HETEROGENEOUS ETHNIC DISTRIBUTION OF THE FACTOR V LEIDEN MUTATION

Rendrik F. Franco1, Jacques Elion2, Sidney E.B. Santos3, Amélia G. Araújo1, Marli H. Tavella1 and Marco A. Zago1

ABSTRACT

Inherited resistance to activated protein C caused by the factor V Leiden (FVL) mutation is the most common genetic cause of venous thrombosis yet described, being found in 20-60% of patients with venous thrombophilia. A relationship between the FVL mutation and an increased predisposition to arterial thrombosis in young women was recently reported. We assessed the prevalence of the FVL mutation in 440 individuals (880 chromosomes) belonging to four different ethnic groups: Caucasians, African Blacks, Asians and Amerindians. PCR amplification followed by Mnl I digestion was employed to define the genotype. The FVL mutation was found in a heterozygous state in four out of 152 Whites (2.6%), one out of 151 Amerindians (0.6%), and was absent among 97 African Blacks and 40 Asians. Our results confirm that FVL has a heterogeneous distribution in different human populations, a fact that may contribute to geographic and ethnic differences in the prevalence of thrombotic diseases. In addition, these data may be helpful in decisions regarding the usefulness of screening for the FVL mutation in subjects at risk for thrombosis.

INTRODUCTION

Venous thromboembolism is an important clinical condition currently understood as a multifactorial disease in which circumstantial acquired risk factors acting on genetically predisposed individuals lead to thrombosis (Seligsohn and Zivelin, 1997). The most important recognized genetic cause of venous thrombophilia is inherited resistance to activated protein C (APC) (Dählback et al., 1993). Inherited APC resistance is in most cases due to a single point mutation in the blood coagulation factor V gene: a G → A transition at nucleotide position 1691, which predicts the replacement of arginine (R) at amino acid position 506 by glutamine (Q) (Bertina et al., 1994). The mutant factor V is known as factor V R506Q or factor V Leiden (FVL). In addition to predisposing for venous thrombophilia, FVL has also been reported to be a genetic risk factor for premature cardiovascular disease (myocardial infarction) in women (Rosendaal et al., 1997).

The prevalence of FVL should be determined in different ethnic groups since this knowledge may influence decisions regarding the utility of mutation screening in individuals exposed to circumstantial risk factors for thrombosis. In addition, information concerning the heterogeneity of the prevalence of this important risk factor may help in understanding ethnic or geographical differences in the incidence of thrombotic diseases.

In the present study, we investigated the prevalence of the FVL mutation in 440 individuals belonging to four different ethnic groups: Whites, African Blacks, Asians and Amerindians.

SUBJECTS AND METHODS

Subjects

FVL mutation analysis was performed in 440 individuals (880 chromosomes) belonging to four different ethnic groups: 152 Whites, 97 Blacks, 40 Asians and 151 Amerindians. The Whites were in most cases first or second generation descendants of Southern and Western European immigrants (mainly Portuguese, Spanish, Italian and German). The Black population sample included 97 African natives from Zaire and Cameroon, and the Asians were represented by 40 Japanese descendants. The 152 Amerindians came from seven tribes in the Brazilian Amazon region (20 Arara, 20 Kayapo, 21 Wayampi, 21 Y anomami, 23 A wa-Guaja and 26 Poturujara). All individuals investigated were unrelated, apparently healthy, and denied any racial admixture for at least three generations. The subjects participated in the study as volunteers.

Methods

Genomic DNA was obtained from peripheral blood leucocytes by standard methods (Sambrook et al., 1989). Exon 10 of the factor V gene was amplified by PCR, and the amplified products were digested with the restriction enzyme MnI to define the genotypes. The primers and PCR conditions employed have been reported elsewhere (Bertina et al., 1994). A test for the homogeneity of proportions was used to evaluate differences in allele frequencies between populations.
RESULTS AND DISCUSSION

A heterogeneous distribution was observed for the prevalence of the FVL mutation in individuals with different ethnic backgrounds. The FVL mutation was detected in heterozygous state in 4 out of 152 Whites (2.6%) and in 1 out of 151 Amerindians (0.6%) but was absent among 97 African Blacks and 40 Asians. No homozygote for the FVL mutation was observed.

The prevalence of the FVL mutation in Whites confirmed that this mutation is relatively common among Brazilian Caucasians, in agreement with a previous study performed in the Brazilian population (Arruda et al., 1995). In contrast, FVL was not found among the Asians and African Blacks studied. These findings agree with the suggestion that the mutation occurred 21,000-34,000 years ago, after the divergence of Caucasians and Mongolians (Zivelin et al., 1997). The finding of the FVL mutation in one Amerindian was unexpected, since the mutation was probably absent in the original populations of America (Zivelin et al., 1997). Even though the admixture with Blacks and Caucasians was evaluated at less than 2% for these Amerindian populations on the basis of classic protein markers (Salzano and Callegari-Jacques, 1988), we have observed the presence of alleles of Black origin among Amerindians (Zago et al., 1995), and the finding of one heterozygote may be the result of some admixture with Whites.

The absence of the FVL mutation in African Blacks was particularly interesting. Since virtually no racial admixture was expected to exist in this sample, it may be considered highly representative of a native Black population. Hence, our data provide further evidence that the FVL mutation is absent among Blacks, and suggest that the finding of this mutation among Afro-Americans in previous studies (Arruda et al., 1996; Gregg et al., 1997) might well be the result of miscegenation with Whites. The prevalence of venous thromboembolism was claimed to be lower among native Africans compared to other human populations (Thomas et al., 1960; Gore et al., 1964; WHO, 1993-1994). Our data agree with these observations since this lower incidence may partly reflect the absence of the most important known cause of venous thrombophilia (the FVL mutation) in this ethnic group. The possibility that FVL might be a genetic risk factor for arterial thrombotic disease has been investigated in several studies, but with conflicting results (Prohaska et al., 1995; Kontula et al., 1995; van der Bom et al., 1996; Foley et al., 1997). However, a recent study demonstrated a clear relationship between the presence of FVL and increased predisposition for myocardial infarction in young women (Rosendaal et al., 1997). In particular, the absence of FVL among African Blacks may contribute to the low incidence of cardiovascular disease observed among African natives (Hames and Greenlund, 1996). These studies indicate that the heterogeneous ethnic distribution of the FVL mutation may contribute to our understanding of differences in the prevalence of thrombotic vascular disease in different human populations.

The identification of the FVL mutation may affect the adoption of prophylactic and therapeutic regimens for venous thrombosis (Dählback, 1997). For this reason, determining the prevalence of the FVL mutation in different populations has become an important means of taking decisions about which subjects at risk for thrombosis should be stratified for the FVL mutation. The data of this study should be helpful in formulating decisions about screening for FVL in patients of different populations, including the Brazilian population, since the results strengthen the observation that FVL is not prevalent among non-Caucasians (Rees et al., 1995; Arruda et al., 1996; Dählback, 1997; Pepe et al., 1997).

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