Plasma Thrombin-Activatable Fibrinolysis Inhibitor Antigen Concentration and Genotype in Relation to Myocardial Infarction in the North and South of Europe

I. Juhan-Vague, P.E. Morange, H. Aubert, M. Henry, M.F. Aillaud, M.C. Alessi, A. Samnegård, E. Hawe, J. Yudkin, M. Margaglione, G. Di Minno, A. Hamsten, S.E. Humphries on behalf of the HIFMECH Study Group*

Abstract—The thrombin-activatable fibrinolysis inhibitor (TAFI) is a recently described inhibitor of fibrinolysis that decreases plasminogen binding to the fibrin surface. The plasma TAFI concentration is almost entirely genetically determined. We investigated whether plasma TAFI levels and polymorphisms located in the TAFI gene could constitute risk markers of myocardial infarction (MI). Plasma TAFI antigen (Ag) levels were assayed by ELISA and 2 TAFI gene polymorphisms (Ala147Thr and C+1542G in the 3′ untranslated region) were determined in a large European case-control study. This study compared 598 men recruited 3 to 6 months after MI with 653 age-matched controls from North Europe (Stockholm, Sweden, and London, England) and South Europe (Marseilles, France, and San Giovanni Rotondo, Italy). A TAFI Ag value above the 90th percentile was associated with a significantly lower risk of MI (odds ratio 0.55, P<0.02), indicating that elevated TAFI may be protective against MI. As previously shown, the 2 TAFI gene polymorphisms were in strong linkage disequilibrium and were associated with the TAFI Ag concentration, with carriers of the Thr147 and 1542C alleles having higher levels (P<0.0005). These effects were similar in controls and cases and in each center. There was a difference in allele frequency between cases and controls for the Ala147Thr polymorphism, with Thr147 allele carriers being more frequent in controls than in cases in 2 centers, Stockholm (P=0.03) and San Giovanni Rotondo (P=0.03); the odds ratio for the entire cohort was 0.78 (P<0.05). In conclusion, patients with a recent MI presented lower values of TAFI Ag and higher frequencies of the “TAFI-decreasing” alleles. The geographical differences observed do not contribute to explaining the North-South gradient in MI risk in Europe. (Arterioscler Thromb Vasc Biol. 2002;22:867-873.)

Key Words: thrombin-activatable fibrinolysis inhibitors ■ myocardial infarction ■ genetic polymorphisms ■ fibrinolysis

The thrombin-activatable fibrinolysis inhibitor (TAFI), also known as procarboxypeptidase B and procarboxypeptidase U, has recently been described.1–3 It can potentiate inhibit fibrinolysis by removing carboxy-terminal lysine residues from partially degraded fibrin, decreasing plasminogen binding on its surface.4–7 Because of its role in the fibrinolytic system, TAFI may be implicated in atherothrombotic diseases. Studies conducted in different animal models support a physiological role of TAFI in the regulation of fibrinolysis.8–11 In humans, van Tilburg et al,12 have shown that an increased plasma TAFI antigen (Ag) concentration could be a risk marker for venous thrombosis.13 In a pilot study of men with stable angina pectoris and angiographically verified coronary artery disease, it was found that the plasma levels of TAFI were significantly higher in the patients than in healthy population-based age-matched men.13 The between-individual differences in plasma TAFI concentration are only partly explained by environmental factors, suggesting a strong influence of genetic factors.14,15 The human TAFI gene is located on chromosome 13q14.11 and consists of 11 exons spanning ~48 kb.16 Recently, by performing a molecular screening of the promoter and the 3′ untranslated region, we have identified several polymorphisms, including a C to G substitution at nucleotide 1542.17 This polymorphism was in strong linkage disequilibrium with the previously described Ala147Thr polymorphism.18 These
2 polymorphisms were associated with the plasma TAFI Ag concentration and individually contributed to a large fraction of the variation in plasma TAFI levels (52% for the C+1542G and 23% for Ala147Thr) in a sample of healthy men from the Marseilles area (France).

