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A Case Control Study on the Contribution of Factor V-Leiden, Prothrombin G20210A, and MTHFR C677T Mutations to the Genetic Susceptibility of Deep Venous Thrombosis

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***Abstract. Background*: Insofar as the inherited prothrombotic single nucleotide polymorphisms (SNPs) factor V G1691A (FV-Leiden), prothrombin (PRT) G20210A, and methylenetetrahydrofolate reductase (MTHFR), C677T are inherited risk factors of venous thromboembolism (VTE), the aim of this study was to determine the prevalence of single and combined SNPs in 198 patients with documented deep venous thrombosis (DVT), and 697 control subjects, and to estimate the associated risks.**

***Methods*: Factor V-Leiden, PRT G20210A, and MTHFR C677T were analyzed by PCR and restriction fragment length polymorphism (RFLP).**

***Results*: The prevalence of the heterozygote and homozygous variants for FV-Leiden (52.02 vs. 14.78%, RR 6.28), PRT G20210A (19.2 vs. 3.6%; RR 6.38), and to a lesser extent the T/T genotype of MTHFR C677T (20.71 vs. 11.0%; RR 1.49) were higher among DVT patients vs. controls, respectively. Two or more SNPs were detected in 90 of 198 patients (45.5%) and in 60 of 697 controls (8.6%), with odds ratios of 16.754 for joint occurrence of FV-Leiden and PRT G20210A, 10.471 for FV-Leiden and MTHFR C677T, and 6.283 for PRT G20210A SNPs and MTHFR 677T/T. Logistic regression analysis showed a further increased odds for FV-Leiden in combination with PRT G20210A (85.198) or homozygous MTHFR C677T (81.133), and to a lesser extent for PRT G20210A in combination with homozygous MTHFR C677T (20.812).**

***Conclusions*: This indicates that FV-Leiden and PRT G20210A, more than MTHFR C677T, are important risk factors for DVT, and that the presence of more than one prothrombotic SNPs was associated with a significant risk of DVT.**

***Key Words.* Venous Thrombosis; Factor V-Leiden, Prothrombin G20210A; MTHFR C677T; PCR**

Introduction

Venous thromboembolism (VTE) is a multi-factorial disease, resulting from the interaction of genetic and environmental factors [1]. Among the inherited risk factors are single nucleotide polymorphisms (SNPs) in the genes coding for blood coagulation factors which induce either the synthesis of a defective protein, or the enhanced production of a procoagulant protein, and hence precipitate VTE events. The former mechanism is exemplified by the factor V gene G1691A SNP (FV-Leiden) which renders factor V resistant to activated protein C (APC) degradation [2]. The latter is exemplified by the prothrombin/factor II (PRT) G20210A, a SNP in the 3′-untranslated region of the PRT gene, which alters PRT mRNA stability, resulting in higher PRT levels. Both FV-Leiden and PRT G20210A SNPs are associated with heightened risk of VTE [3,4], and are relatively frequent among white/Caucasian populations [5], with a founder effect being suggested [6].

Methylenetetrahydrofolate reductase (MTHFR) catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, and plays a critical role in the homocysteine-to-methionine methylation. A reduction in MTHFR level or activity leads to hyperhomocysteinemia, characterized by increased plasma total homocysteine (Hcy) levels, and is often seen in patients with vascular diseases [7]. The C677T SNP in the MTHFR gene (A223V) results in a thermolabile enzyme and reduced enzymatic activity, and homozygotes (677 T/T) for this SNP were associated with a 50% reduction in the MTHFR activity. Whereas FV-Leiden or PRT G20210A polymorphism were considered risk factors for deep venous thrombosis (DVT), similar association between MTHFR C677T SNP and heightened risk of DVT was

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controversial, with some reports suggesting an association [8,9], while others indicated a weak [10] or no association [10,11] of MTHFR C677T with DVT. Furthermore, it was suggested that DVT was associated with hyperhocysteinemia, independent of MTHFR C677T [12–14].

Coinheritance of multiple genetic defects was significantly associated with increased risk of thrombosis [7], and the simultaneous occurrence of hereditary thrombophilias and/or prothrombotic polymorphisms was shown to substantially increase the risk of VTE [14–16]. This was highlighted by the findings that the co-presence FV-Leiden with PRT G20210A [17,18] increased the predicted risk of thrombotic events, since the odd ratios increased from 4.9 for FV-Leiden and 3.8 for PRT G20210A, to 20.0 for double heterozygotes [18]. Similarly, an increased risk of thrombosis was reported for FV-Leiden and hyperhocysteinemia, without necessarily involving the MTHFR C677T SNP [12,13]. Collectively, this indicated that the presence of more than one prothrombotic risk factor precipitates a substantial risk of VTE [19]. Here, we investigate the prevalence of the prothrombotic SNPs FV-Leiden, PRT G20210A, and MTHFR C677T, in 198 patients with idiopathic DVT, compared to 697 healthy subjects.

