Clinical and Applied Thrombosis/Hemostasis
18(1) 40-44

DOI: 10.1177/1076029611412369
http://cath.sagepub.com

The Role of Factor V Leiden in Adult Patients With Venous Thromboembolism: A Meta-Analysis of Published Studies from Turkey

Aydan Eroglu[1], Durdu Sertkaya[2], and Nejat Akar[3]

Abstract

Factor V Leiden (FVL) is the most common inherited risk factor for venous thromboembolism (VTE). The frequency of FVL in patients with VTE has been reported from different parts of Turkey. A meta-analysis was performed to estimate the risk of VTE associated with FVL in Turkish population. Published studies were retrieved from Pubmed and Science Citation Index/Expanded. We selected studies comparing the prevalence of FVL in patients with VTE with controls. The analysis was performed by the software comprehensive meta-analysis. The analysis consisted of 10 studies including 1202 patients with VTE and 1283 controls. The pooled frequency of FVL was significantly higher in patients with VTE (22.8%) than controls (7.6%). The pooled odds ratio (OR) was 3.4 (95% confidence interval [CI], 2.6-4.5). The study showed homogeneity (*Q* value, 9.955). No publication bias was observed in any comparison model. Our meta-analysis showed an association of FVL with VTE in Turkey.

Keywords

factor V Leiden, venous thromboembolism, Turkey, Turkish population

Introduction

Factor V Leiden (FVL) causing activated protein C resistance is the most common inherited risk factor for venous thromboembolism (VTE).[1,2] Factor V Leiden increases the thrombosis risk approximately by 7-fold. Heterozygosity for FVL causes 5- to 10-fold increased risk of VTE, whereas the risk of homozygosity is 80- to 100-fold higher than the normal population.[1,2]

The frequency of FVL mutation shows a geographic distribution. The high prevalence of FVL is seen in Middle East, Southern Europe, and Mediterranean region; however, it is not observed in some populations like Chinese.[3-6] In several studies, the prevalence of FVL in Turkish people with VTE has been reported from different parts of Turkey. Factor V Leiden frequency in healthy Turkish population is 7.9% (range, 3.5%-15%).[7] We performed a meta-analysis to estimate the risk of VTE associated with FVL in Turkish population.

Materials and Methods

The data were compiled from Medline/Pubmed and Science Citation Index/Expanded databases. The keywords used for search were "factor V Leiden," "factor V 1691 G-A," "FVL," "mutation," "polymorphism," "venous thrombosis," "pulmonary embolism," "Turkey," and "Turkish population."

Eligible studies fulfilled the following criteria: retrospective or prospective cohort case–control studies, with sufficient data to estimate an odds ratio (OR) with 95% confidence interval (CI), the study with 2 arms comparing patients with idiopathic VTE to those without VTE. For overlapping and republished studies by the same investigators, we selected the most recent ones with large sample sizes or available genotype data. Case reports and the studies including pediatric patients were excluded from the meta-analysis. Besides, patients with specific disease such as cancer, the Behcet disease, and the Crohn disease were excluded from the analysis (Figure 1).

Meta-analysis was performed to obtain a full and comprehensive summary of the related studies. The correlation coefficients (*r*) were combined using the fixed- and random-effects models. Heterogeneity of the studies was evaluated by the homogeneity test (*Q*). If homogeneity is found between the studies, the outcome of a fixed-effects model is performed.

[1] General Surgery, Ankara University Medical School, Ankara, Turkey
[2] Faculty of Science, Statistics Section, Hacettepe University, Beytepe/Ankara, Turkey
[3] Pediatrics, TOBB-ETU University Hospital

Corresponding Author:
Aydan Eroglu, Department of General Surgery, Ankara University Medical School, Cebeci Kampus, Dikimevi, 06590, Ankara, Turkey
Email: aydaneroglu@hotmail.com

