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References


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Prevalence of FVR506Q and Prothrombin 20210A Mutations in the Navarrese Population

Dear Sir,

A point mutation in the procoagulant protein factor V (FVR506Q or factor V Leiden), associated with the phenotype of resistance to activated protein C, is the common inherited risk factor for venous thrombosis (VT) as described (1). More recently, a sequence variation in the 3’-untranslated region of the prothrombin gene (nt20210A) has been described and its presence also associated with an increased risk for VT (2). We have studied the prevalence of both genetic variants in Navarra, a region in Northern Spain where the majority of people share a Basque genetic background which differs from the rest of the Spanish and other nearby populations. Genomic DNA from 304 healthy Navarrese subjects (collected at the Blood Bank of Navarra, Pamplona) was extracted from the individual blood leukocytes by the phenol/chloroform procedure to be subsequently analyzed by PCR. The amplified product spanning the G to A substitution at FV nucleotide position 1691 was cleaved with the restriction enzyme Mnl I to detect the FVR506Q mutation. The normal sequence generates products of 163, 67 and 37 bp whilst the mutant sequence, where there is loss of an Mnl I site, generates products of 200 and 67 bp (3). The amplified region comprising the 20210 G → A mutation in the prothrombin gene was cleaved with the restriction enzyme Hind III, which produces a 345 bp band for the wildtype or a 322 bp band for the mutation (2).

Only two out of 304 Navarrese subjects carried the FVR506Q mutation, both of them in the heterozygous form, which gives a prevalence of 0.66% with a corresponding allele frequency of 0.33% (95% CI: 0.04-1.18%). These results, which are somewhat different from those reported for the majority of European populations, whose prevalences range between 1 and 15% (1, 4), are in agreement with previously released data by Rees (5) in a limited sample of Spanish Basques (0 carriers out of 28 probands) and by Lucotte and Mercier (6) in a more comprehensive study performed with 198 French Basques, only two of whom were shown to carry the mutation. As Basques seem to be the only present-day representatives of a people which was present in much of Western Europe before Neolithic times, but is nowadays confined to the Western Pyrenees (Aquitaine in France, Navarra and Euzkadi in Spain), the lower factor V Leiden frequency observed in this population when compared with other Europeans strongly supports the hypothesis proposed by Rees which claims that this mutation originated

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in the European founding population and was subsequently propagated in Western Europe by the Neolithic farmers migrating from the Middle East (5).

We found the prevalence of the 20210 G→A mutation in the prothrombin gene in Navarra to be higher than that observed for the factor V Leiden. Thirteen out of 304 healthy subjects were shown to carry this genetic variant, all of them in the heterozygous form, which gives a prevalence of 4.2% with an allele frequency of 2.14% (95% CI: 1.14-3.63%). Although much fewer reports on the world distribution of this mutation are currently available when compared with published data for factor V Leiden, we are presenting the highest prevalence described so far in a healthy population, provided that prevalences range between 0 and 3.2% in studies performed with European and Brazilian populations (2, 7–13). The unquestionable presence of the 20210 G→A variant in the prothrombin gene within the Basque population, taken together with its relative frequency (2% prevalence) among Brazilians of African descent (8) would support the hypothesis proposed by Arruda et al. about a more uniform world distribution of nt20210A when compared with the FVR506Q mutation, which is not restricted to Caucasian populations, implying that the prothrombin variant would have originated historically before factor V Leiden (8). Finally, the ancient origin of nt20210A would also support a positive selection pressure of a slightly hypercoagulable state in humans.

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Prevalence of FXIII V34L in Populations with Different Cardiovascular Risk

Dear Sir,

Activated factor XIII (FXIIIa) catalyses the formation of ß-(γ-glutamyl) lysine bonds between fibrin molecules thereby stabilising fibrin clots making them more resistant to fibrinolysis (1). Recent studies in Caucasian subjects have demonstrated that a common G→T point mutation in exon 2 of the FXIII A-subunit gene, that results in the substitution of an amino acid (V34L) three amino acids from the thrombin activation site, is protective against myocardial infarction (MI) (2). The frequency of this allele is around 25% in Caucasian populations (2–4) although no data is available for other ethnic groups. We therefore determined FXIII V34L genotype in three populations with markedly different cardiovascular risk. In both Pima and Asian Indian populations there is a high incidence of type II diabetes (5, 6) a factor known to associate with a high risk of MI in Caucasians. In Asian Indians the incidence of MI is correspondingly high (7) however despite the prevalence of diabetes in Pima Indians coronary heart disease is unusual (5), suggesting vascular disease is not an inevitable consequence of diabetes, and genetic and environmental factors must cause the differences in disease prevalences.

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