Subjects and Methods

Study group

The demographics of study participants are summarized in Table 1. The study consisted of 198 DVT patients comprising 84 males and 114 females (age, 38.2 ± 11.4 years). DVT was diagnosed according to Doppler ultrasound (continuous wave Doppler sonography), duplex scan (color flow duplex sonography), D-Dimer levels and phlebogram. Where DVT could not be confirmed by ultrasound, D-Dimer levels (determined by ELISA) were of great diagnostic value. A normal (but not high) D-Dimer level has a high negative predictive value, and thus excluded DVT diagnosis. Phlebogram was performed as a secondary diagnostic procedure, especially in calf vein thrombosis, where the results of ultrasound were not conclusive. As control, 697 healthy individuals comprising 299 males and 398 females (age, 33.4 ± 11.8 years) were included, and were matched to patients with regards to age ($p = 0.234$), gender ($p = 0.935$), and residence. Exclusion criteria included personal or family history of thrombosis, cardiovascular disease, and diabetes. All subjects were Lebanese, and represent the two major sectarian groups (Moslem:Christian ratio, 64:134 and 294:403 for patients and controls, respectively). Higher percentage of smokers was found among patients (29.3 vs. 20.9%; $p = 0.018$). All participants were asked to sign a consent form indicating their acceptance to participate in the study, which was conducted after all institutional ethics requirements were met. EDTA-anticoagulated blood (5 ml sample) was obtained from each participant, and was processed shortly thereafter.

Mutation analysis

PCR-restriction fragment length polymorphism (RFLP) analysis was used for the genotype analysis. A typical PCR comprised genomic DNA (50–200 ng), Taq DNA polymerase (2.5 U; Life Technologies, Paisley, UK), 1.0 mM $MgCl_2$, dNTP mixture (0.2 mM final concentration for each of dNTP; Promega), and 0.2 μM of sense and antisense oligonucleotide primers (Interactiva, Ulm, Germany), in a volume of 50 μl. PCR conditions consisted of an initial denaturation at 95°C for 3 min, followed by 36 cycles of denaturation (95°C for

Table 1. *Demographics of Study Participants*

Characteristic	Group	Patients	Controls	P^1	OR	95% CI
Number		198	697			
Gender	Males	84 (42.9)[2]	299 (42.4)	0.935	1.020	0.741–1.403
	Females	114 (57.6)	398 (57.1)			
Smokers		58 (29.3)	146 (20.9)	0.018	1.564	1.099–2.236
Religion	Moslems	64 (32.3)	294 (42.2)	0.014	1.527	1.094–2.132
	Christians	134 (67.7)	403 (57.8)			
Age groups	≤45 years	178 (89.9)	602 (86.4)	0.234	0.712	0.437–1.201
	>45 years	20 (10.1)	95 (13.6)			
Region	Beirut	82 (41.4)	281 (40.5)	0.845	1.047	0.761–1.443
	Mount Leb.	48 (24.2)	169 (24.4)	0.926	1.000	0.696–1.450
	South	25 (12.6)	88 (12.7)	0.904	1.000	0.632–1.622
	North	28 (14.1)	124 (17.9)	0.272	0.761	0.495–1.197
	Bekaa	11 (5.6)	27 (3.9)	0.403	1.460	0.737–3.033
	Others	4 (2.0)	4 (0.6)	0.139	3.572	0.956–13.298

[1]Pearson chi-square test.

[2]Percent of total within status.

30 sec), primer annealing (55°C for 30 sec), and extension (72°C for 45 sec), followed by final extension at 72°C for 5 min. Amplified PCR products were then digested with appropriate restriction enzyme for genotypic analysis: M*nl* I for FV-Leiden [2], H*ind* IIII for PRT G20210A mutation [4], and H*inf* I for MTHFR C677T mutation (all obtained from New England Biolabs; Madison, WI). Distinction between heterozygote, homozygote, and non carriers of these mutations was assessed by agarose gel electrophoresis, and evaluated by 2 individuals.