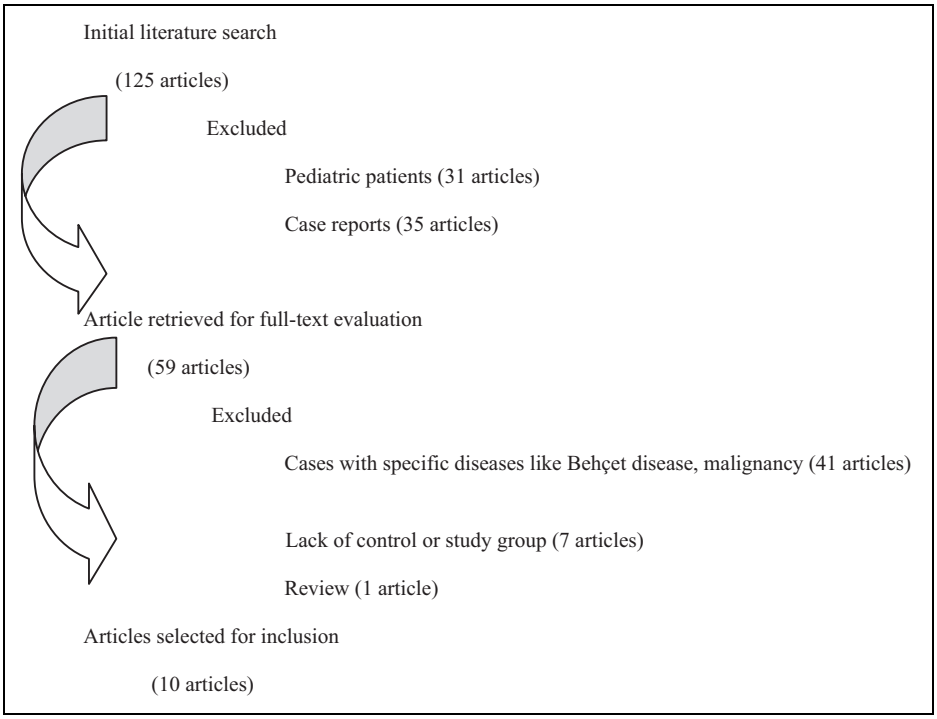


Figure 1. Summary of trial search and eligibility process.

In the event of a heterogeneity, it is appropriate to use the result of a random-effects model.[8]

Heterogeneity assumption was checked by the chi-square-based Q test. The pooled OR was calculated through the fixed-effects model. Begg funnel plot and Egger linear regression test were used to assess the potential publication bias of the literature.[9] $P < .05$ was considered the representative of statistically significant publication bias. The analyses were performed using the software Comprehensive Meta-Analysis, version 2.2 (Biostat, Englewood, NJ).

Results

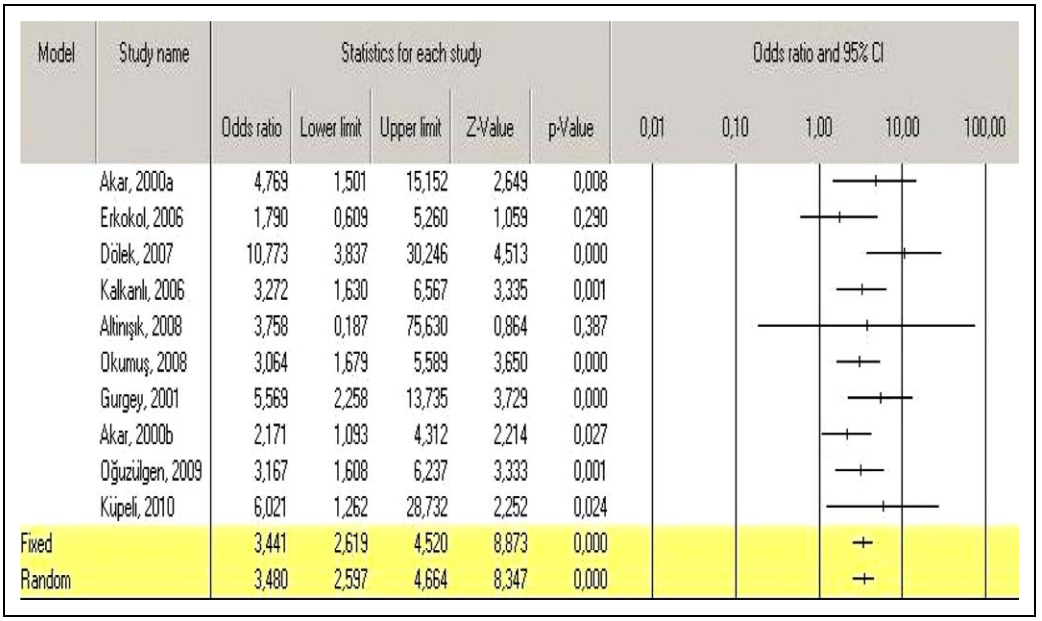
A total of 10 studies[10-19] including 1202 patients with VTE and 1283 control cases were involved in this meta-analysis. Table 1 summarizes the characteristics of each study. The pooled frequency of FVL was significantly higher in patients with VTE (22.8%) than the control participants (7.6%). The main results of meta-analysis and the forests of the studies are shown in Figure 2. When the homogeneity test was performed, the study was found to be homogeneous. Therefore, the fixed-effects model was used. The Q value was 9.955 ($P = .354$). The pooled OR was 3.4 (95% CI, 2.6-4.5; $P < .0001$). In addition, no evidence of the publication bias was observed in any comparison model. As shown in Figure 3, the plot of the 10 studies had a funnel image and therefore there was no publication bias. Possible publication bias was assessed by the rank correlation test and yielded $P = .17$, which reveals that there was no publication bias at the 95% CI. Besides, the Begg test ($P = .21$, with continuity correction) and the Egger test ($P = .29$) also revealed no publication bias at the 95% CI.

