Turk J Hematol 2006; 23:100-103
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RESEARCH ARTICLE

Frequency of five thrombophilic polymorphisms in the Egyptian population

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Received: *Oct 22, 2005* • ***Accepted:*** *Dec 22, 2005*

ABSTRACT

This study was conducted to evaluate the frequency of FV1691 G-A, FV4070 A-G, PT20210 G-A, EPCR 23 gene bp insertion and ACE gene 300 bp deletion among healthy Egyptians. One hundred and eighty eight healthy Egyptians were included to the study. Previously reported molecular techniques were used for the determination of mutations. Thirthy one individuals had FV1691 G-A (16.5%) mutation with an allele frequency of 0.09. R2 and R3 haplotypes were found in 21 (11.2%) and 4 (2.1%) individuals, respectively. Only one healthy individual had EPCR gene 23 bp insertion (0.53%) and two individuals (1.06%) had PT20210 G-A mutation, respectively. The ACE gene -300 bp del in homozygous state was present in 92 (48.9%) individuals. The frequency of D allele was 0.718. Our preliminary data revealed that FV1691 G-A mutation is very frequent among Egyptians and it will be meaningfull to study the mutation also in the thrombotic events in Egypt.

Key words: Thrombophilia, polymorphism

ÖZET

Mısır populasyonunda tromboza yatkınlığa yol açan beş polimorfizmin sıklığı

Bu çalışma, sağlıklı Mısır populasyonunda FV1691 G-A, FV4070 A-G, PT20210 G-A, EPCR geni 23 bç insersiyonu ve ACE geni 300 bç delesyon sıklığını araştırmak için planlanmıştır. 188 sağlıklı birey çalışmaya dahil edilmiştir. Mutasyonlar daha önceki moleküler teknikler kullanılarak tespit edilmiştir. 31 bireyin (%16.5) FV1691 G-A mutasyonunu taşıdığı ve allel sıklığının 0.09 olduğu belirlenmiştir. R2 ve R3 haplotipleri sırasıyla 21(%11.2) ve 4 (%2.1) olarak tespit edilmiştir. EPCR geni 23 bç insersiyonunu heterozigot olarak taşıyan bir birey (%0.53), PT20210 G-A mutasyonunu taşıyan iki birey (%1.06) olduğu belirlenmiştir. Anjiotensin dönüştürücü enzim geni -300 bç delesyonunu homozigot olarak taşıyan 92 birey (%48.9) olduğu ve D allel sıklığının 0.718 olduğu saptanmıştır. Bu başlangıç çalışmamız, tromboza yatkınlığa neden olan FV1691 G-A mutasyonunun Mısır populasyonunda sık olduğunu ve bu nedenle trombotik olaylarda da araştırılmasının anlamlı olabileceğini ortaya koymuştur.

Anahtar sözcükler: Trombofili, polimorfizm

INTRODUCTION

The practice of medical genetics has evolved from focusing on rare single gene disorders to including more prevalent multigenic disorders. The geneticist may be called upon to participitate in the diagnosis and management of individuals with relatively common multigenic disorders or for advice on testing or counseling of at-risk family members. Venous thromboembolism (VTE) is one such multigenic disorder that often triggers a consultation for both laboratory evaluation and interpretation as well as genetic counseling service [1]. Until the discovery of a novel inherited thrombophilia in 1993, all described cases were caused by the loss of function of regulatory proteins. Within the past decade, dramatic progress has been made in the ability to identify one or more inherited thrombophilic disorders, thanks largely to the discovery of two relatively common polymorphisms, namely, factor V 1691 G-A (FV Leiden) and the prothrombin gene 20210 G –A (PT20210 G-A) mutation [2].

To date, genetic factors leading to thrombosis have been investigated within different populations. There is an ethnic variation related with thrombotic risk factors. FV1691 G-A and factor V 4070 A-G mutations [3, 4], PT20210 G-A genetic change in the 3'-UTR of the prothrombin gene, endothelial protein C receptor (EPCR) gene 23 bp insertion and angiotensin converting enzyme (ACE) gene 300 bp deletion polymorphisms were conceived to have an effect on thrombosis [5-8]. It has been reported that there is a different restriction pattern with Rsa I digestion in the exon 13 of the factor V gene. The haplotype has been reported to have 3935 A-G (His 1254 Arg) polymorphism instead of 4070G-A (His1299Arg), and it has been referred to as R3 haplotype [9].

