To the Editor:

in grey collies1 adopting this point of view was necessary to explain hematopoiesis can emerge.” This is precisely the point of view that has provided detailed predictions (so) a truly quantitative description of each other,” and that “the challenge to modelers would seem to be viewed as a whole, as a web of coupled feedback loops that interact with pointing this out clearly and explicitly.

We agree with Prof Morley that the hematopoietic “system should be viewed as a whole, as a web of coupled feedback loops that interact with each other,” and that “the challenge to modelers would seem to be to provide detailed predictions (so) a truly quantitative description of hematopoiesis can emerge.” This is precisely the point of view that has emerged from our own research. Indeed, in our recent study of cycling in grey collies1 adopting this point of view was necessary to explain (from a modeling perspective) the data that we presented.

No Association Between Factor V Leiden and C282Y Mutation in the Hereditary Hemochromatosis Gene

To the Editor:

In a preliminary paper in Blood, Xie et al1 have reported on a surprising observation that documented a highly significant association between the heterozygous states for the factor 5 Leiden and the HFE C282Y mutations in a population referred for a molecular study of hyper coagulability.1 In this population composed of 87 patients, the carrier frequency for the HFE C282Y mutation was 18.7%, compared with 6% in their normal population. The C282Y mutation is the most common mutation in the hereditary hemochromatosis gene (HH). Hemochromatosis is an autosomal-recessive iron-metabolism disorder with a high prevalence, 2 to 5 of 1,000, in the white population. The gene responsible for the disease was cloned 2 years ago and designated HFE.2 A very prevalent mutation, cys 282 Tyr, was detected in 80% to 90% of patients and a second mutation resulting in a change from histidine to aspartic acid was found also in 5% of patients suffering from hemochromatosis.3,4 The preliminary work of Xie et al was based on the fact that thromboembolism events are caused by a combination of genetic and environmental factors; therefore, they suggested that the C282Y mutation in the HFE gene could be a genetic cofactor in addition to the factor 5 Leiden mutation (R506Q). As we have had the opportunity of confirming or infirming these data from our population under study, we report on our results determined from a large cohort of 481 patients, all diagnosed for venous thrombosis and all positive for the factor 5 Leiden mutation. This population issued from the western part of Brittany (France) is characterized by an 8% allele frequency for the C282Y mutation, which constitutes one of the highest frequencies recorded in European populations. Thus, we are in charge of a large cohort of more than 500 hemochromatosis patients.5

In this population of 481 factor 5–positive patients, we found 82 patients heterozygous for the C282Y mutation and 2 who were homozygous. This corresponds to a carrier frequency of 17% and to an allelic frequency of 8.89% among this group of individuals, whereas the allelic frequency was 8% in our control population from the same ethnic origin; these frequencies between patients and controls are not statistically significant.

Our observations based on a large cohort of factor 5–positive patients with venous thrombosis did not enable us to confirm an association between the heterozygous state for the factor 5 Leiden and the C282Y mutation. Consequently, the hypothesis of an influence of HFE C282Y mutation on the risk of venous thrombotic event does not seem to be relevant.

REFERENCES


Nuclear Localization of the Fanconi Anemia Protein FANCC Is Required for Functional Activity

To the Editor:

Fanconi anemia (FA) is an autosomal recessive disease characterized by bone marrow failure and cancer susceptibility. At least eight complementation groups for FA have been identified, and the genes corresponding to groups A, C, and G have been cloned. An understanding of the biochemical function of the FANCA, FANCC, and FANCG proteins would yield considerable insight to the cellular function of the FA pathway. Unfortunately, the three cloned FA proteins have no recognizable structural or functional motifs, and studies regarding their interaction and cellular localization in most cases have been conflicting. First, some studies show that the FANCA and FANCC protein bind in a functional complex,1,2 while other studies fail to detect the complex.3 Second, some studies show that the FANCC protein is localized to the cytoplasm and nucleus,1,4 while other studies show that FANCC is primarily cytoplasmic.5

To resolve this controversy, Hoatlin et al6 have used confocal microscopy to determine that FANCC is localized to both cytoplasmic and nuclear compartments. We have new evidence that strongly supports this model of Hoatlin et al. We analyzed the subcellular localization of FANCC polypeptide in retrovirally infected HeLa cells by immunofluorescence microscopy (Fig 1). The wild-type FANCC protein was detected in both nucleus and cytoplasm in varying ratios (Fig 1B), confirming the results of Hoatlin et al.6 In most cells, the protein was predominantly localized to the nucleus. In a small percentage of cells, a strong cytoplasmic localization of FANCC was also detected. An examination of the cell morphology and DAPI staining showed that these cells expressing cytoplasmic FANCC were

Fig 1. Cellular localization of the wild-type FANCC protein and the L554P mutant. (A) The HeLa cell line expresses low levels of endogenous FANCC protein that is undetectable by anti-FANCC immunofluorescence. HeLa cells were infected with retroviral supernatants, pMMP-FANCC (B) or pMMP-FANCC-L554P (C). Pools of infected cells were stained with anti FANCC and the DNA-specific dye, DAPI (4',6-diamidino-2-phenylindole) (bottom images) and analyzed by immunofluorescence, as previously described.4

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