DVT and genetic predisposition

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70TH ESCVS CONGRESS & 7TH IMAD MEETING

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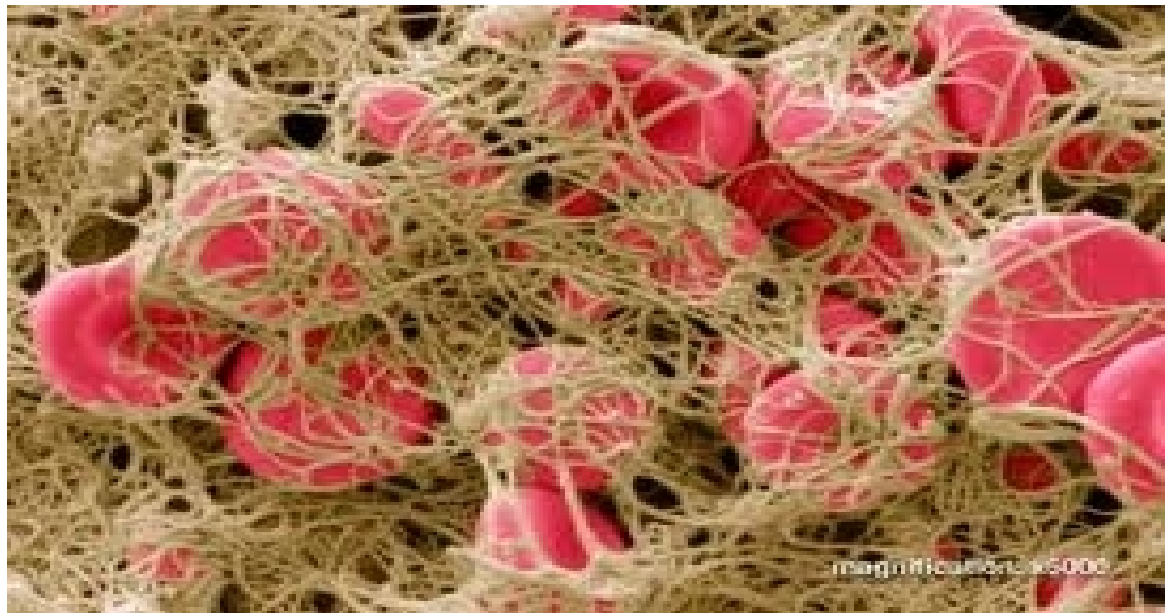
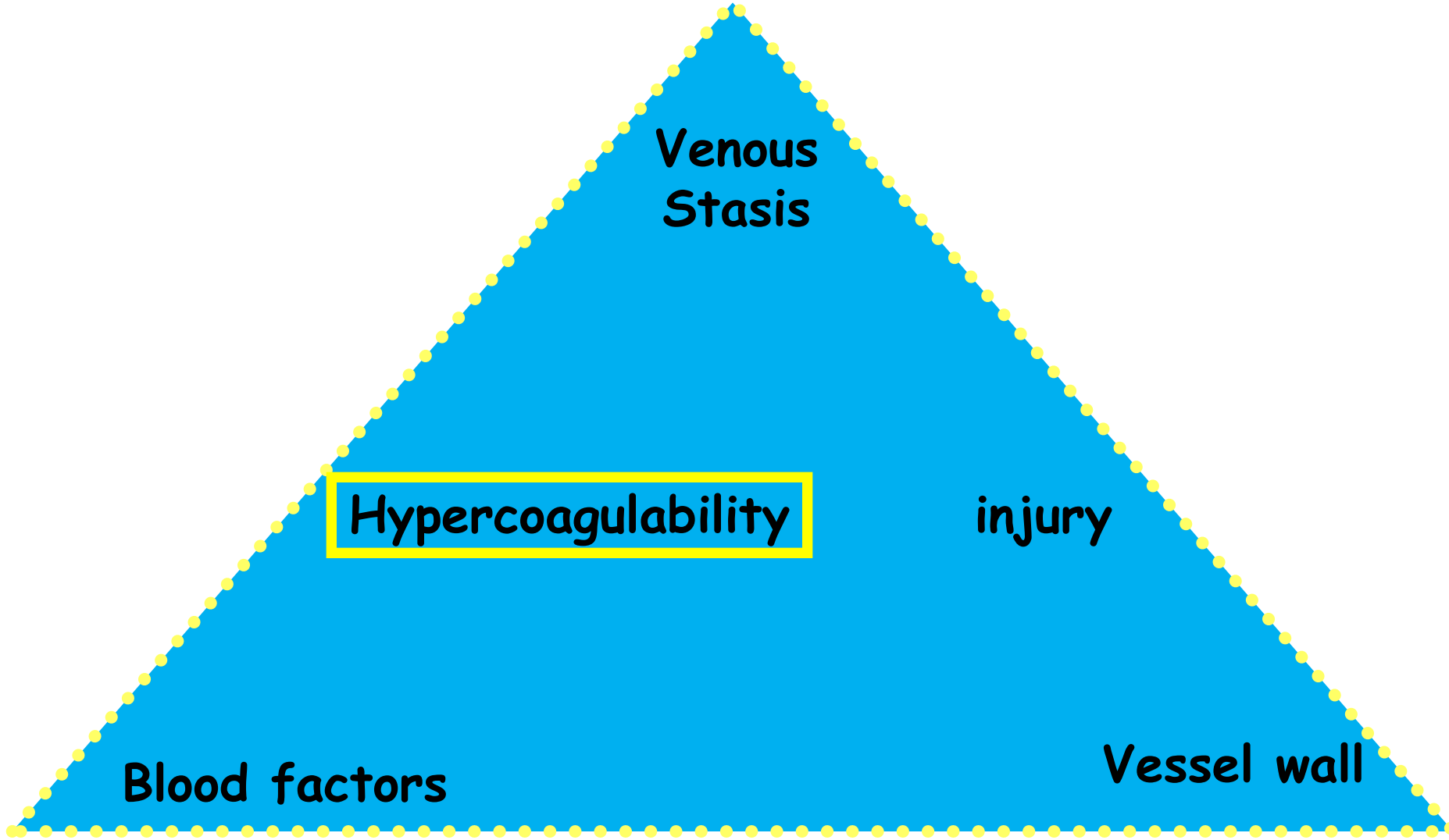