Discussion

The frequency of FVL has been reported in different surveys carried out in many countries, depending on the geographical location and the ethnic background of the population. Its frequency is reported to be 2% to 15% and the highest prevalence rates are seen in Mediterranean countries.[4,6] Factor V Leiden mutation has been estimated to be approximately 15 000 to 30 000 years ago during the Neolithic period. Lucotte and Mercier proposed that FVL in Europe was expanded from Turkey, Anatolia, which lies central to 3 continents and is at crossroads of several numbers of civilizations.[6] The prevalence of FVL in Turkish people with VTE and healthy Turkish population has been reported from different parts of Turkey.[7,20] The existence of mutation in Anatolia is expected to be high. This situation has been recently supported by a study by Alakoc et al, indicating the presence of FVL in Urartians.[21]

There exist limited information about why genetic diseases are present in a high frequency rather than not being eliminated by natural selection.[22] Most probably, the answer lies in the survival advantage caused by the mutation. Even a small increase in the frequency of FVL for 1 generation would have yielded a significant difference through hundreds of generations.[23]

Turkish population seems to be a very good candidate to study the possible effects of FVL on VTE with its significantly high FVL. We therefore performed the meta-analysis of 10 eligible studies including 1202 cases and 1283 controls for a better evaluation of this association in Turkish population. When all studies were pooled together, our results demonstrated that FVL is associated with VTE development. Our meta-analysis also showed that pooled frequency of FVL in healthy Turkish



Model	Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
	Akar, 2000a	4,769	1,501	15,152	2,649	0,008
	Erkokol, 2006	1,790	0,609	5,260	1,059	0,290
	Dölek, 2007	10,773	3,837	30,246	4,513	0,000
	Kalkanlı, 2006	3,272	1,630	6,567	3,335	0,001
	Altınışık, 2008	3,758	0,187	75,630	0,864	0,387
	Okumuş, 2008	3,064	1,679	5,589	3,650	0,000
	Gurgey, 2001	5,569	2,258	13,735	3,729	0,000
	Akar, 2000b	2,171	1,093	4,312	2,214	0,027
	Oğuzülgen, 2009	3,167	1,608	6,237	3,333	0,001
	Küpeli, 2010	6,021	1,262	28,732	2,252	0,024
Fixed		3,441	2,619	4,520	8,873	0,000
Random		3,480	2,597	4,664	8,347	0,000

Figure 2. Results of meta-analysis based on a quality score (pooled estimate and 95% confidence intervals).

