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Letter to Editor

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The c.1787G>T and c.1787G>A Mutations are not Found in the Prothrombin Gene in a Spanish Population

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Although more than 60% of the variability in the risk of venous thrombosis is attributed to the genes [1], only about 5% of this genetic component has been explained [2]. That is why there is an increasing interest in finding new genetic variants and new pathophysiologic explanations for this common disease.

It is known that mutations in the prothrombin gene are a risk factor for thrombosis. For example, heterozygous carriers of the F2G20210A mutation have 30% higher plasma prothrombin levels than normal and an increased risk of venous thrombosis [3].

Miyawaky et al. have identified recently a new prothrombin gene mutation c.1787G>T in a Japanese family with hereditary thrombophilia [4]. This mutation is located in the last exon of the prothrombin gene resulting in Arg596Leu replacement. Djordjevic et al. [5] also have described another mutation at the same prothrombin gene position (c. 1787G>A prothrombin Belgrade) that results in aminoacid change (Arg596Gln). The mutant prothrombins were shown to have reduced activity in clotting assays and the produced thrombin was markedly resistant to inhibition by antithrombin.

In one hand, their procoagulant activity is somewhat impaired. It can be explained because the mutation at residue Arg596 affects the sodium-binding region of thrombin and, accordingly, decreases its affinity for fibrinogen. Sodium free thrombin also participates on the physiological activation of protein C conferring anticoagulant properties. In addition there is a slower conversion of the mutant prothrombin to thrombin evidenced in clotting assays.

In the other hand, these mutations influence the thrombin-antithrombin complex formation. They express antithrombin resistance conferring a major susceptibility to thrombosis [4,5].

We performed an analysis in order to determine the presence of these mutations in a case control study of consecutive adult Caucasian Spanish patients with venous thromboembolism (VTE) objectively diagnosed. All patients were included when they had been referred to our hospital from November 1997 to April 2002. This case-control study has been described previously in detail [6]. The patients were included consecutively if they had a first thrombotic event when younger than 70 years of age. Patients with malignancies or with history of liver failure or nephrotic syndrome were excluded.

Of 250 patients with VTE (113 males and 137 females, mean age 47y, range 33-61y), deep vein thrombosis was found in 155 cases (60%), pulmonary embolism in 73 (29.2%), upper arm thrombosis in 17 (6.8%) and intracranial vein thrombosis in 5 (2%). Ninety seven patients (38.8%) had family history of thrombosis and existed approximately the same ratio of spontaneous (119, 48%) than secondary (131, 52%) causes of venous embolism.

A control group of 250 unrelated sex and age-matched persons was analyzed (109 males and 141 females, mean age 49 y, range 34-64 y). The controls were inhabitants of the same geographic area as the experimental group.

In a previous manuscript published6, we founded that individuals who were non-O had a higher risk of thrombosis (OR:2.6) and higher FVIII levels (over 232%) indicating that FVIII is an independent risk factor of thrombosis. We also have screened the factor V Leiden and the 20210A prothrombin mutations [7]. We detected a higher prevalence of the prothrombin gene 20210A variant among patients.

We analyzed the prothrombin Yukuhashi (c.1787G>T) and the prothrombin Belgrade (c.1787G>A) in prothrombin gen by polymerase chain reaction with restriction fragment length polymorphism (PCR-RFLP) method. A 467bp fragment of exon 14 of prothrombin gene was amplified using the following primers: forward F214-A-5'-AGGGCCTGGTGAACACATCTTC-3' and reverse F214-B-5'- CCAGGTGGTGGATTCTTAAGTCTTC-3' with minor modifications. PCR products were digested using the Msp I restriction enzyme (NEBiolabs, Berverly, MA). Normal (280 and 187pb) and mutated (467pb) alleles were distinguished by the size off the restriction fragments, using electrophoresis with QIAXCEL® system (Qiagen ®). To avoid false negatives, the pattern was confirmed by direct sequencing. The c.1787 mutations were not detected in 250 DVT patients neither 250 healthy controls of our case control study.

The absence of these mutations in our sample leads us to conclude that they must be very uncommon in our country and probably negligible as risk factors of thrombosis at the population level. A similar result has been obtained in studies developed in Japanese, Serbian and Italian populations [4,5,8].

Conflict of Interest

The authors declare that they have no conflict of interest.

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