by comparing the frequency of carriers of the Leu allele (Val/Leu + Leu/Leu genotypes) with the frequency of Val/Val homozygotes in cases and controls.

†Using conditional logistic regression for matched sets, after adjustment for cardiovascular history.

‡Using conditional logistic regression for matched sets, after restricting the analysis to cases and matched controls free of cardiovascular and cerebrovascular history (N is the number of matched pairs).

§Test for Hardy-Weinberg equilibrium: P = .42.
BI associated with smoking remained significant (P for interaction = .02).

Kohler et al\(^2\) reported that the FXIII Val34Leu polymorphism and the PAI-1 4G/5G polymorphism might interact in determining the risk of myocardial infarction. We did not find a significant association between the 4G/5G polymorphism and ischemic stroke (data not shown), in agreement with others.\(^7\) In addition, we did not find a significant interaction (P = .25) between the Val34Leu polymorphism and the PAI-1 4G/5G polymorphism; ORs associated with the Leu allele were 0.42 (0.15-1.20) in subjects with the VAL/VAL genotype, and 0.65 (0.44-0.94) among carriers of the 4G/5G and 5G/5G genotypes.

### Discussion

This study suggests that carrying the Leu allele of the Val34Leu polymorphism in the FXIII gene is negatively associated with BI, thus suggesting a protective effect of this polymorphism. Allelic and genotypic frequencies found in this study were very similar to those reported by others. Protection against BI was observed for Leu homozygotes and heterozygotes, thus suggesting a dominant effect. Furthermore, our results suggest that among carriers of the Leu allele, the protective effect of the polymorphism outweighed the effect of smoking.

Catto et al\(^10\) investigated the relation between stroke and the Val34Leu polymorphism and found that the mutant allele was more frequent in 62 cases (54.8%) with hemorrhagic stroke than in controls (41.7%; P = .05), whereas no significant difference was observed between cases with BI (46.5%) and controls. In their study, cases and controls were not individually matched, and the same control group was used for BI and hemorrhagic strokes. In addition, several authors have pointed that failure to take into account an interaction, when it does exist, may obscure an association.\(^18\) and as we will discuss later, our findings suggested that smoking and the Val34Leu polymorphism may interact in determining the risk of BI. Finally, the frequency of the Leu allele was lower in the control group in the stroke study than in other studies carried by the same team in the same country.\(^2,4,6\)

Recent studies suggest that the Val34Leu polymorphism may be protective against myocardial infarction and venous thrombosis.\(^2,5\) As in our study, both Leu homozygotes and homozygotes were more frequent among controls in all of them, except 1, in which the protective effect was restricted to Leu homozygotes.\(^3\) Thus, these findings suggest that being a carrier of the Leu allele is protective both for arterial and venous disease. It is also interesting to note that in our study, the negative association between the polymorphism and BI was observed for all subtypes (although with different strengths of association) and that the frequency of the Leu allele was very similar in cases belonging to different BI subtypes. This is in agreement with the role of FXIIIa as a stabilizer of the fibrin clot, which can be hypothesized to be a mechanism in common for BI of different causes.

The protective effect of the FXIII Val34Leu polymorphism is not well understood and needs to be elucidated. An increased FXIII activity has been reported in carriers of the Leu allele, with Leu homozygotes having the higher activities compared with Val homozygotes, and Leu heterozygotes having intermediate activities.\(^7-9\) The close proximity of the polymorphism to the thrombin activation site may account for these findings. Higher FXIII activities would therefore be expected to be associated with a higher resistance of the fibrin clot to fibrinolysis. Kohler et al\(^7\) hypothesized that increased rates of FXIII activation could lead to ineffective cross-linking, or that the kinetics of the cross-linking reactions may be considerably disrupted as a result of the effects of FXIIIa on other proteins. We cannot exclude, however, that this association may reflect linkage disequilibrium between the Val34Leu polymorphism and another functional variant. However, Kohler et al\(^9\) investigated the relation between myocardial infarction and 3 other common point mutations in the FXIII A-subunit gene. They confirmed that the Leu allele was more frequent in controls than in cases, but did not find any difference between the 2 groups of subjects for the other polymorphisms; they concluded that the FXIII Val34Leu polymorphism was the only common polymorphism in the coding region of the FXIII A-subunit gene associated with myocardial infarction.

The relation between FXIII concentration and smoking has been investigated in pregnant women to better understand the cause of fetal wastage.\(^12\) Both in smokers and nonsmokers FXIII concentration declined as pregnancy progressed. FXIII level was higher in smokers than in nonsmokers at various stages of gestation. Recently, Ariens et al\(^13\) also reported that the FXIII A-subunit level increased with smoking in healthy subjects. Interestingly, we found an interaction between current smoking and the FXIII Val34Leu polymorphism in determining the risk of BI. ORs associated with smoking were lower in Leu carriers than in...
noncarriers, thus suggesting that the protective effect of the polymorphism outweighed the effect of smoking among Leu carriers. Because lifestyle modifications (eg, smoking cessation) may take place after a cardiovascular event, we restricted our analyses to subjects free of previous cardiovascular or cerebrovascular history, and similar results were observed. It could be hypothesized that the relation between smoking and FXIII level is modified by the polymorphism. Investigation of FXIIIα activity in a healthy population, while taking smoking and the FXIII Val34Leu polymorphism into account, should be helpful to better understand these findings.

Allelic association studies may suffer from survival bias if they include prevalent cases and if survival is related to the gene under investigation. We included cases in the week after the event. Because early case fatality rates in BI are low, we do not believe that survival bias is likely to account for these results. In addition, to avoid the risk of stratification population bias, we only included subjects of Caucasian ancestry.19

In conclusion, we have identified a negative association between BI and the FXIII Val34Leu polymorphism. Our data are consistent with a gene-environment interaction model, according to which the effect of smoking is weaker among carriers of the Leu allele. The mechanism accounting for this protective effect remains to be elucidated, and further studies investigating the relation between FXIII activity, smoking, and the Val34Leu polymorphism may contribute to a better understanding. Finally, prospective studies are needed to evaluate more precisely the risk of BI and other thrombotic diseases, as well as their recurrence risk, associated with this polymorphism, and the use of its screening in such diseases.

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Appendix

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Data Monitoring and Coordinating Centre, Centre of Department, Neurology, Saint-Antoine Hospital: Pierre Amarenco, Homma Madrakian, Valérie Lebreton, Chantal Nouharet.

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