I have no potential conflict of interests



Defined by Virchow at 1856

Risk factors for DVT

- **Severe risk**

- Bone fractures (extremity or sacral)
- Sacral or knee prosthesis
- Severe surgical interventions
- Severe body injuries
- Spinal cord injuries

- **Intermediate risk**

- Arthroscopic knee surgery
- Central venous catheter
- Chemotherapy
- Congestive heart failure / respiratory insufficiency
- Hormone replacement therapies / oral contraceptives
- Malignancies
- Previous DVT
- Stroke
- Pregnancy / post pregnancy
- Thrombophilies

- **Mild risk**

- Bed rest > 3 days
- Resting during flights > 8 hours
- Aged
- Laporoscopic surgery
- Pregnancy and before labor
- Varicous veins

Anderson FA, Spencer F. Circulation. 2003;107: (23 suppl 1) 19-16

Hypercoagulability

- Primary
- Secondary

Primary hypercoagulability

1. Abnormal fibrin formation:

- Factor V Leiden mutation
- AT III deficiency
- Protein C and its cofactor Protein S deficiency
- Heparin kofactor II deficiency

2. Fibrinolitic system deficiencies:

- Plasminogen deficiency
- Plasminogen activator (PA) deficiency
- Plasminogen activator inhibitor (PAI) redundancy
- Alpha 2 antiplasmin deficiency
- Dysfibrinogenemi

3. Endothelial dysfunction:

- Homosystinuria
- Paroxysismal Nocturnal Hemoglobinuria (PNH)
- Lupus Anticoagulant

Secondary hypercoagulability

1. Coagulation and fibrinolitic system:

- Malignacies
- Pregnancy
- Nephrotic syndrome
- Oral CS (Estrogen)