Statistical analysis

Allelic frequencies were calculated by gene-counting method. Linkage analysis, the non-random association between FV-Leiden, PRT G20210A, and MTHFR C677T, as defined by the delta (D') coefficient, was calculated using the HLAStat-2000 software. Multiple linear regression model was performed with the dependent variable being VTE and the independent variables were age, gender, smoking, and FV-Leiden, PRT G20210A, and MTHFR C677T, individually and in combination. Statistical analysis was performed using SPSS v. 12.0.1 statistics software which also calculated the odds ratios (OR) and 95% confidence intervals (CI). Statistical significance was set at $p < 0.05$.

Results

FV-Leiden and PRT G20210A genotype analysis

The frequency of FV-Leiden A allele (p 0.001, OR = 5.426), PRT G20210A allele ($p = 0.009$, OR = 2.1739), but not the MTHFR 677T allele ($p = 0.282$, OR = 1.2675) allele, were significantly higher among patients than controls (Table 2). Higher frequency of the G/A (44.4 vs. 13.8%; $p < 0.001$; O.R., 4.872) and the A/A (7.6 vs. 1.0%; $p < 0.001$; O.R., 7.473) FV-Leiden genotypes, the G/A (18.7 vs. 3.6%; $p < 0.001$; O.R., 6.472) PRT G20210A genotypes were seen among patients vs. controls, respectively (Table 2). While the prevalence of MTHFR 677C/T genotype was similar between patients and controls (38.1 vs. 38.7%; $p = 0.540$), higher prevalence of the 677T/T genotype (20.7 vs. 11.0%; $p < 0.001$; O.R., 4.872) were seen in patients respectively (Table 2). The genotypes distribution among controls was in Hardy-Weinberg equilibrium.

Linkage disequilibrium analysis

Linkage disequilibrium analysis, as defined by the delta (D') coefficient, was determined for FV-Leiden, PRT-G20210A, and MTHFR C677T. Linkage disequilibrium was seen for FV-Leiden **A** and PRT 20210**A** genotypes among patients (D', 0.0267; $p = 0.002$) and controls (D', 0.0104; $p < 0.001$) (Table 3). No significant linkage disequilibrium was noted among other loci (Table 3).

Combined inherited risk factors

The frequencies of combinations of homozygous MTHFR 677 T/T, FV-Leiden carriers (G/A + A/A), and PRT G20210A carriers (G/A + A/A) among DVT patients and controls were determined. In contrast to MTHFR 677T/T-only carriers ($p = 0.160$; OR, 1.571), higher frequencies of FV-Leiden-only

Table 2. *Factor V-Leiden, PRT-G20210A, and MTHFR C677T Allele and Genotype Analysis*

	Genotype frequency			Allele frequency	
FV-Leiden	G/G	G/A	A/A	G	A
Controls[1]	594 (85.2)[2]	96 (13.8)	7 (1.0)	0.9211 ± 0.072[3]	0.0789 ± 0.072
Patients[1]	95 (48.0)	88 (44.4)	15 (7.6)	0.7020 ± 0.023	0.2980 ± 0.023
P[4]	<0.001	<0.001	<0.001	<0.001	<0.001
R.R.[5]	0.165	4.872	7.473	0.1286	6.2251
PRT G20210A	G/G	G/A	A/A	G	A
Controls	672 (96.4)	25 (3.6)	0 (0.00)	0.9706 ± 0.045	0.0294 ± 0.045
Patients	160 (80.8)	37 (18.7)	1 (0.5)	0.9419 ± 0.012	0.0581 ± 0.012
P	<0.001	<0.001	0.59	1.000	0.009
R.R.	0.150	6.472	N/A	0.8550	2.1739
MTHFR C677T	C/C	C/T	T/T	C	T
Controls	350 (50.2)	270 (38.7)	77 (11.0)	0.6908 ± 0.012	0.3092 ± 0.012
Patients	80 (40.4)	77 (38.9)	41 (20.7)	0.6162 ± 0.024	0.3838 ± 0.024
P	<0.001	<0.001	0.59	0.002	0.282
O.R.	0.150	6.472	N/A	0.4859	1.2675

[1]Study subjects comprised 198 DVT patients and 697 healthy subjects (Controls).

[2]Number of individuals (percent of total) carrying the indicated genotype.

[3]Allele frequency ± SE.

[4]Pearson Chi square test.

[5]R.R. = relative risk, calculated according to Haldane method.

