

## Factor V Leiden Is Associated with Higher Risk of Deep Venous Thrombosis of Large Blood Vessels

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**Aim** To determine the prevalence of factor V Leiden mutation in patients with different presentation of venous thromboembolic disease and healthy individuals in the Republic of Macedonia.

**Methods** The retrospective case control study involved 190 patients with venous thromboembolic disease and 200 healthy individuals, who were screened for the presence of factor V Leiden mutation, using a polymerase chain reaction-restriction fragment length polymorphism method. The prevalence of factor V Leiden was analyzed according to the localization of thrombosis, presence of risk factors, and family history of thrombosis. The odds of deep venous thrombosis were calculated with respect to the presence of factor V Leiden mutation.

**Results** The prevalence of factor V Leiden mutation among patients with venous thromboembolic disease was 21.1%, compared with 5.5% in the healthy individuals. Factor V Leiden positive patients had the first episode of deep venous thrombosis at a younger age, and the prevalence of the mutation was the highest among patients with a positive family history of thrombosis (33.9%,  $P=0.003$ ) and in patients with deep venous thrombosis affecting a large blood vessel (37.7%,  $P=0.001$ ). The prevalence of factor V Leiden mutation was lower in patients with calf deep venous thrombosis and primary thromboembolism (13.3% and 13.1%, respectively;  $P>0.05$ ). The odds ratio for ilio-femoral or femoral deep venous thrombosis in factor V Leiden carriers was 10.4 (95% confidence interval, 4.7-23.1).

**Conclusion** The prevalence of factor V Leiden mutation was high in patients with venous thromboembolic disease and healthy individuals in the Republic of Macedonia. Factor V Leiden carriers have the highest odds of developing deep venous thrombosis affecting a large venous blood vessel.

Factor V Leiden mutation has been recognized as the most prevalent genetic risk factor for venous thromboembolic disease (1-7). Single nucleotide substitution (G1691A) in factor V gene leads to an amino acid substitution, Arg506Gln, in factor V molecule, disrupting the cleavage site recognized by activated protein C (3). Activated protein C is a natural anticoagulation molecule, which acts by cleaving the molecule of activated factor V, thus limiting its procoagulation activity. The prolonged half-life and procoagulation activity of the activated factor V cause increased thrombotic tendency in patients carrying even a single copy of the mutated gene (4-7).

It has been estimated that the prevalence of factor V Leiden among patients with deep venous thrombosis varies between 20% and 30% (8). Based on these data, it has been proposed that heterozygous carriers have 7-fold and homozygotes 80-fold higher risk of deep venous thrombosis (8). Factor V Leiden prevalence is lower in patients with pulmonary thromboembolism – only 7-9% (3,9,10). Several studies have shown that factor V Leiden mutation is associated with an increased risk for recurrent thrombotic episodes, justifying screening patients with deep venous thrombosis for factor V Leiden (11-13). Women carriers of factor V Leiden are at a higher risk of obstetric complications, such as eclampsia, pre-eclampsia, abruption of the placenta, recurrent abortions, and intrauterine retardation of the fetal growth (14-16).

The frequency of factor V Leiden mutation in the studied healthy populations varies from 3% to 12% in Europe (17,18) and from 1% to 6% in North America (19), and it is almost absent in the indigenous populations in Africa and Australasia (17,20).

The aim of this study was to determine the prevalence of factor V Leiden mutation in patients with venous thromboembolic disease and healthy individuals in the Republic of Macedonia and to compare the findings with the published data for other countries in the region.

We also analyzed the differences in the prevalence of factor V Leiden mutation with respect to the clinical presentation of the venous thromboembolic disease (deep venous thrombosis or primary thromboembolism), age, sex, presence of acquired risk factor, and localization of the thrombotic process.