2. Platalet count and function:

- Myeloproliferative disease
- DM
- Hyperlipidemia
- Heparine related thrombositopeni
- Anticardiolypin anticors

3. Vascular system:

- Venous Stasis
- Polysitemia Vera
- Sicle cell anemia
- Spherositosis
- Paraproteinemia
- Vasculitis
  - -infection
  - -radiation
  - -chronic occlusive vessel d.
  - -Behcet disease

Who develops DVT generally looks like this:

"over the age of 60, have a history of smoking, had recent surgery or a leg injury, and have been immobile for some time" = DVT

If a person under age 45 develops DVT

The reason can probably be found in their **genes**;

In about half of all young patients with DVT,
a family member has also had the condition.

The first thrombophilic disorder to be recognized was antithrombin (III) deficiency, described by Egeberg O. in a large Norwegian kindred in 1965.

Egeberg O. Inherited antithrombin deficiency causing thrombophilia. *Thromb Diath Haemorrh 1965;13:516–530*

Within the past decade, the identification of two mutations that are relatively prevalent among the white population;

the factor V Leiden and
prothrombin G20210A gene mutations

has paved the way for a number of large cohort studies that have greatly advanced our understanding of the pathogenesis of DVT.

Inherited thrombophilias may tip the balance in favor of thrombosis;

- partial deficiency of a regulatory anticoagulant protein;

  antithrombin,
  protein C,
  protein S

- dysfunction of an existing anticoagulant mechanism

  Activated protein C resistance

- "gain of function" mutations; elevated levels of procoagulants

  elevated prothrombin levels

Table 3. Genetic mutations

Reason for test	Significant abnormality	Factor V Leiden	Prothrombin 20210A	MTHFR*	Antithrombin	Protein C	Protein S	Homocysteine
All DVT	27/44 (61%)	10/44 (23%)	6/44 (14%)	6/44 (14%)	1/44 (2%)	3/44 (7%)	2/44 (5%)	4/44 (9%)
CVT only	5/12 (42%)	1/12 (8%)	0/12 (0%)	0/12 (0%)	0/12 (0%)	0/12 (0%)	0/12 (0%)	2/12 (17%)
SVT only	14/39 (36%)	5/39 (13%)	3/39 (8%)	1/39 (3%)	0/39 (0%)	1/39 (3%)	1/39 (3%)	4/39 (10%)
Recurrent DVT	5/9 (56%)	3/9 (33%)	1/9 (11%)	1/9 (11%)	0/9 (0%)	1/9 (11%)	3/9 (33%)	1/9 (11%)
History of DVT	41/73 (56%)	17/73 (23%)	9/73 (12%)	3/73 (4%)	1/73 (1%)	5/73 (7%)	1/73 (1%)	10/73 (14%)
History of PE	16/32 (50%)	3/32 (9%)	4/32 (13%)	2/32 (6%)	0/32 (0%)	1/32 (3%)	1/32 (3%)	5/32 (16%)
Family history of DVT	23/54 (43%)	11/54 (20%)	6/54 (11%)	2/54 (4%)	0/54 (0%)	1/54 (2%)	0/54 (0%)	5/54 (9%)
Any DVT/SVT with >1	18/18 (100%)	7/18 (39%)	6/18 (33%)	5/18 (28%)	1/18 (6%)	3/18 (17%)	5/18 (28%)	7/18 (39%)

* Homozygous only.

Risk factor	Prevalence in general population (white) (%)	Prevalence in patients with VTE (%)	Relative Risk for VTE
Factor V Leiden heterozygote	5.0[35]	20[29]	4.0–7.0[32,52]
Factor V Leiden homozygote	0.02[36]	1.5[36]	80.0[36]
Prothrombin G20210A heterozygote	0.7–4.0[37]	6[19]	2.8[19]
Factor V Leiden/prothrombin compound heterozygote	0.1[26]	2.2[26]	20.0[26]
Protein C deficiency[24,28,29,33]	0.2–0.4[39]	2.5–3[28,31]	3.4–7.8
Heterozygote			
Protein S deficiency heterozygote	0.03–0.13[25]	1–3[27]	2.4–20.0[27,30]
Antithrombin deficiency heterozygote	0.07–0.2[38,40]	0.5–3[31,34]	5.0–50.0[30,40]