In a stepwise regression analysis including all polymorphisms, the combination of C+1542G associated with Ala147Thr was shown to explain 62% of the TAFI plasma levels. The aim of the present study was to evaluate the contribution of plasma TAFI Ag and of 2 polymorphisms located in the TAFI gene to the risk of myocardial infarction (MI) by using a large European multicenter case-control study, the Hypercoagulability and Impaired Fibrinolytic function MECHANisms predisposing to myocardial infarction (HIFMECH) study, which has as its aim the identification of differences in risk markers for MI between subjects living in the North (Stockholm, Sweden [STK] and London, England [LDN]) and the South (Marseilles, France [MRS] and San Giovanni Retondo, Italy [SGR]) of Europe.

## Methods

### Description of the Study Population

Male survivors of a first MI aged <60 years (excluding patients with familial hypercholesterolemia and insulin-dependent diabetes mellitus) and population-based individuals of the same age were recruited from the 4 centers. Consecutive patients were invited to participate along with randomly selected healthy individuals from the same catchment areas. In all, a total of 598 postinfarction patients and 653 controls were included in the present study.

Postinfarction patients were investigated 3 to 6 months after the acute event. Patients and control subjects were examined in parallel in the early morning after an overnight fast. The general characteristics of the population are described. This assay is based on affinity-purified sheep anti-TAFI IgG raised against TAFI purified from plasma. These antibodies do not recognize carboxypeptidase N and are able to recognize the proenzyme as well as the active form of TAFI. Results were expressed as percentage of pooled plasma from 30 healthy volunteers. Plasma was diluted 1:200. Each plasma sample was run in duplicate. Interassay variation coefficients of 2 controlled plasma samples were, respectively, 8% and 9% (n=28; 79.5±6.54% and 81.6±7.52%, respectively). Fibrinogen concentration was determined by the Clauss thrombin-clotting method. Plasminogen activator inhibitor (PAI)-1 Ag was assayed by a commercially available kit (Asserachrom PAI-1, Stago).

### Genotyping for Polymorphisms in the TAFI Gene

Genomic DNA was extracted from peripheral blood leukocytes by the salting-out method. Genotyping for TAFI polymorphisms was performed by using allele-specific polymerase chain reactions as described. Because the intronic sequence flanking the Ala147Thr polymorphism is unknown, genotyping of this polymorphism was performed by using only 1 allele-specific and 1 reverse primer: allele Ala-specific primer, GTTTCTGGAAGAAAACAG (annealing temperature 59°C); allele Thr-specific primer, GTTCTGGAAAA- CCAAC. The allele-specific primers were chosen in reverse sequence to obtain specific amplification: allele G-specific primer, AGTCAAGCTCGAAACT; allele C-specific primer, AGTCAAGCTCGAAAGT (with an annealing temperature of 55°C in each case).

### Statistical Analysis

Statistical analysis was conducted by using the statistical package Intercooled Stata, version 6.0. For the Hardy-Weinberg equilibrium and case-control frequency differences, genotype data for all recruited individuals were used, whereas for the analysis of the influence of genotype on TAFI, only individuals with complete environmental data were considered. As a result of the nonnormality of the distribution of TAFI Ag, analyses were performed on logarithmically transformed values. To present the results in more familiar form, the antilogarithm of the adjusted mean of logarithmically transformed values is reported, along with approximate standard deviations; in other instances, medians and interquartile ranges are stated. Differences in TAFI Ag, by center, were examined by ANOVA or by ANCOVA when adjustment was required. The response variable for these analyses was the logarithm of TAFI Ag.
levels. Differences in the frequency distribution of categorical variables by center were examined via the $\chi^2$ test or the Fisher exact test, as appropriate. The linkage disequilibrium between 2 genotypes was assessed by $3 \times 3$ tables, and its magnitude was estimated by $\delta$ values. Differences between cases and controls were analyzed by conditional logistic regression; hence, because of the matching of cases with controls (inasmuch as individuals were matched by center and by age), corresponding probability values are from likelihood ratio tests. The percentage of the variation in plasma TAFI Ag concentration explained by the 3 genotypes in each center was considered by the adjusted $R^2$ from ANOVA, with the use of sequential sums of squares.

Ethical Considerations
The present study was approved by the local ethics committees of the 4 centers, and all subjects gave informed consent to their participation.

Results
Plasma TAFI Ag Concentration and the Risk of MI
The frequency distribution of TAFI levels in cases and controls is presented in the Figure, panel A.