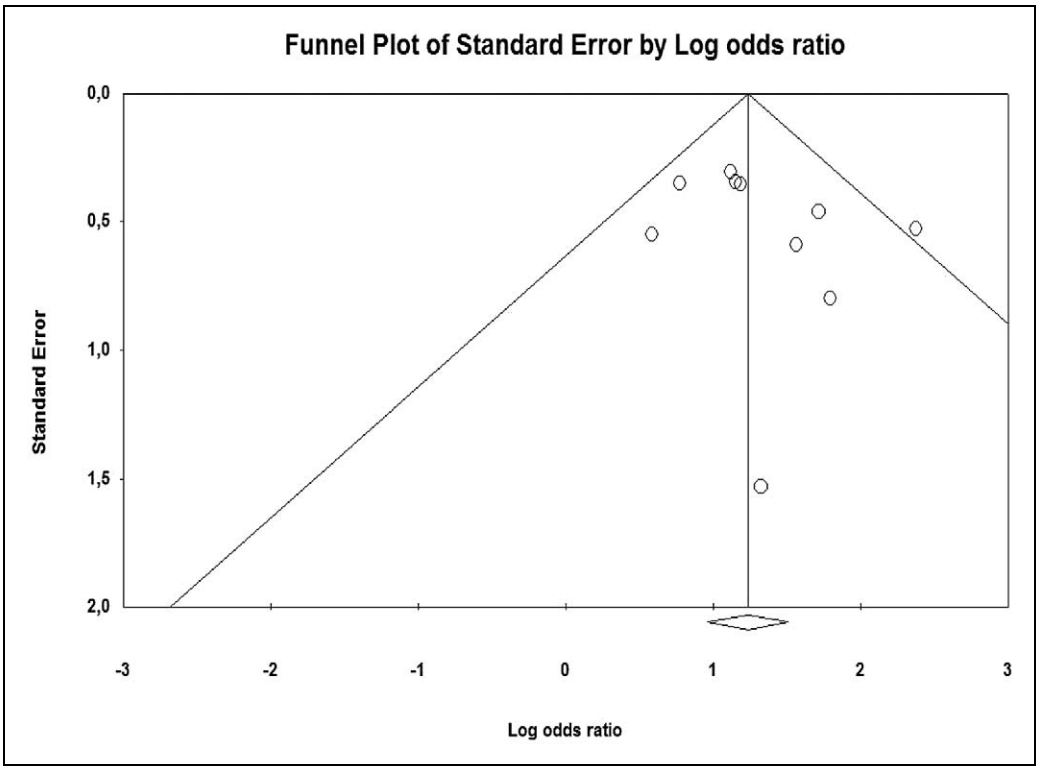


Figure 3. Funnel plot of 10 studies including log odds ratio.

people is 7.6%. As a conclusion, we can hypothesize that every individual with VTE should be screened for FVL whether or not carrying a risk factor.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Table 1. Characteristics of Study Participants

			Patients with VTE			Control Participants		
			FVL Mutation			FVL Mutation		
Study	Ref Number	Year	Positive (%)	Negative (%)	Total	Positive (%)	Negative (%)	Total
Akar et al[a]	10	2000	16 (23.5)	52 (76.5)	68	4 (6.06)	62 (93.04)	66
Erkekol et al	11	2006	10 (15.6)	54 (84.4)	64	6 (9.4)	58 (90.6)	66
Dolek et al	12	2007	76 (28.2)	194 (71.8)	270	4 (3.5)	100 (96.5)	114
Kalkanli et al	13	2006	15 (24.6)	46 (75.4)	61	29 (9.1)	291 (90.9)	320
Altinisik et al	14	2008	3 (6)	47 (94)	50	0	25	25
Okumus et al	15	2008	44 (23)	147 (77)	191	17 (8.9)	174 (91.1)	191
Gurgey et al	16	2001	45 (30.7)	101 (69.3)	146	6 (7.4)	75 (92.6)	81
Akar et al[b]	17	2000	26 (20.1)	103 (79.9)	129	15 (10.4)	129 (89.6)	144
Oguzulgen et al	18	2009	30 (21)	113 (79)	143	14 (7.7)	167 (92.3)	181
Kupeli et al	19	2010	9 (11.3)	71 (88.7)	80	2 (2.1)	95 (97.9)	97
Total number of cases			274 (22.8)	928 (77.2)	1202	97 (7.6)	1186 (92.4)	1283

Abbreviations: FVL, factor V Leiden; VTE, venous thromboembolism.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