[redacted] Estimated prevalence of Factor V Leiden among patients with thrombotic complications

Thrombotic complication	Prevalence (%)
First idiopathic VTE[3]	25
Recurrent VTE[40,42]	30–50
Upper extremity thrombosis[43–45]	9–20
Cerebral vein thrombosis[46,47]	10–20
Pregnancy-associated VTE[48–51]	20–46
Oral contraceptive-associated VTE[49,52]	20–60
Pregnancy loss[11,53–55]	8–30

Genet Med 2011:13(1):1–16.

Table 1 Worldwide prevalence of Factor V Leiden[a,b]

Population	Prevalence (%)[9–11,12–17]
European whites	3–15
Spain	3.3
France	3.8
Germany	4
Iceland	5.2
United Kingdom	8.8
Greece	15
Sweden	11
Africa	Absent
Southeast Asia	Absent
Asia minor	1.2
Australia (indigenous)	Absent
Japan	Absent
Jordanian Arabs	12.2
Lebanon	14
Western Iran	2.97
Canada	5.3
United States	
Whites	5.2
Hispanic Americans	2.2
African Americans	1.2
Asian Americans	0.45
Native Americans	1.25

[a]Healthy individuals with no history of venous thromboembolism.
[b]Includes heterozygous and homozygous individuals.

Genet Med 2011:13(1):1–16.

DVT is clearly a multigenic disorder, with well-characterized examples of gene-gene and gene-environment interactions underlying its pathogenesis.

Family History	Environmental Risk Factor	Genetic Risk Factor	Odds of DVT
-	-	-	1 (Reference)
+	-	-	2.5
-	+	-	9.5
-	-	+	2.3
-	+	+	21.2
+	+	-	16.4
+	-	+	6.3
+	+	+	64.1

http://blog.23andme.com/news/family-history-in-addition-to-genetic-and-environmental-risk-factors-predicts-risk-of-deep-vein-thrombosis/