When the 4 centers were compared, values of TAFI Ag concentration were significantly higher in LDN than in the 3 other centers (Table 2) because of the use of Stabilyte instead of citrate as the anticoagulant. Thus, for the comparison of the TAFI Ag values between centers, LDN was excluded. As shown in Table 2, there were significant differences in TAFI concentration among controls from the 3 centers, with median TAFI Ag levels being higher in STK than in MRS or SGR (87.0% versus 72.0% and 77.1%, respectively; $P<0.002$).

When the 4 centers were considered separately, no significant differences in median levels of TAFI were observed between cases and controls (Table 2). However, after adjustment was made for differences between centers, levels were slightly lower in cases than in controls (74.5% versus 77.5%, respectively; $P=0.08$). Table 3 shows the assignment of A, Distribution of plasma TAFI Ag levels among controls and cases (excluding samples from LDN). B, Influence of the polymorphisms of the TAFI gene on plasma TAFI Ag levels (median, controls and cases combined). Values above the bar indicate the number of individuals carrying the genotype.

| TABLE 2. Plasma TAFI Antigen Concentration (%) by Center in Cases and in Controls |
|---------------------------------|---------------|---------------|-------|
| Centers                        | Controls      | Cases         | $P$   |
| Stockholm                      | 87.0 (66.5 to 106.2) | 81.9 (62.9 to 100.6) | 0.11  |
| n=159                          | n=159         |               |       |
| London*                        | 236.9 (191.9 to 343.3) | 245.9 (210.0 to 307.6) | 0.57  |
| n=73                           | n=54          |               |       |
| Marseille                      | 72.0 (58.7 to 92.9) | 73.0 (57.9 to 89.5) | 0.88  |
| n=123                          | n=86          |               |       |
| San Giovanni Rotondo           | 77.1 (62.0 to 96.8) | 74.7 (58.7 to 95.5) | 0.16  |
| n=198                          | n=199         |               |       |
| All†                           | 77.5 (29.4)   | 74.5 (28.3)   | 0.08  |
| n=480                          | n=444         |               |       |
| $P$‡                           | 0.002         | 0.04          |       |

Values represent median with interquartile range.
*Results obtained with Stabilyte.
†Means and standard deviation, excluding London and adjusted for differences between centers.
‡$P$ value from conditional logistic regression for difference in risk by log TAFI.
§$P$ value from analysis of variance for difference in log TAFI by center (excluding London).

| TABLE 3. Risk of Myocardial Infarction in Relation to Plasma TAFI Antigen Concentration |
|---------------------------------|---------------|---------------|-------|
| Centers                        | Controls n (%) | Cases (%)     | OR 95% CI |
| All†                           |                |               |       |
| $<$p90                         | 498 (90.0)     | 467 (93.8)    | 1*     |
| $\geq$p90                      | 55 (10)        | 31 (6.2)      | 0.55   | 0.34–0.91 |
| Stockholm                      |                |               |       |
| $<$p90                         | 143 (89.9)     | 151 (95.0)    | 1*     |
| $\geq$p90                      | 16 (10.1)      | 8 (5.0)       | 0.38   | 0.14–1.08 |
| London                         |                |               |       |
| $<$p90                         | 65 (89.0)      | 49 (90.7)     | 1*     |
| $\geq$p90                      | 8 (11.0)       | 5 (9.3)       | 0.73   | 0.21–2.51 |
| Marseille                      |                |               |       |
| $<$p90                         | 111 (90.2)     | 81 (94.2)     | 1*     |
| $\geq$p90                      | 12 (9.8)       | 5 (5.8)       | 0.56   | 0.20–1.62 |
| San Giovanni Rotondo           |                |               |       |
| $<$p90                         | 179 (90.4)     | 186 (93.5)    | 1*     |
| $\geq$p90                      | 19 (9.6)       | 13 (6.5)      | 0.63   | 0.28–1.38 |