## Patients and methods

### Patients

The retrospective case-control study included 190 consecutive patients with pulmonary thromboembolic disease hospitalized at the Department of Hematology or referred for nuclear medicine diagnostics to the Institute of Pathophysiology and Nuclear Medicine, Skopje University Hospital, Macedonia. There were 114 women aged  $40 \pm 15$  years (mean  $\pm$  standard deviation) and 76 men aged  $45 \pm 14$  years. The diagnosis of venous thromboembolic disease was based on patient's history, clinical findings, radioisotope venography, and ventilation/perfusion scintigraphy. In some cases, additional diagnostic procedures, such as ultrasound and D-dimer testing, were also used. An acquired risk factor for deep venous thrombosis was identified in nearly half of the patients (66 of 114 women and 33 of 76 men). The most frequent acquired risk factors in women were pregnancy and delivery (44 of 114) and surgical procedure (12 of 114), whereas surgical procedure (18 of 76) and trauma (10 of 76) were the most frequent in men. Family history of thromboembolic disease was present in 75 of 114 women and 53 of 76 men. Patients were divided into 3 groups according to the deep venous thrombosis localization: patients with iliofemoral or femoral thrombosis ( $n=61$ ), calf thrombosis ( $n=84$ ), and primary thromboembolism ( $n=45$ ). The control group consisted of 200 randomly selected, age and sex non-matched healthy individuals (120 women

and 80 men, 130 Macedonian and 70 Albanian DNA samples).

All patients and healthy individuals signed a written consent to participate in the study, which was approved by the Committee of the Tempus-Phare postgraduate program.

#### **Venography and ventilation/perfusion scintigraphy**

The assignment of patients into one of the study groups according to localization of thrombosis was based on clinical findings, combined radionuclide flow venogram, and perfusion/ventilation radioisotope findings. Deep venous thrombosis was diagnosed by radionuclide flow venogram obtained after a simultaneous injection of 110-150MBq <sup>99m</sup>Tc-labeled macro-aggregates of albumin (<sup>99m</sup>Tc-MAA) into superficial foot veins. The bolus of injected radioactivity was followed through the deep venous system, as tourniquets were applied above the ankle and below the knee, with a large field of view gamma camera. Deep venous thrombosis was diagnosed in cases of reduced speed of passage of the bolus, incompletely filled deep vessels, and lack of visualization of the deep venous system with present collateral flow due to a complete blood flow obstruction. The lung perfusion study was carried out following the acquisition of the radionuclide flow venogram (static equilibrium acquisition in 4 standard positions). The diagnosis of pulmonary thromboembolism was based on the combination of perfusion defects, which are almost completely filled with <sup>99m</sup>Tc-DTPA aerosols in the ventilation radionuclide study according to the PLOPED criteria for high probability of pulmonary thromboembolism (21).

#### **Factor V Leiden mutation analysis**

Genomic DNA was isolated from peripheral blood leucocytes by using standard SDS-proteinase K digestion and phenol-chloroform extraction protocol (22). Factor V Leiden mutation was detected using polymerase chain reaction

(PCR) restriction fragment length polymorphism method (3). Briefly, the region flanking the mutation was amplified by PCR (forward primer CCC AGT GCT TAA CAA GAC CA, reverse primer TGT TAT CAC ACT GGT GCT AA) and the PCR product digested with the restriction enzyme *Mnl*I (New England Biolabs, Ipswich, MA, USA). The products from the digestion were separated on a 3% agarose gel, stained with ethidium bromide and visualized on a UV transilluminator.

#### **Statistical analysis**

Factor V Leiden prevalence results are presented as proportions (carrier and allele frequencies) and 95% confidence interval (CI). The differences in the distribution of Factor V Leiden mutation were analyzed with  $\chi^2$  test, and the differences in age were analyzed with *t* test with StatGraphics for Windows 5.0. *P*<0.05 was considered statistically significant. Odds ratios (OR) with 95% CI were calculated to estimate risk of thromboembolism (<http://www.hutchon.net/ConfidOR.htm>).

#### **Results**

Among 190 patients with venous thromboembolic disease, 2 were factor V Leiden homozygotes and 38 were factor V Leiden carriers. Thus, the overall prevalence of factor V Leiden was 21% (95% CI, 14.3-25.7) and the overall factor V Leiden allele frequency was 11.1% (7.9-14.3). Only 11 carriers were identified among 200 healthy individuals. Thus, in the general population in Macedonia, factor V Leiden prevalence was 5.5% (2.3-8.7) and allele frequency was 2.8% (1.2-4.4). Factor V Leiden prevalence was somewhat higher among Macedonians (6.9%; 2.5-11.3) than among Albanians (2.9%; 0-6.8) (Table 1). The odds ratio for venous thromboembolic disease was 4.6 (2.3-9.2) in factor V Leiden carriers.