Genetic risk assesment for DVT

1. How many genes are involved?

2. What are the contributions of known vs unknown genes?

3. Are specific gene-gene interactions synergistic, additive or overlapping functions with regard to DVT risk?

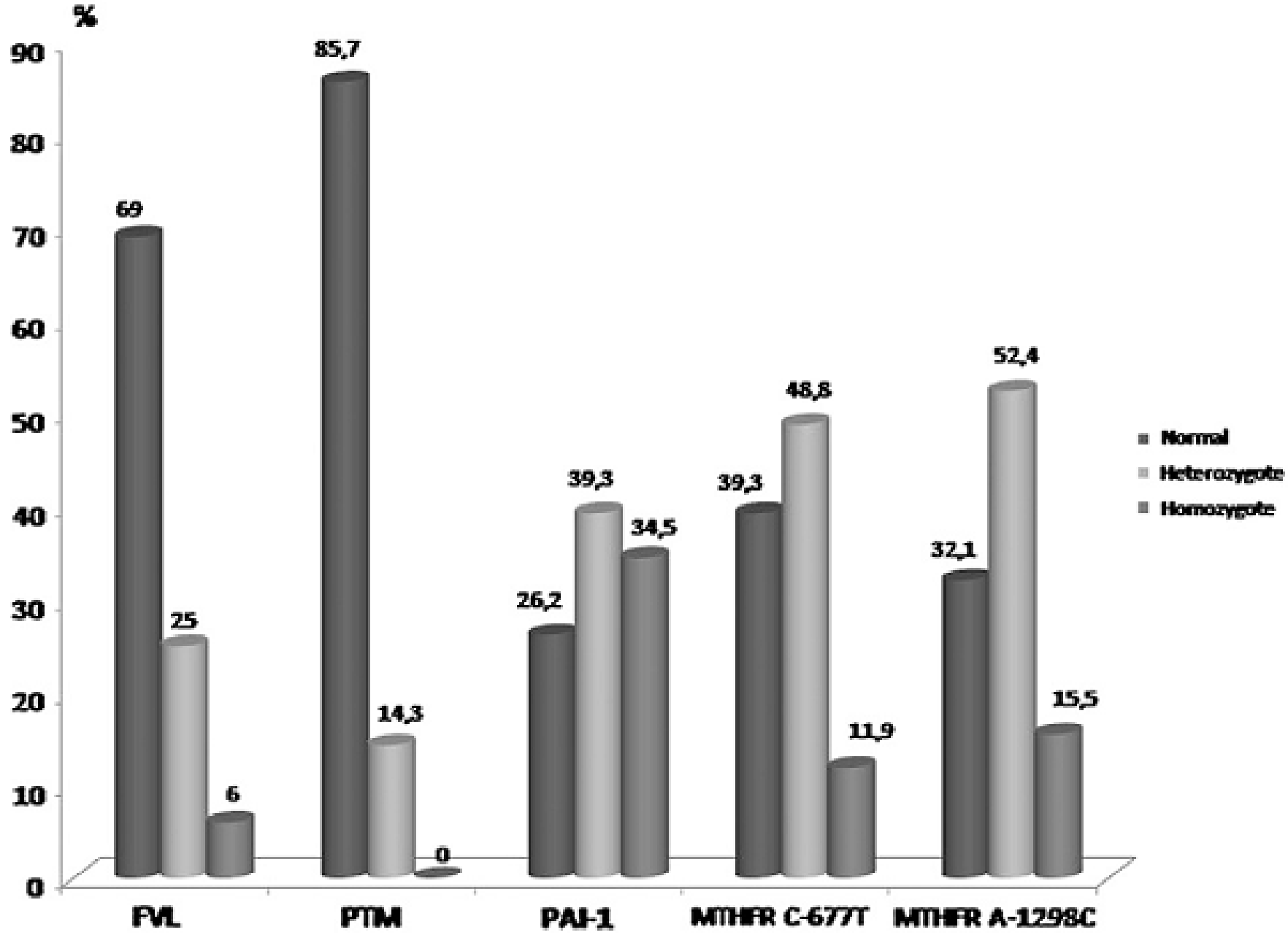
Combined genetic mutations have remarkable effect on deep venous thrombosis and/or pulmonary embolism occurence

