The Turkish Journal of Pediatrics 1997; 39: 313-315

THE PREVALENCE OF FACTOR V LEIDEN (1691 G → A) MUTATION IN TURKEY*

*Aytemiz Gürgey MD***, *Lütfiye Mesci BS****

SUMMARY: Gürgey A, Mesci L. (Hematology Unit, Department of Pediatrics, Hacettepe University, Faculty of Medicine, Ankara, Turkey). The prevalence of factor V Leiden (1691 G→A) mutation in Turkey. Turk J Pediatr 1997; 39: 313-315.

Resistance to activated protein C (APC), which is caused by a single point mutation in the gene for factor V, is a common risk factor for thrombosis. In this study, we screened factor V (FV) Leiden mutation in 81 subjects. The mutation in the heterozygous form was found in 7.1 percent of our normal population. This high frequency suggests that screening for the FV mutation should be considered in patients with a family history of thrombosis. *Key words: factor V, activated protein C resistance, factor V Leiden.*

Venous thrombosis is a serious problem causing significant morbidity and mortality. Resistance to activated protein C (APC) has been shown to be one of the major risk factors for venous thrombosis. The molecular basis for APC resistance involves a mutation in the coagulation factor V (FV) gene at nucleotide 1691, which causes the mutation Arg 506 Gln (FV-Leiden)[1-3].

The FV mutation has been demonstrated in 20 to 40 percent of patients with thrombophilia and has a prevalence of five percent in the general population[1,2]. The frequency of FV mutation in Turkey is unknown. We have studied the frequency of the FV mutation.

Material and Methods

Fourty-eight adults and 33 children with no history of familial thrombophilia were screened for the 1691 G→A mutation in the FV gene. Genomic DNA was extracted from white blood cells and amplified by polymerase chain reaction (PCR). The 1691 G→A mutation was detected by loss of a cleavage site for Mnl I digestion. A 267-bp fragment was amplified using 5' primer TGCCCAGTGCTTAACAAGACCA-3' and 3' primer TGTTATCACACTGGTGCTAA-3'. The PCR conditions were as follows: 250 µl DNA was heated to 96 °C for five minutes and 34 °C for 30 seconds, and then held at 60 °C for two minutes and at 72 °C for three minutes together with the amplification solution and the primers as described[3]. Aliquots were digested for 12 hour at 37 °C with Mnl I (1 U). The fragments were separated on two percent agarose gels and visualized with ethidium bromide (Fig. 1).

* From the Hematology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara.