*Reference category.
†As TAFI levels are different by center, p90 was calculated in each center separately and then combined.
patients and control subjects into 2 groups according to the 90th percentile of the plasma TAFI Ag concentration observed in control subjects. Crude odds ratios (ORs) were calculated for patients with TAFI concentrations above the 90th percentile, with the group below the 90th percentile used as the reference category. In the entire sample, higher TAFI concentrations were associated with a decreased risk of MI (OR 0.89, 95% CI 0.73 to 1.09). Logarithmically normalized TAFI was not correlated with conventional cardiovascular risk factors, such as age (r = -0.05, P = 0.26), total cholesterol (r = -0.05, P = 0.19), triglycerides (r = -0.1, P = 0.89), systolic blood pressure (r = -0.07, P = 0.11), diastolic blood pressure (r = -0.03, P = 0.41), body mass index (r = 0.05, P = 0.22), or fibrinogen (r = 0.03, P = 0.30). Significant correlation was found between TAFI and PAI-1 (r = 0.15, P = 0.008). The relationship between TAFI and myocardial infarction remained statistically significant after controlling for PAI-1 (OR 0.54, 95% CI 0.30 to 0.97). An additional increase in the cutoff point to the 95th percentile resulted in a further decrease of the OR (OR 0.41, 95% CI 0.17 to 0.97).

This difference was not statistically significant when each center was considered separately.

### Association Between TAFI Genotypes and Plasma TAFI Ag Concentration

In the control groups, the distribution of TAFI genotypes was as expected from Hardy-Weinberg predictions (all P > 0.1), except for 1542G in SGR (P = 0.04). This may reflect a chance effect, because of small sample size and multiple comparisons (4 centers and 2 genotypes). There was strong evidence of allelic association, with the Ala147 and 1542G alleles occurring together more often than would occur by chance alone (Ala147Thr and C + 1542G, δ value −0.34).

In the sample as a whole, the 2 polymorphisms were strongly associated with the plasma TAFI Ag concentration (P < 10^-4; Figure, panel B), with carriers of the Thr147 or 1542C alleles having higher mean levels of TAFI Ag. The effect of genotypes on TAFI concentration was similar in cases and controls and was taken separately in each center (data not shown). Alleles associated with higher values of TAFI Ag, Thr147/1542C, were more frequent in STK than in LDN, MRS, and SGR (P = 0.002 and P = 0.005 for each allele, respectively; Table 4). This difference in allele frequency explained some, but not all, of the higher TAFI levels observed in STK. The percentage of the variation in plasma TAFI Ag concentration explained by the 2 genotypes ranged from 45% for STK and 39% for LDN to 54% for MRS and 57% for SGR.

### TAFI Genotypes and the Risk of MI

When the entire sample was taken into consideration, the genotype distribution of the Ala147Thr polymorphism was different between cases and controls (P = 0.06, Table 5). This difference was observed in 2 centers, STK and SGR (P = 0.03), but not in the 2 others, LDN and MRS. Carriers of

### Table 4. Comparison of Rare Allele Frequencies (95% CI) of Each TAFI Polymorphism Between Centers in Controls

<table>
<thead>
<tr>
<th>Genotypes</th>
<th>Stockholm</th>
<th>London</th>
<th>Marseille</th>
<th>San Giovanni Rotondo</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ala147Thr</td>
<td>0.31</td>
<td>0.17</td>
<td>0.26</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>C + 1542G</td>
<td>0.23</td>
<td>0.27</td>
<td>0.29</td>
<td>0.37</td>
<td></td>
</tr>
</tbody>
</table>

*For difference between Stockholm and the 3 other centers.

### Table 5. Distribution of Ala147Thr Genotype in Cases and Controls

<table>
<thead>
<tr>
<th>Genotypes</th>
<th>Stockholm</th>
<th>London</th>
<th>Marseille</th>
<th>San Giovanni Rotondo</th>
<th>All Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
<td>Cases</td>
<td>Controls</td>
<td>Cases</td>
</tr>
<tr>
<td>Ala147Thr</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ala/Ala</td>
<td>103 (58)</td>
<td>80 (46)</td>
<td>50 (75)</td>
<td>52 (72)</td>
<td>60 (49)</td>
</tr>
<tr>
<td>Ala/Thr</td>
<td>59 (33)</td>
<td>82 (47)</td>
<td>16 (24)</td>
<td>16 (22)</td>
<td>59 (48)</td>
</tr>
<tr>
<td>Thr/Thr</td>
<td>15 (8)</td>
<td>13 (7)</td>
<td>1 (1)</td>
<td>4 (6)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>P*</td>
<td>0.03</td>
<td>0.54</td>
<td>0.75</td>
<td>0.03</td>
<td>0.06</td>
</tr>
<tr>
<td>OR†</td>
<td>0.60</td>
<td>1.07</td>
<td>1.15</td>
<td>0.68</td>
<td>0.78</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.39–0.92</td>
<td>0.51–2.26</td>
<td>0.71–1.86</td>
<td>0.44–1.05</td>
<td>0.62–0.99</td>
</tr>
<tr>
<td>P‡</td>
<td>0.02</td>
<td>0.85</td>
<td>0.57</td>
<td>0.08</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*Values are number of patients (%).