In this study we aimed to investigate two common mutations of the factor V gene, (1691 G-A and 4070 A-G), PT20210 G-A mutation, EPCR gene 23 bp insertion and ACE gene ins/del polymorphisms in the Egyptian population.

The Egyptian population has a mixed genetic background with an ethnic heterogeneity and no African origin. Most of the population is of Mediterranean or Arabic origin and migrated from Saudi Arabia and surrounding areas.

Table 1. Frequency of the five risk factors in Egyptians

Genetic changes	*Number of samples* (n)	%	*Frequency*
FV 1691 G-A	31(3)*	16.5	0.090
FV4070A-G			
R2 haplotype	21	11.2	0.055
R3 haplotype	4	2.1	0.010
PT20210 G-A	2	1.06	0.005
EPCR 23 bp insertion	1	0.53	0.002
ACE ins/del			
I/I	10	5.3	-
I/D	86	45.7	-
D/D	92	48.9	-
I allele	106	28.2	0.281
D allele	270	71.8	0.718

***( ):** Homozygous individuals. **EPCR:** Endothelial protein C receptor. **ACE:** Angiotensin converting enzyme. **I:** Insertion. **D:** Deletion.

As reflected in the Table, the distributions of factor V gene defects and of the ACE ins/del polymorphism were found to be frequent; the rare R3 haplotype was also found in the population.

We aimed to study five thrombophilic polymorphisms in the Egyptian population living in the capital city, Cairo.

MATERIALS and METHODS

We assessed the genetic frequency of these thrombotic risk polymorphisms in all 188 randomly selected healthy individuals with Egyptian origin from Cairo, which included a mixture of all cultural groups in Egypt. It is considered as a referral center with people coming from different regions and districts all over Egypt. The control group was in Hardy-Weinberg equilibrium. The population was not chosen from any isolates or members from the same family and those with a familial history of thrombosis of any kind were excluded. The mean age was 31.9 years and the median age was 29. A written consent was obtained from each individual. FV1691 G-A and PT20210 G-A mutations were analyzed with Real-Time polymerase chain reaction (PCR)

method using Light Cycler-FVL and PT20210 G-A mutation detection kits (Roche Diagnostics GmbH, Roche Molecular Biochemicals, Mannheim, Germany). Detection of insertion/deletion polymorphisms of ACE and EPCR genes and HR2 haplotype of factor V gene was done according to previously described PCR and restriction fragment length polymorphism (RFLP) techniques [10,12].

RESULTS

The frequencies of the five genetic alterations are shown in Table 1. Both mutations in the factor V gene were found to have a high frequency 16.5% for 1691 G-A heterozygotes and 11.2% for 4070 A-G. PT 20210 G-A mutation and EPCR gene 23 bp insertion were found to be very rare in Egypt. Of the 188 individuals, we found 21 carrying the R2 haplotype and four carrying the R3 haplotype.

DISCUSSION

It is worth noting that most of our understanding of inherited risk factors for thrombosis is derived from the study of largely white populations [13]. Thus, although studies have begun to elucidate the basis of familial thrombophilia in white populations, a great deal remains to be learned in other populations.

Our study is the first report presenting the frequency of five thrombosis-related polymorphisms in healthy Egyptians. The two factor V gene mutations were both found to be very frequent, as reported in other Middle Eastern countries, whereas PT20210 G-A mutation was rare. The frequency of FV1691 G-A mutation has been reported for many populations and there is a marked difference in genetic backgrounds [14,15]. Since it has been claimed that the factor V Leiden mutation is not found in populations of African origin, the high frequency of FV1691 G-A and 4070 A-G mutations appearing in the Egyptian population may be a clue supporting the notion that the Egyptian population is of non-African origin, as stated above. However, the presence of the R3 haplotype of the factor V gene may confirm the suggestion that the mutation is of African origin and imply an African admixture [9].

With this study, we revealed the genetic frequency in the Egyptian population of the five thrombophilic risk polymorphisms. Further studies are needed in thrombotic Egyptian patients, as testing may be used for better evidence-based management.

ACKNOWLEDGEMENTS

This study was supported by a grant from Ankara University Biotechnology Institute, grant # 2004-123.

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