Table 3. *Linkage Analysis*[1]

		Patients			Controls		
Locus 1	Locus 2	D'	χ^2	p^2	D'	χ^2	p^2
FV-Leiden A	PRT G20210 A	0.0267	9.755	0.002	0.0104	36.08	<0.001
	MTHFR 677 T	0.0095	0.249	0.618	0.0009	0.032	0.8585
	MTHFR 677 C	−0.0183	0.603	0.4374	−0.0101	2.294	0.1299
FV-Leiden G	MTHFR 677 T	−0.0073	0.078	0.7802	−0.0325	3.479	0.0622
	MTHFR 677 C	−0.0006	<0.001	0.9838	0.0200	2.149	0.1426
PRT G20210 A	MTHFR 677 T	0.0081	0.793	0.3733	−0.0003	0.007	0.9330
	MTHFR 677 C	−0.0021	0.038	0.8452	−0.0012	0.073	0.7868

[1]Analyzed using HLA Stat2000 software.
[2]Determined by the Fisher's exact test.

($p = 0.001$; OR, 2.710) and PRT G20120A-only ($p = 0.048$; OR, 3.590) were seen among patients (Table 4). Significantly higher frequencies of FV-Leiden/PRT G20210A-only ($p < 0.001$; OR, 16.754), FV-Leiden/MTHFR 677T/T-only ($p < 0.001$; OR, 10.471), and PRT G20210A/MTHFR 677T/T-only ($p = 0.011$; OR, 6.283) carriers were seen among patients than controls (Table 4).

Age differences among VTE patients

In view of the high prevalence of FV-Leiden among VTE patients, the majority of whom were ≤45 years of age, we examined the age-dependent association of FV-Leiden with VTE. Higher carrier frequency of FV-Leiden was seen in younger (≤45 years) vs. older (>45 years) VTE patients (51.7 vs. 15.4%; $p = 0.011$; OR, 5.232) (Table 5). The carrier frequency

Table 4. *Combined Inherited Prothrombotic Risk Factors*

Condition	Controls	Patients	p^1	O.R.	95% C.I.
FV −ve; PRT −ve; MTHFR −ve	289 (86.3)[2]	46 (13.7)	<0.001		
FV +ve[3]; PRT −ve; MTHFR −ve	51 (69.9)	22 (30.1)	0.001	2.710	1.504–4.883
FV −ve; PRT +ve[a]; MTHFR −ve	7 (63.6)	4 (36.4)	0.048	3.590	1.011–12.749
FV −ve; PRT −ve; MTHFR +ve[4]	64 (80.0)	16 (20.0)	0.160	1.571	0.837–2.949
FV +ve; PRT +ve; MTHFR −ve	3 (27.3)	8 (72.7)	<0.001	16.754	4.288–65.464
FV +ve; PRT −ve; MTHFR +ve	9 (37.5)	15 (62.5)	<0.001	10.471	4.330–25.321
FV −ve; PRT +ve; MTHFR +ve	4 (50.0)	4 (50.0)	0.011	6.283	1.518–26.002
FV +ve; PRT +ve; MTHFR +ve	0 (0.0)	6 (100.0)	N/A	N/A	N/A

[1]Pearson chi-square.
[2]Percentage of individuals with the indicated genotype.
[3]Includes both heterozygous (G/A) and homozygous (A/A) genotype carriers.
[4]Includes only MTHFR 677 T/T (homozygous) genotype carriers.

Table 5. *Distribution of Factor V Mutation-Leiden*

Group	Age group	Non carrier	Carrier[1]	p^2	O.R. (95% C.I.)
		FV-Leiden			
Patients	≤45 years	71 (48.3)[3]	76 (51.7)		1.000
	> 45 years	11 (84.6)	2 (15.4)	0.011	5.232 (1.198–22.854)
Controls	≤45 years	498 (85.6)	84 14.4		1.000
	> 45 years	75 (83.3)	15 (16.7)	0.337	0.864 (0.518–1.441)
		PRT G20210A			
Patients	≤45 years	71 (86.6)	11 (13.4)		1.000
	> 45 years	11 (84.6)	2 (15.4)	0.564	0.872 (0.218–3.495)
Controls	≤45 years	498 (96.7)	17 (3.3)		1.000
	> 45 years	75 (94.9)	4 (5.1)	0.301	0.687 (0.278–1.701)

[1]Includes both heterozygote (G/A) and homozygote (A/A) carriers.
[2]Pearson chi-square test.
[3]Percent of total within subgroup of patients or control subjects.

of FV-Leiden was similar in both age groups among control subjects (14.4 vs. 16.7%; $p = 0.337$; OR, 0.864) (Table 5). In contrast to FV-Leiden, no age-dependent association was seen in the prevalence of PRT G20210A, since the carrier frequency of PRT G20210A was similar in younger and older VTE patients (13.4 vs. 15.4%; $p = 0.564$; OR, 0.872), and among control subjects (3.3 vs. 5.1%; $p = 0.301$; OR, 0.687) (Table 5).