†P value for differences in genotype distribution, from Fisher’s exact test.

‡P value relating to differences in risk by lumped genotype, considering matching, from conditional logistic regression, by using likelihood ratio test.
Thr147 allele who have higher TAFI Ag concentration were more frequent in controls than in cases in the whole sample (OR 0.78, 95% CI 0.62 to 0.99; P < 0.05) and in STK (OR 0.60, 95% CI 0.39 to 0.92; P = 0.02). A slight nonsignificant effect of the Thr allele was also observed in SGR (OR 0.68, 95% CI 0.44 to 1.05; Table 5). The genotype distributions of the C+1542G polymorphism were similar in patients with MI and in controls (data not shown). Combined analysis of both polymorphisms did not significantly alter the risk information (data not shown).

Discussion

For many years, it has been believed that impaired fibrinolysis might be a risk factor for coronary artery disease. Indeed, several studies have underlined a relationship between high plasma levels of PAI-1 and the risk of MI. Plasma PAI-1 levels are primarily determined by metabolic factors belonging to the insulin resistance syndrome, with the contribution of the PAI-1 gene being modest. Recently, a new fibrinolytic inhibitor called TAFI, which functions in a different way from PAI-1, has been described. Although PAI-1 is a true inhibitor, interacting with the plasminogen activators, TAFI is a procarboxypeptidase that after activation decreases plasmin generation by removing carboxy-terminal lysine residues from partially degraded fibrin. Moreover, in contrast to PAI-1, the plasma concentration of TAFI is highly genetically determined, with a very low contribution from measured environmental factors. Several sets of data, obtained in different animal models, support a physiological role of TAFI in the regulation of fibrinolysis, but little is currently known about its role in humans. Two studies were recently conducted in individuals with vascular disease. The first was in patients who had suffered a deep venous thrombosis, and the second was in individuals with stable angina pectoris. Although different TAFI assays were used, both studies showed that plasma concentrations of TAFI were higher in patients than in age-matched controls. Given the putative physiological effect of TAFI and results from these 2 previous studies, our hypothesis was that individuals with MI would have plasma TAFI Ag levels higher than those in age-and sex-matched controls. Similarly, we expected there to be a higher frequency of alleles associated with higher TAFI levels in MI subjects compared with controls. In contrast to these expectations, the mean plasma TAFI Ag concentration was slightly lower in cases than in controls, with a significantly lower risk of MI in individuals with higher TAFI levels; TAFI Ag above the 90th percentile led to an OR of 0.55 (95% CI 0.34 to 0.91). When the hypothesis that low plasma TAFI levels are associated with a higher risk of MI was tested by comparing the (center-specific) proportion of cases below and above the 10th percentile of the TAFI distribution in the controls from each center, no significant association with risk was observed (OR 0.82, 95% CI 0.55 to 1.24). This suggests that high TAFI levels are protective of MI, whereas low values do not increase the risk.

