To the editor:

Association between the methylenetetrahydrofolate reductase 677C>T polymorphism and the risk of secondary lymphoproliferative disease in patients with a first idiopathic thrombosis

A series of recent studies have pointed out the association between the known functional polymorphisms of a main folate-metabolizing enzyme, methylenetetrahydrofolate reductase (MTHFR), and the risk of malignant lymphoma in Japanese adults[1] or the risk of acute lymphoblastic leukemia in British adults[2] and in childhood,[3] suggesting that folate metabolism plays an important role in their genesis. But these studies are case-control ones performed in patients recently diagnosed with these lymphoproliferative diseases, and we have, to date, no available data on the evolution of homogeneous cohorts of patients who were initially tested for *MTHFR* polymorphisms for nonmalignancy related reasons.

Our group has focused on the links between the metabolism of folates and the risk for venous thromboembolism. All patients investigated for idiopathic thromboembolism in our outpatient department of hematology were therefore tested, beside the classical hemostasis-related biological risk factors, for the MTHFR 677C>T polymorphism since it has been described. We finally found that low levels of red blood cell methylfolate are strongly associated with the risk of venous thromboembolism, particularly in subjects who do not carry the mutated TT genotype.[4]

We report here data concerning 852 consecutive adults aged between 55 and 76 years old and diagnosed between September 1995 and September 2000. All these patients and their general practitioners were thereafter questioned, between September and December 2001, for the subsequent occurrence of any malignant lymphoproliferative disease: the answer was based on the nature of known antecedents and on the results of a recent (less than one month prior) clinical exam, blood cell count, and serum immunofixation electrophoresis, with secondary specific investigations in case of any abnormalities. Forty-two cases were finally recorded: 29 chronic lymphocytic leukemias, 10 non-Hodgkin lymphomas, 1 Hodgkin disease, and 2 multiple myelomas. The median values [lower-upper quartiles] (range) of lengths of follow-up, given in months, were respectively 39 [23-52] (12-76) in patients negative for secondary lymphoproliferative diseases and 42 [27-55] (14-76) in positive patients ($P = .79$).

The frequencies of the 3 *MTHFR* genotypes are given in Table 1. The distribution of the various genotypes is apparently different in groups of patients with or without the subsequent development of any chronic lymphoproliferative disease, with a relative excess in the homozygous mutated genotype among asymptomatic patients (presence versus absence of the *MTHFR* 677T homozygous genotype: $P = .02$ using the Fisher exact test). Using logistic regression, the wild-type genotype being taken as a reference, the calculated odds ratio for developing a chronic lymphoproliferative disease is 0.91 (95% confidence interval: 0.48-1.76, $P = .79$) in the case of an heterozygous genotype, but, in the case of a 677T homozygous genotype, is 0.26 (0.077-0.88, $P = .031$).

Table 1. Number of *MTHFR* 677 genotypes in patients aged 55-76 years, initially investigated for idiopathic thromboembolism

	CC (wild type)	CT	TT
Group A	342	289	179
Group B	22	17	3
All patients	364	306	182

Group A data concerns the 810 patients who did not develop any chronic lymphoproliferative disease within 1-6 years after genotyping. Group B data concerns the 42 patients who subsequently developed any chronic lymphoproliferative disease.

Thus in a large group of patients with a minimum age of 55 years and investigated for idiopathic thomboembolic disease, the *MTHFR* 677T homozygous genotype seems to protect against the subsequent development, within 1-6 years after testing, of a chronic lymphoproliferative disease. No mutated gene-dose effect could be observed in this study, a fact concordant with what has been suggested by Matsuo et al for lymphomas.[1] Patients with idiopathic venous thromboembolism are at increased risk for malignant diseases, with odds ratios for a new cancer diagnosis within 6-12 months after the episode in the range of 4- to 7-fold increased risk[5]: this is a sensitizing factor that probably concurred with the positive result of this study. As DNA analysis had been performed after its extraction from blood before any evidence of circulating abnormal leukocytes, the *MTHFR* genotypes that we obtained are likely to be constitutional ones and are probably not modified by any loss of heterozygosity in circulating abnormal lymphoid cells. But only a minority of the patients developed a lymphoproliferative disease, and quite limited differences in the distribution of their *MTHFR* genotypes would have nullified the statistical conclusion of our study: a confirmation in larger series of thrombotic patients with secondary lymphoid neoplasia is required.

The *MTHFR* 677T homozygous genotype leads to reduced MTHFR activity and results in the upstream accumulation of 5,10-methylene tetrahydrofolate, which accelerates the methylation of uridylate to thymidylate and, in turn, reduces the chance for the misincorporation of uracil into DNA, a cause of genetic instability due to double-strand breaks during uracil excision repair by uracil DNA glycosylase. If this interpretation is correct, in patients with idiopathic venous thromboembolism not carrying the *MTHFR* 677T homozygous genotype, increasing 5,10-methylene tetrahydrofolate levels by folic acid supplementation, which may protect from recurrence,[4] may also reduce the risk for chronic lymphoproliferative diseases: these speculations warrant further investigations.

Jean-Christophe Gris, Eric Mercier, Isabelle Quéré, and Michel Dauzat

Correspondence: Jean-Christophe Gris, Laboratoires d'Hématologie, CHU de Nîmes et UFR des sciences pharmaceutiques et biologiques, Montpellier, EA 2992, Nîmes, France

References

1. Matsuo K, Suzuki N, Hamajima M, et al. Association between polymorphisms of folate- and methionine-metabolizing enzymes and susceptibility to malignant lymphoma. Blood. 2001;97:3205-3209.
2. Skibola CF, Smith MT, Kane E, et al. Polymorphisms in the methylenetetrahydrofolate reductase gene are associated with susceptibility to acute leukaemia in adults. Proc Natl Acad Sci U S A. 1999;96:12810-12815.
3. Wiemels JL, Smith RN, Taylor M, Eden OB, Alexander FE, Greaves MF. Methylenetetrahydrofolate reductase (MTHFR) polymorphisms and risk of molecular defined subtypes of childhood acute leukemia. Proc Natl Acad Sci U S A. 2001;98:4004-4009.
4. Quéré I, Perneger TV, Zittoun J, et al. Red blood cell methylfolate and plasma homocysteine as risk factors for venous thromboembolism. Lancet. 2002;359:747-752.
5. Rickles FR, Levine MN. Epidemiology of thrombosis in cancer. Acta Haematol. 2001;106:6-12.