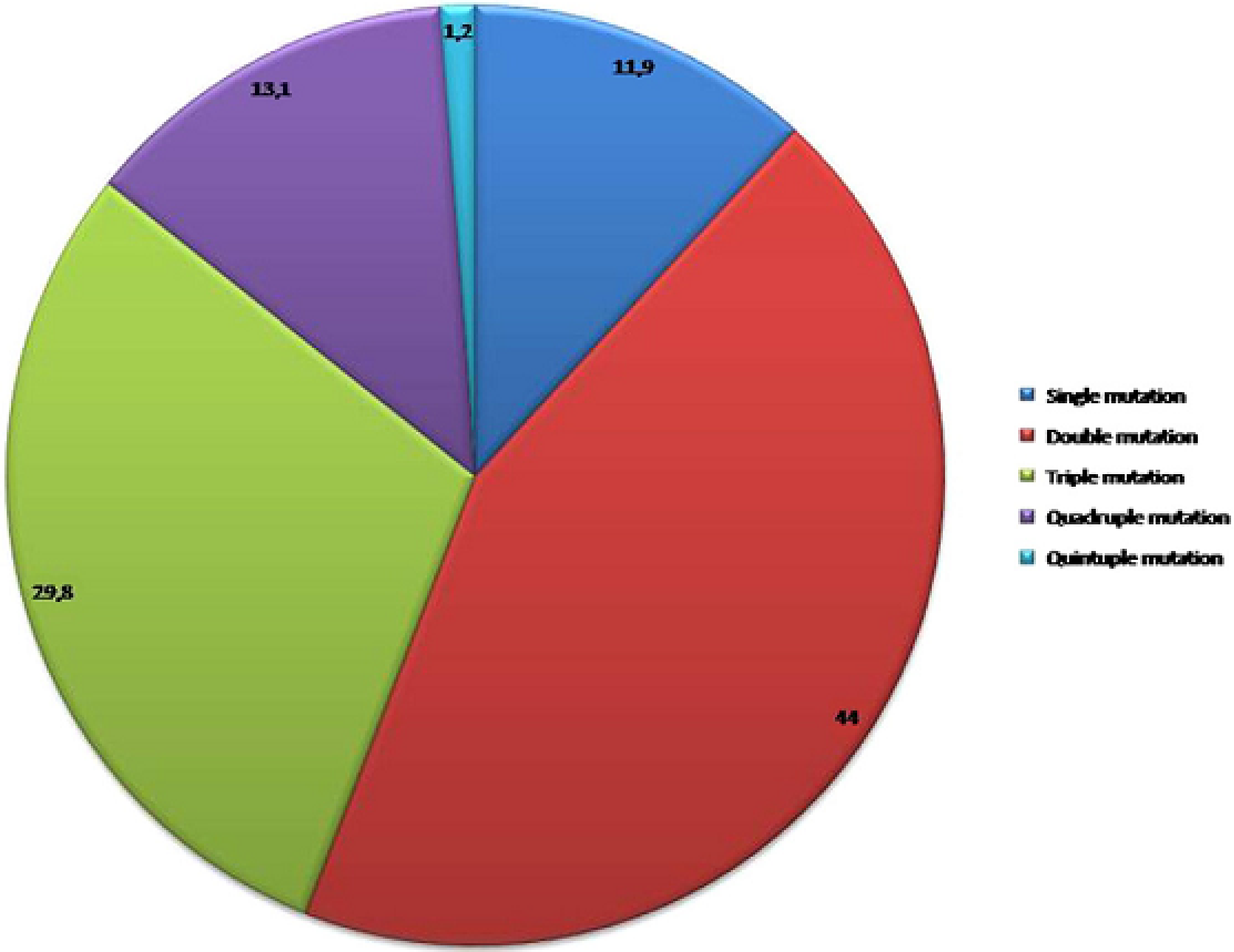
Erdal Simsek [a,*,1], Ahmet Yesilyurt [b,*,1], Ferda Pinarli [b], Nilnur Eyerci [b], A. Tulga Ulus [a]

Gene 536 (2014) 171–176

Methods: Between January 2011 and May 2013, patients who were traced for deep vein thrombosis and/or pulmonary embolism were evaluated retrospectively. 84 patients (53.6% males and 46.4% females) were included in the study. Their family histories, predisposing factors and treatments were researched. Factor V Leiden (G 1691A), Factor II G20210A, Plasminogen Activator Inhibitor-Type 1 (4G/5G), and Methylene Tetrahydrofolate Reductase (C677T, A1298C) mutations were investigated from peripheral venous blood.

Results: Among the genetic mutations we searched, the incidence of single mutation rate was observed at 11.9%, double mutation collocation at 44%, triple mutation collocation at 29.8%, quadruple mutation collocation at 13.1%, and finally, quintuplet mutation collocation at 1.2%. Our approximate mutation number was found as 2.47 ± 0.91.


%
90
80
70
60
50
40
30
20
10
0
69
25
6
85,7
14,3
0
26,2
39,3
34,5
39,3
48,8
11,9
32,1
52,4
15,5
FVL
PTM
PAI-1
MTHFR C-677T
MTHFR A-1298C
Normal
Heterozygote
Homozygote


1,2
11,9
13,1
29,8
44
Single mutation
Double mutation
Triple mutation
Quadruple mutation
Quintuple mutation

Conclusion: We observed that multiple mutations were high in number compared to single genetic mutations. The patients who have multiple mutations should be more in the front line considering their diagnosis, treatment and following up, and also in terms of decreasing mortality, morbidity and recurrence.

