The Prothrombin Gene 3’-Untranslated Region Mutation Is Frequently Associated With Factor V Leiden in Thrombophilic Patients and Shows Ethnic-Specific Variation in Allele Frequency

To the Editor:

As data accumulate on the recently identified genetic variant in the 3’-untranslated region of the prothrombin (factor II) gene (G20210A), it is apparent that this modification confers a moderate risk for venous thrombosis. Data from several abstracts presented at the 1997 ISTH meeting in Florence, Italy and a recent manuscript from Dr Rosendaal and coworkers, which revealed an association of this genetic variant with an increased risk of myocardial infarction in young women, suggest that an ethnic-specific variability in the frequency of the prothrombin gene mutation exists in healthy controls from European populations, analogous to that reported for factor V Leiden. The ethnic distribution frequency of the G20210A mutation in Americans has not yet been reported. In addition, as pointed out in a recent letter to BLOOD summarizing results from a moderate size study of French families, an increased cosegregation frequency of heterozygosity for the prothrombin gene mutation and carriership for factor V Leiden in families with hereditary thrombophilia has not unequivocally been shown. In contrast to data obtained from the Dutch population, the French study showed that the prothrombin gene A20210 allele is not frequently found in their thrombophilic families carrying the Leiden allele of the factor V gene. In fact, none of the probands or family members had the prothrombin gene mutation. Therefore, the hypothesis that cosegregation of the prothrombin gene mutation and heterozygosity for activated protein C resistance results in increased expressivity of hypercoagulability and thrombophilia within these families remains unproved.

We investigated the frequency of the prothrombin gene mutation in consecutive thrombosis patients at Emory Hospital (Atlanta, GA). Seventy-two out of 477 thrombosis patients were found to be heterozygous for factor V Leiden (15.1%) and 4 were homozygous (0.8%). Genomic DNA samples were available for 48 of these 76 thrombosis patients that were either heterozygous or homozygous for factor V Leiden. The factor II gene mutation was identified in 5 of these 48 patients (10.4%). Out of 278 apparently healthy subjects, we identified the prothrombin gene variant in 7 (2.5%). These data are comparable to that found in the Dutch population (2.3% in a population-based case/control study and 1% in healthy controls). Although not representing a family study, our data does suggest that the coexistence of these two prothrombotic genetic variants may increase the clinical expressivity of thrombophilia and thus provides further validation of the “double hit” theory as a mechanism of thrombophilia in the younger patient.

Interestingly, as reported for the factor V Leiden mutation, the frequency of the G20210A mutation was very rare in African Americans. In fact, none of the 52 healthy African Americans in our study carried the prothrombin mutation and none of the 5 thrombosis patients who were double heterozygotes for the factor II and V variants were of African ancestry.

We conclude that in our population, the G20210A prothrombin allele is frequently associated with activated protein C resistance and most likely confers an increased thrombosis risk for these individuals. In addition, a better understanding of the apparent ethnic-specific variability of the factor II gene mutation should help to provide better diagnostic algorithms that optimize cost-effective laboratory evaluation of the thrombophilic patient.

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REFERENCES

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