Two factor V Leiden homozygotes and 21 carriers were identified in the group of patients

**Table 1.** Prevalence of factor V Leiden in patients with venous thromboembolic disease and healthy individuals in the Republic of Macedonia

	total	No. (%) of subjects*		OR (95% CI)†
		A/G or A/A	G/G	
Patients with venous thromboembolic disease:	190	40 (21.1)	150 (78.9)	4.6 (2.3-9.2)
deep venous thrombosis	145	34 (23.5)	111 (76.5)	5.3 (2.6-10.8)
iliofemoral deep venous thrombosis	61	23 (37.7)	38 (62.3)	10.4 (4.7-23.1)
calf deep venous thrombosis	84	11 (13.1)	73 (86.9)	2.6 (1.1-6.2)
primary pulmonary thromboembolism	45	6 (13.3)	33 (86.7)	2.6 (0.9-7.6)
Healthy controls:	200	11 (5.5)	189 (94.5)	
Macedonians	130	9 (6.9)	121 (93.1)	
Albanians	70	2 (2.9)	68 (97.1)	

\*A/G – factor V Leiden carrier, A/A – factor V Leiden homozygote, G/G – normal.

†Odds ratio (OR) with 95% confidence interval (CI) for development of venous thromboembolic disease in carriers of factor V Leiden mutation calculated relative to factor V Leiden prevalence in the group of healthy subjects.

with iliofemoral or femoral thrombosis, with the prevalence of factor V Leiden mutation of 37.7% (25.5-49.8) and factor V Leiden allele frequency of 20.5% (13.3-27.7). The odds ratio for iliofemoral or femoral deep venous thrombosis was 10.4 (4.7-23.1) in factor V Leiden carriers (Table 1).

The prevalence of the mutation in the group of patients with deep venous thrombosis of the calf was 13.1% (5.9-20.3). Factor V Leiden allele frequency in this patient group was 6.6% (3.1-10.1) and the OR for calf thrombosis in factor V Leiden carriers was 2.6 (1.1-6.2) (Table 1).

In the group of patients with primary thromboembolism, factor V Leiden prevalence was 13.3% (2.3-23.2) and the odds ratio for primary thromboembolism in factor V Leiden carriers was 2.6 (0.9-7.6) (Table 1).

#### Distribution of factor V Leiden mutation

There was no difference in the prevalence of the mutation between men and women with venous thromboembolic disease (19.9% vs 23.7%, respectively;  $P=0.468$ ) (Table 2). The analysis of the age of the first thrombotic event was carried out in 100 patients with deep venous thrombosis in whom the age of the first thrombotic event could be unambiguously determined (Table 2). The mean age of first deep venous thrombosis was  $33.7 \pm 11.5$  years for factor V Leiden positive and  $41.1 \pm 15.7$  years for factor V Leiden negative patients ( $P=0.033$ ). Such a difference was not found in the group of patients with primary thromboembolism.

**Table 2.** Prevalence of factor V Leiden with respect to age, sex, presence of acquired risk factor, and family history of venous thromboembolism\*

Parameter	No. (%) of subjects			P
	total	A/G or A/A	G/G	
Age:				
DVT (years; mean±SD)	100	25 (33.7 ± 11.5)	75 (41.1 ± 15.7)	0.033
PTE (years; mean±SD)	45	6 (45.3 ± 8.9)	39 (46.1 ± 11.5)	0.872
Sex:				
men	76	18 (23.7)	58 (76.3)	0.468
women	114	22 (19.9)	92 (80.1)	
Acquired risk factor:				
absent	91	20 (22.0)	71 (78.0)	0.764
present	99	20 (20.2)	79 (79.8)	
pregnancy or delivery	44	8 (18.2)	36 (71.8)	
Family history of VTE:				
positive	62	21 (33.9)	41 (66.1)	0.003
negative	128	19 (14.8)	109 (85.2)	

\*Abbreviations: A/G – factor V Leiden carrier, A/A – factor V Leiden homozygote, G/G – normal, DVT – deep venous thrombosis, PTE – primary thromboembolism, VTE – venous thromboembolic disease.