CONCLUSION

1. Idiopathic DVT has a strong genetic component and higher recurrence rate, representing multiple gene defects.

2. Improved DVT management will require:
   a. rapid genetic screening
   b. therapies with improved safety for chronic usage


ACADEM

J Thromb Haemost. 2018 December ; 16(12): 2432–2441. doi:10.1111/jth.14279.

Targeted sequencing to identify novel genetic risk factors for deep vein thrombosis: a study of 734 genes

H. G. DE HAAN[*], **A. VAN HYLCKAMA VLIEG**[*], **L. A. LOTTA**[†], **M. M. GORSKI**[†], **P. BUCCIARELLI**[†], **I. MARTINELLI**[†], **T. P. BAG LIN**[‡], **F. PEYVANDI**[†], **F. R. ROSENDAAL**[*], and **FOR THE INVENT CONSORTIUM**[1]

Conclusions: We confirmed associations between DVT and common variants in *F5, ABO, FGA–FGG,* and *CYP4V2–KLKB1–F11,* and observed secondary signals in *F5* and *CYP4V2–KLKB1–F11* that warrant replication and fine-mapping in larger studies.

Associations between common variants and first deep vein thrombosis ($P < 1.38 \times 10^{-5}$)

rsID	Chromosome	Position	Class	Gene	A1/A2	RAF	Discovery analysis OR (95% CI)	Discovery analysis P-value	Conditional analysis[#] OR (95% CI)[#]	Conditional analysis[#] P-value
rs7761110	1	169551183	Intronic	*F5*	C/A	0.774	1.54 (1.27–1.86)	1.07×10^{-5}	NA	NA
rs7761111	1	169551304	Intronic	*F5*	C/T	0.773	1.57 (1.29–1.91)	6.82×10^{-6}	NA	NA
rs7761113	1	169551307	Intronic	*F5*	G/A	0.770	1.55 (1.28–1.88)	8.59×10^{-6}	NA	NA
rs6672695	1	169551556	Intronic	*F5*	T/C	0.757	1.58 (1.29–1.92)	6.11×10^{-6}	NA	NA
rs6659	4	155557569	Missense	*FGA*	T/C	0.393	1.66 (1.37–2.02)	2.33×10^{-7}	NA	NA
rs2066865	4	155552276	Downstream	*FGA*	G/A	0.382	1.60 (1.33–1.92)	4.86×10^{-7}	1.36 (0.81–2.31)	0.245
rs1732482	4	187150654	Missense	*KLKB1*	G/A	0.573	1.55 (1.30–1.86)	1.27×10^{-6}	1.37 (1.08–1.64)	0.006
rs4253399	4	187180654	Intronic	*F11*	T/G	0.458	1.50 (1.25–1.79)	6.34×10^{-6}	1.16 (0.89–1.49)	0.246
rs2289257	4	187180852	Intronic	*F11*	A/C	0.545	1.44 (1.20–1.73)	6.71×10^{-5}	0.91 (0.62–1.35)	0.642
rs2036914	4	187190401	Intronic	*F11*	T/C	0.602	1.65 (1.38–1.97)	2.47×10^{-8}	NA	NA
rs8176719	9	136132908	Frameshift	*ABO*	T/TC	0.451	1.90 (1.61–2.24)	1.95×10^{-14}	NA	NA
rs579459	9	136133531	Intronic	*ABO*	C/A	0.504	1.51 (1.26–1.82)	3.67×10^{-6}	1.22 (0.88–1.41)	0.355

Genetic Risk Factors For VTE

Risk Factor	Prevalence (%) (+) VTE	Prevalence (%) Pop.	Relative Risk	Attributable Risk (%)
Protein C	2.1	0.3	7.1	1.8
Antithrombin	1.1	0.02	55	0.9
Protein S	2.2	0.2	11.2	2.0
PT 20210A	6.2	2.3	2.8	4.0
FV Leiden	20	4	6.0	16.7
Hyperhomo-cystinemia	10	4.8	2.2	4.0
Factor VIII	25	11	2.7	15.6

Antithrombin III, does a single gene make a large impact on relative risk. The more common defects have lower relative risk.