** Professor of Pediatrics, Hacettepe University Faculty of Medicine.

*** Biologist, Hacettepe University Faculty of Medicine.

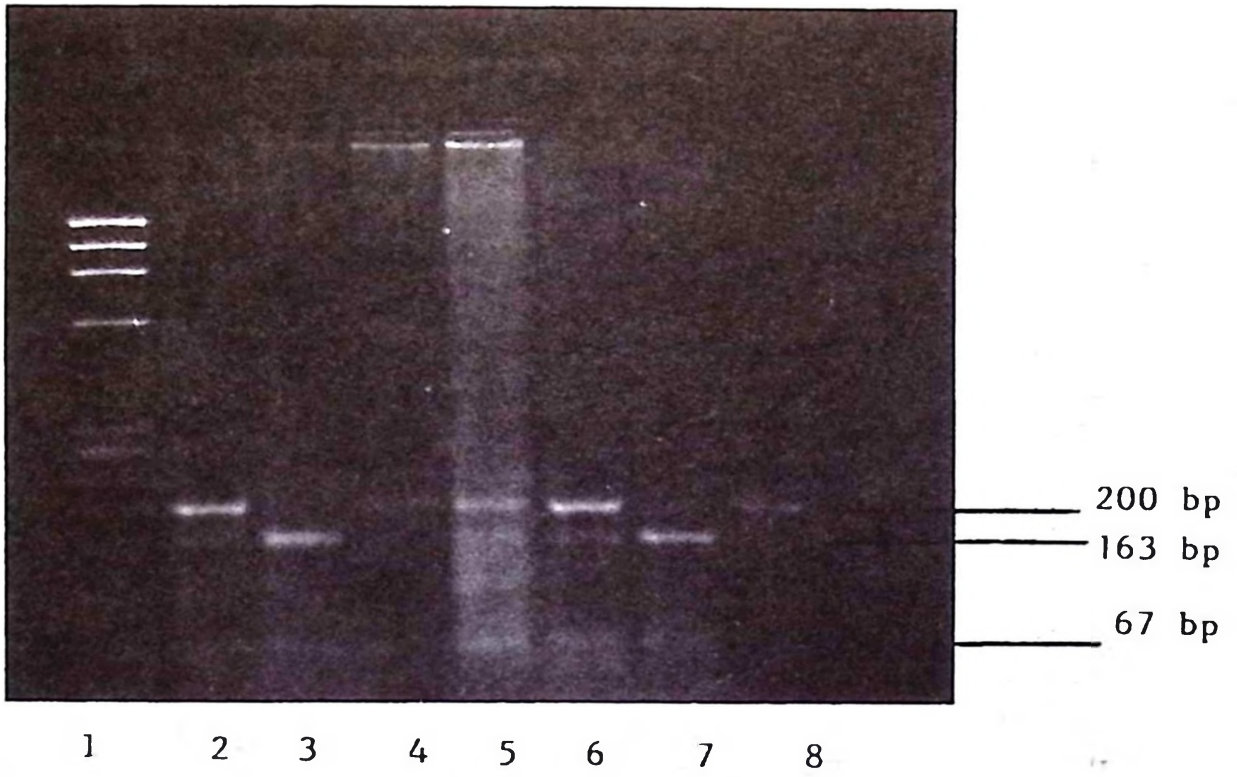

Fig. 1: Restriction analysis with Mnl I. 1: Marker (OX 174), 2, 4, 5, 6 heterozygote, 3, 7 normal.

Results

Among 81 individuals, we found six (7.1%) who were heterozygous for the FV mutation, while the other 75 were normal (Table I).

Table I: Carrier Rate For Factor V Leiden Mutation in Selected Countries

Country	Carrier Rate (%)	References
1. Turkey	7.1	Present study
2. Germany	4.0	5
3. Finland	4.0	7
4. Netherlands	2.9	8
5. United Kingdom	8.8	5
6. Greece	15.0	5
7. Africa	0.0	5

Discussion

The frequency of the FV mutation in Western Europe has been estimated at three to five percent[1,2,4]. The frequency of 7.1 percent found in our series is close to that in the United Kingdom (8.8%) and less than that of Greece (15%)[5] (Table I). It has been suggested that the FV mutation, like heterozygous protein C deficiency, is not enough solely to cause thrombosis, but is associated with

a life-long increased risk of venous thrombosis[3,4]. Recently, the FV mutation has been found in five healthy centenarians. It is interesting that none of them developed thrombotic episodes[6]. Heterozygotes for the FV mutation usually have a five-to 10-fold increased risk of venous thrombosis, and homozygotes are 50- to 100-fold more susceptible[7-9].

The FV mutation accounts for 21 percent of deep vein thromboses and up to 50 percent of familial thromboses[2,7]. The mutation was shown in eight (50%) of 16 children with thrombosis in our previous publication[10]. Deficiencies of protein C, protein S, antithrombin III and dysfibrinogenemia were together accountable for only five to 10 percent of cases, indicating the FV mutation to be at least 5 times more common than any of the other known genetic defects[1].

In conclusion, because of the approximately seven percent prevalence of FV Leiden in our population, it is suggested that family members of any subject with APC resistance should be screened to identify those who should receive prophylactic anticoagulant therapy during periods of increased risk of thrombosis, such as major surgery, pregnancy or the use of oral contraceptives.

Acknowledgement

We thank Dr. C. Altay for her continuous support.

REFERENCES

1. Sensson PJ, Dahlback B. Resistance to activated protein C as a basis for venous thrombosis. N Engl J Med 1994; 330: 517-522.
2. Koster T, Rosendaal FR, de Ronde H, et al. Venous thrombosis due to poor anticoagulant response to activated protein C: Leiden Thrombophilia Study. Lancet 1993; 342: 1503-1506.
3. Bertina RM, Koeleman BP, Koster T, et al. Mutation in blood coagulation factor V associated with resistance to activated protein C. Nature 1994; 369: 64-67.
4. Beauchamp NJ, Daly ME, Hampton KK, et al. High prevalence of a mutation in the factor V gene within the U.K. population: relationship to activated protein C resistance and familial thrombosis. Br J Haematol 1994; 88: 219-222.
5. Rees DC, Cox Clegg JB. World distribution of factor V Leiden. Lancet 1995; 346: 1133-1134.
6. Dari D, Manucci PM, Duca F, Bertolini S, Franceschi C. Mutant factor V (Arg 506 Gln) in healthy centenarians. Lancet 1996; 347: 1044.
7. Dahlback B. Inherited thrombophilia: resistance to activated protein C as a pathogenic factor of venous thromboembolism. Blood 1995; 85: 607-614.
8. Petaja J, Jalanko H, Holmberg C, et al. Resistance to activated protein C as an underlying cause of recurrent venous thrombosis during relapsing nephrotic syndrome. J Pediatr 1995; 127: 103-105.
9. Rosendaal FR, Koster T, Vandenbroucke JP, Reitsma PH. High risk of thrombosis in patients homozygous for factor V Leiden (activated protein C resistance). Blood 1995; 85: 1504-1508.
10. Gurgey A, Mesci L, Renda Y, Olcay L, Kocak N, Erdem G. The factor VQ 506 mutation in children with thrombosis. Am J Hematol 1996; 53: 37-39.