This unexpected finding could have several different explanations. First, the 2 previous clinical studies used methods different from ours for TAFI determination, and the studies also differed with respect to the types of subjects studied. In particular, the immunological assays used previously and those used in the present study (electroimmunoassay and ELISA, respectively) are based on different polyclonal antibodies directed against TAFI. It is possible that these antibodies recognize different molecular forms of TAFI circulating in plasma, including complexes of TAFI with other proteins, such as plasminogen or fibrinogen. Silveira et al used a different method based on quantitative activation of the zymogen by the thrombin-thrombomodulin complex, followed by determination of the total activity of TAFI. The subjects studied were also different; van Tilburg et al studied individuals with venous thrombosis, and it is well known that there are many differences between arterial and venous thrombosis. Silveira et al studied a group of individuals with stable angina pectoris, and 1 of the exclusion criteria was the evidence of a recent MI (< 3 months). In the present study, although all the cases were investigated 3 to 6 months after the acute event, it could be that the lower levels of TAFI result from greater local consumption. Whether or not the lower TAFI Ag was the cause or the consequence of the MI requires investigation in a prospective study. It is also relevant to note that measurement of TAFI Ag levels does not measure the enzymatic activity essential for the biological function of TAFI, because TAFI needs to be activated by the thrombin-thrombomodulin complex to exert its antifibrinolytic effect. Also, it does not provide any information about the stability of activated TAFI in patients. This may be critical, because Brouwers et al recently described a Thr325Ile polymorphism of the TAFI gene that affects the stability of activated TAFI. This polymorphism seems particularly of interest, inasmuch as the Thr325 allele could have opposite effects by increasing TAFI Ag levels and decreasing TAFI stability at the same time, exerting a complex effect. In addition to its antifibrinolytic potential, TAFI may have additional important roles. For example, TAFI has been proposed to be a substrate for factor XIIIa, and recently, antithrombin has been shown to be cleaved by carboxypeptidase B. In addition, by cleaving bradykinin, TAFI could inhibit inflammation and modify vascular tone.

In the present study, we confirmed our previous results by showing a strong and highly significant association between each TAFI polymorphism and the plasma TAFI concentration, with carriers of the Thr147 or 1542C alleles having higher levels. These effects were similar in controls and cases and in each center. Recently, we have performed a quantitative trait loci segregation linkage analysis emphasizing that neither of the genotyped variants is functional by itself, suggesting that they are in linkage disequilibrium with another yet-unknown polymorphism that is yet to be discovered.

When genotype distributions are compared between cases and controls, significant differences were observed only for the Ala147Thr polymorphism. Carriers of the Thr147 allele were more frequent among controls than cases in the entire population, leading to an OR of 0.78 (95% CI 0.68 to 0.99). This was observed in 2 centers (STK and SGR) but not in the other 2 centers (MRS and LDN). It is of relevance to note that...
the power to detect differences in genotype distribution in the 2 last centers was lower because of smaller numbers. This genotype result is in line with that of TAFI levels, inasmuch as Thr147 carriers have higher levels of TAFI Ag. These results indicate that the differences observed in TAFI Ag levels between cases and controls could be of genetic origin. TAFI Ag levels were higher in STK than in MRS or SGR. Interestingly, alleles associated with higher values of TAFI Ag (Thr147/H11032) were more frequent in STK than in the 3 other centers, with no difference between the other 3. This explained some, but not all, of the higher mean plasma TAFI concentrations observed in STK.

In conclusion, patients with a recent MI presented lower values of TAFI Ag and higher frequencies of the “TAFI-decreasing” alleles. These findings need to be confirmed in a separate population and preferably in a prospective study. A geographical difference was shown, with subjects in STK having higher levels of TAFI Ag and a higher frequency of the “TAFI-raising” alleles. These differences do not contribute to explaining the North-South gradient in MI risk in Europe.

Appendix: HIFMECH Investigators

In STK, the investigators were A. Hamsten (coordinator), S. Boquist, C.G. Ericsson, P. Lundman, A. Samnegard, A. Silveira, and P. Tornvall.

In LDN, the investigators were J. Yudkin, V. Mohamed-Ali, and A. Holmes.

In MRS, the investigators were J. Yudkin, M.F. Aillaud, P.E. Montague, Y. Sibille, and J. Bouchard.

In SGR, the investigators were G. Di Minno, M. Margaglione, D. Ciminio, N. Dello Iacono, A. Cimino, G. Gaeta, C. Blasich, and G. Pucciarelli.

In LDN, the investigators were S.E. Humphries, E. Hawe, and A. Ahn Luong.

In Leiden, the Netherlands, the investigators were V. van Hinsbergh and T. Kooistra.

In Milan, Italy, the investigators were E. Tremoli, C. Banfi, and L. Mussoni.

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References


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