Genetic risk factors for thrombosis in a Basque population and their possible contribution to the analysis of a complex disease such as thrombophilia

We analyzed factor V Leiden (FVL), methylenetetrahydrofolate reductase (MTHFR) C677T and prothrombin (PT) 20210G/A mutations in a large sample of autochthonous Basques. Although the difference between the Basque and Spanish populations was statistically significant only for FVL (p=0.0057), it tends to be lower also for the PT20210G/A mutation. There is, however, no difference in the incidence of cardiovascular disease between these two populations. In conclusion, the Basque population may be a useful tool for searching for new genetic risk factors for cardiovascular disease.

Cardiovascular disease is a general term defining not only ischemic heart disease and stroke, but also venous thrombosis.[1] In this complex disease multiple genes with varying effects are involved. Among them, the factor V Leiden (FVL) and the PTG20210A mutations predispose individuals to a substantial increase risk of venous[2] and arterial[3] thrombosis. In addition, the C677T in the MTHFR gene has a direct effect on the level of homocysteine, which in turn is a well-established cause of vascular disease.[4]

As genes that predispose people to common diseases are more readily identified in isolated rather than diverse continental populations,[5] we compared the allelic frequencies of these three mutations, genotyped as previously described,[4,6] between 283 unrelated individuals from the Basque country in the north of Spain (all with at least four generations of family names of Basque origin) and 204 unrelated Spanish blood donors. Only 9 out of 283 Basques were heterozygous for the PT20210A mutation, which corresponds to a prevalence of 3.2% (95% CI: 0.46-5.59). We did not find FVL mutation carriers in this sample. The prevalence of the C677T mutation was 50.6% (95% CI: 44.2-57.0) heterozygotes and 14.9% (95% CI: 10.3-19.4) homozygotes. The allelic frequencies of the PT20210A and the C677T mutations were both in Hardy-Weinberg equilibrium.

We calculated that the prevalence of FVL in the Basque sample presents a difference of 2.9% (95% CI: 0.6-5.3) with our Spanish population, corresponding to a p=0.0057. For the PT20210A the difference was 3.3% (95% CI: -0.06-7.3), and although this was not statistically significant it was lower. The difference for the C677T was clearly not significant (Table 1).

Data on the frequency of these mutations in a well-documented Basque sample may help to explain the origin of the Basque population. The age of the C677T mutation in the MTHFR gene is unknown, but it must be very old since it is distributed widely among different ethnic groups.[7] However, it has been postulated that the FVL mutation originated in the European founding population 21,000 to 34,000 year ago and was subsequently propagated in Western Europe by Neolithic farmers migrating from the Middle East.[8] The Basques were isolated at the time of the Last Glacial Maximum (18,000 B.C.) according to archaeological and linguistic data. The absence of FVL in the Basque population supports the hypothesis that this mutation is younger than previously reported.[8] Furthermore, the presence of the PT20210A mutation in this isolated population strongly supports the hypothesis that this mutation originated before the FVL, that is, before the isolation of the Basques from other populations.

To add new insights into thrombotic disease several genetically-isolated populations have been analyzed for the presence or absence of thrombotic genetic risk factors. The FVL and PT20210A mutations are absent in the Inuit (Greenland population) and Pyma Indians.[9,10] As might be expected, these two populations have a low incidence of cardiovascular disease.[9,10]

Table 1. Comparison of the different prevalences (%) of the analyzed mutations between Spanish and Basque populations by a Fisher's exact test and Chi-squared test.

	Prevalence in controls (%)		
Mutation	*Spanish*	*Basque*	*p value*
FVL	2.9 (6/204)	0.0 (0/283)	*p*=0.0057
PT20210A	6.5 (13/201)	3.2 (9/283)	N.S.
C667T heterozygous	47.2 (97/204)	50.7 (119/235)	N.S.
T677T Homozygous	17.5 (36/204)	14.9 (35/235)	N.S.

N.S.: not significant.

It is clear that the most prevalent genetic risk factors for thrombosis are also absent (FVL) or have a lower prevalence (PT20210A) in the Basque population than in the rest of Spain (Table 1). These results might have clinical relevance not only for the absence of an important genetic risk factor such as FVL, but also because there is no synergistic effect of FVL with other genetic and environmental risk factors[2] as a result of the absence of this mutation. However, in an epidemiological study on the incidence of cardiovascular disease in the Spanish population, which included Basque autochthonous subjects, no significant differences were reported in the incidence of thrombosis compared with incidences in other European populations.[11] Since thrombosis is a complex disease caused by multiple genes interacting with each other and with the environment, and based on ours results we might expect that unknown genetic risk factors in the Basque population could account for the incidence of thrombosis being the same as that in European populations. It follows that studies of the Basque population might detect new genetic thrombosis-susceptibility risk factors.

In conclusion, given the many difficulties that can hamper genetic dissection of complex traits such as thrombosis, it is advantageous to restrict the patient population to a specific ethnic group,[5] such as the Basques. This approach has been successfully applied to other isolated populations for a variety of complex diseases.[5]

José Manuel Soria,* Montserrat Baiget,° Luis Castaño,# Maria Isabel Tejada,@ Guimar Perez-Nanclares,@ Jordi Fontcuberta*

*Hemostasis and Thrombosis Unit. Department of Hematology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; °Genetic Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; #Endocrinology and Diabetes Research Group, Hospital de Cruces. Barakaldo, Spain; @Genetic Unit, Hospital de Basurto, Bilbao, Spain

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Correspondence: José Manuel Soria Fernández, Ph.D., Unitat d´Hemostasi i Trombosi. Departament d´Hematologia, Hospital

de la Santa Creu i Sant Pau. C/ Sant Antoni Mª i Claret, 167, 08025 Barcelona, Spain. Phone: international +34.9.32919193. Fax: international +34.9.32919192. E-mail: jsoria@hsp.santpau.es

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