Overall, patients with family history of thromboembolism had a higher prevalence of factor V Leiden compared with the patients without family history of thromboembolism (33.9% vs 14.8%, respectively;  $P=0.003$ ) (Table 2). Whereas patients with deep venous thrombosis and positive family history had higher prevalence of factor V Leiden than the ones without positive family history (44.4% vs 14.1%, respectively;  $P=0.001$ ), factor V Leiden prevalence was not significantly different in patients with primary pulmonary thromboembolism with respect to the presence of family history of thrombosis (11.1% vs 13.9%, respectively;  $P=0.782$ ). There was no difference in the prevalence of factor V Leiden between the groups of patients with and without additional acquired risk factor (Table 2). The prevalence of factor V Leiden muta-

tion in the group of women with deep venous thrombosis related to pregnancy and delivery was 20.5% (8 carriers and 1 homozygote), and nearly twice higher among the women with family history of thrombosis (26.1% vs 14.3%) (Table 2).

**Discussion**

We found a high prevalence of factor V Leiden mutation in the general population in the Republic of Macedonia. This finding is consistent with the reported prevalence for other countries in the region, such as Greece, Bulgaria, Serbia, and Croatia (23-26) (Table 3). We found that the overall prevalence of factor V Leiden in patients with venous thromboembolic disease was 21%, increasing the odds for venous thromboembolism in factor V Leiden carriers to 4.6. Our finding of low prevalence of factor V Leiden in patients with primary pulmonary thromboembolism (13.1%), increasing the odds ratio to only 2.3 in factor V Leiden carriers, confirms previously published data (3,6,10).

Given the well established association between factor V Leiden mutation and obstetric complications, we analyzed its prevalence in women with deep venous thrombosis during pregnancy or within the first few weeks after delivery. We found that one in 5 women in this group were factor V Leiden carriers. These findings strongly support the idea of systemic screening for factor V Leiden mutation in the population of women with deep venous thrombosis

related to pregnancy and delivery, as this information may be important in the adequate management of subsequent pregnancies.

There was a 3-fold higher prevalence of factor V Leiden mutation in patients with thrombosis affecting the iliofemoral or femoral vein compared with those with calf thrombosis. In other words, our results show that factor V Leiden carriers are at higher risk of developing deep venous thrombosis affecting a large venous blood vessel compared with thrombosis affecting calf veins or primary pulmonary thromboembolism. A study by Björgell et al (30) on the localization of the thrombotic process in factor V Leiden carriers indicated the opposite. In their study, the prevalence of factor V Leiden was significantly higher in patients with deep venous thrombosis localized below the iliofemoral segment. Other studies dealing with larger number of cases with proximal deep venous thrombosis localization have shown that the prevalence of factor V Leiden in these patients was markedly higher (13,28,31). These differences in the prevalence of factor V Leiden in patients with proximal deep venous thrombosis may be due to the differences in the selection and diagnostic criteria used in the different studies. Alternative explanation could be the different relative contribution of factor V Leiden mutation in the context of the complex interplay of other coagulation defects and alleles in populations from different geographical regions.

In conclusion, the prevalence of factor V Leiden mutation in the healthy population of

**Table 3.** Prevalence of Factor V Leiden mutation in different populations in European countries

Population (ref. No.)	No. (%) of subjects			
	patients with venous thromboembolic disease		general population	
	total	factor V Leiden mutation (%)	total	factor V Leiden mutation (%)
Greece (23)	172	55 (31.9)	104	5 (4.8)
Italy (27)	111	15 (15.3)	121	5 (4.1)
France (28)	165	24 (14.5)	200	7 (3.5)
UK (29)	471	96 (20.4)	511	15 (2.9)
The Netherlands (8)	471	92 (19.5)	474	14 (3.0)
Croatia (24)	160	33 (21.0)	155	6 (4.0)
Serbia (25)	175	52 (29.3)	120	7 (5.8)
Bulgaria (26)	128	32 (25.0)	100	9 (9.0)
Macedonia (this study)	190	40 (21.1)	200	11 (5.5)

the Republic of Macedonia is similar to previously reported high prevalence of this mutation in other populations in the region. In addition, our results suggest that factor V Leiden carriers have the highest risk of developing deep venous thrombosis affecting larger venous blood vessel, such as iliofemoral or femoral vein, and that routine factor V Leiden screening should be carried out in patients who experience the first episode of deep venous thrombosis at younger age, especially if there is a positive family history of thrombosis and deep venous thrombosis related to pregnancy and delivery.

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