References

1. Bertina RM, Koelman BPC, Koster T, et al. Mutation in blood coagulation factor V associated with resistance to activated protein C. *Nature*. 1994;369(6475):64-67.
2. Rosendaal FR, Koster T, Vandenbroucke JP, Reitsma PH. High risk of thrombosis in patients homogygous for factor V Leiden (activated protein C resistance). *Blood*. 1995;85(6):1504-1508.
3. Rees DC, Cox M, Clegg JB. World distribution of factor V Leiden. *Lancet*. 1995;346(8983):1133-1134.
4. Irani-Hakime N, Tamim H, Kreidy R, Almawi WY. The prevalence of factor V R506Q mutation-Leiden among apparently healthy Lebanase. *Am J Hematol*. 2000;65(1):45-49.
5. Chan LC, Bourke C, Lam CK et al. Lack of activated protein C resistance in healthy Hong-Kong Chinese blood donors-correlation with absence of Arg506-Gln mutation of factor V gene. *Thromb Haemost*. 1996;75(3):522-523.
6. Lucotte G, Mercier G. Population genetics of factor V Leiden in Europe. *Blood Cells Mol Dis*. 2001;27(2):362-367.
7. Akar N. Factor V 1691 G-A mutation distribution in a healthy Turkish population. *Turk J Hematol*. 2009;26(1):9-11.
8. Sutton AJ, Abrams KR, Jones DR, Sheldon TA, Song F. Methods for meta-analysis in medical research. In: Cressie NAC, Fisher NI, Johnstone IM et al eds. *Assessing Between Study Heterogeneity, Publication Bias, Study Quality, and Sensitivity Analysis.* Chichester, UK: John Wiley and Sons; 2000:37-151.
9. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a single, graphical test. *BMJ*. 1997; 315(7109):629-634.
10. Akar N, Akar E, Akçay R, Avcu F, Yalcin A, Cin S. Effect of metylenetetrahyrofolate reductase 677 C-T, 1298 A-C, and 1317 T-C on factor V 1691 mutation in Turkish deep vein thrombosis patients. *Thromb Res*. 2000;97(3):163-167.
11. Erkekol FO, Ulu A, Numanoglu N, Akar N. High plasma levels of factor VIII: an important risk factor for isolated pulmonary embolism. *Respirology*. 2006;11(1):70-74.
12. Dolek B, Eraslan S, Eroglu S, et al. Molecular analysis of factor V Leiden, factor V Hong Kong, factor II G20210A, methylenetetrahydrofolate reductase C677T, and A1298C mutations related to Turkish thrombosis patients. *Clin Appl Thromb Hemost*. 2007; 13(4):435-438.
13. Kalkanli S, Ayyildiz O, Tiftik N, et al. Factor V Leiden mutation in venous thrombosis in southeast Turkey. *Angiology*. 2006;57(2): 193-196.
14. Altinisik J, Ates O, Ulutin T, Cengiz M, Buyru N. Factor V Leiden, prothrombin G20210A, and protein C mutation frequency in Turkish venous thrombosis patients. *Clin Appl Thromb Hemost*. 2008;14(4):415-420.
15. Okumus G, Kiyan E, Arseven O, et al. Hereditary thrombophilic risk factors and venous thromboembolism in Istanbul, Turkey: the role in different clinical manifestations of venous thromboembolism. *Clin Appl Thromb Hemost*. 2008;14(2):168-173.
16. Gurgey A, Haznedaroglu IC, Egesel T, et al. Two common thrombotic risk factors: factor V Leiden and prothrombin G20210A in adult Turkish patients with thrombosis. *Am J Hematol*. 2001; 67(2):107-111.
17. Akar N, Akar E, Yılmaz E. Coexistence of factor V 1691 G-A and factor V 4070A-G mutation in Turkish thromboembolic patients. *Am J hematol*. 2000;65(1):87-89.
18. Oguzulgen IK, Yılmaz E, Demirtas S, et al. The role of plasminogen activator inhibitor-1 polymorphism, factor V Leiden, and prothrombin 20210 mutations in pulmonary thromboembolism. *Clin Appl Thromb Hemost*. 2009;15(1):73-77.
19. Kupeli E, Verdi H, Simsek A, Atac FB, Eyupoglu FO. Genetic mutations in Turkish population with pulmonary embolism and deep venous thrombosis. *Clin Appl Thromb Hemost*. 2010 Nov 15 (Epub ahead of print).
20. Akbayram S, Akgün C, Doğan M, Bektaş MS, Öner AF. The prevalence of factor V 1691G-A mutation in Van Region of Turkey. *Turk J Hematol*. 2010;27(3):211-212.

21. Dogan Alakoc Y, Aka S, Egin Y, Akar N. Factor V Leiden in an Urartian, dating back to 1000 BC. *Clin Appl Thromb Hemost*. 2010;16(6):679-683.
22. Flint J, Harding RM, Clegg JB, Boyce AJ. Why are some genetic diseases common? Distinguishing selection from other processes by molecular analysis of globin gene variants. *Hum Genet*. 1993; 91(2):91-117.
23. Lindqvist PG, Dahlback B. Carriership of factor V Leiden and evolutionary selection advantage. *Curr Med Chem*. 2008; 15(15):1541-1544.