Risk factors for VTE

Predictors of VTE were determined by performing stepwise logistic regression analysis, with the independent variables considered being: gender, age, smoking, FV-Leiden, PRT G20210A, and MTHFR 677T/T (individually and in combination) (Table 6). Adjusting for FV-Leiden, PRT G20210A, and MTHFR 677T/T, age was associated with VTE, where the odds of developing VTE was 5.5 times more among younger (≤45 years of age) as compared to older individuals (OR = 5.519, 95%CI: 2.156–14.129). Adjusting for age, gender, and smoking, FV-Leiden-only (OR = 10.418, 95%CI: 3.649–29.747) carriers were associated with increased odds of having VTE (Table 6). In addition, FV-Leiden/PRT G20210A-only (OR = 85.198, 95%CI: 12.273–591.445), FV-Leiden/MTHFR 677T/T-only (OR = 81.133, 95%CI: 23.716–277.555), and PRT G20210A/MTHFR 677T/T-only (OR = 20.812, 95%CI: 2.652–163.352) carriers were associated with highly significant increased odds of having VTE.

Discussion

In the present study, we investigated the association of FV-Leiden, PRT G20210A, and MTHFR C677T SNPs in DVT patients. FV-Leiden and PRT G20210A imparted a significantly higher risk for DVT than the MTHFR C677T SNP which, on its own did not constitute a significant risk factor unless combined with either FV-Leiden or PRT G20210A. This was reminiscent of earlier reports which documented the association of FV-Leiden and PRT G20210A [3,4], and the apparent lack or minor association of MTHFR C677T unless combined with another risk factor [20–22]. The high prevalence rate of FV-Leiden among otherwise healthy subjects in Lebanon confirm our previous data [5,23] and those of others [24], where FV-Leiden prevalence rates of 14% or higher were seen among healthy Lebanese.

Whereas younger patients are likely to develop secondary but not spontaneous/idiopathic VTE [25,26], results obtained indicated a marked increase in the prevalence of FV-Leiden among younger patients with idiopathic DVT (≤45 years of age), which was in accord with previous reports [27]. While these results were in agreement with studies that reported on increased relative risk in FV-Leiden carriers for recurrent VTE [28], but not with others which failed to demonstrate any such trend [29], although this conclusion needs re-evaluation in view of the (relatively) small sample size utilized in those studies.

The PRT G20210A SNP, by inducing high PRT levels, was described as a risk factor for DVT [4,30], and its carrier frequency of 3.6% among controls was is in agreement with the prevalence of 2.7% established earlier for healthy Lebanese [5]. It was significantly more common in DVT patients than in controls, accounting for a 6-fold risk, as shown here and elsewhere [20]. While it synergized with FV-Leiden (OR 3.590 → 16.754) and MTHFR 677T/T (OR 3.590 → 6.283) in increasing the odds of developing DVT [28], PRT G20210A constituted a significant risk of VTE on its own. This was apparently independent of the simultaneous coexistence of either FV-Leiden or homozygous variant of MTHFR C677T, as shown here and elsewhere [31]. However, after adjustming for gender, age, smoking, FV-Leiden and MTHFR 677T/T, the contribution of PRT G20210A became less significant. While explanation for this remains speculative, it is possible that factors other than FV-Leiden and MTHFR 677T/T cooperated with PRT G20210A SNP in increasing the odds of development

Table 6. *Logistic Regression Analysis*

Variable	*p*	O.R.	95% CI
Age Category[a]	<0.001	5.519	2.156–14.129
Gender[b]	0.398	0.719	0.335–1.544
Smoking[c]	0.312	1.532	0.670–3.503
Factor V only[d]	<0.001	10.418	3.649–29.747
PRT G20210A only[d]	0.838	0.007	
FV-Leiden[d] + PRT G20210A[d]	<0.001	85.198	12.273–591.445
FV-Leiden[d] + MTHFR 677 T/T	<0.001	81.133	23.716–277.555
PRT G20210A[d] + MTHFR 677 T/T	0.004	20.812	2.652–163.352

[a]Reference being individuals ≤45 years of age.

[b]Reference being males.

[c]Reference being non-smokers.

[d]Includes both heterozygous (G/A) and homozygous (A/A) genotype carriers.

of VTE. Collectively, this indicated that mutations that enhanced thrombin generation, including FV-Leiden [32] or PRT G20210A [32] were independent risk factors of VTE.

In contrast to FV-Leiden and PRT G20210A, MTHFR C677T SNP on its own was not significantly associated with DVT ($p = 0.160$; OR, 1.571), and the frequency of the mutant allele (T) was similar between patients and controls ($p = 0.282$; RR, 1.27), but apparently increased the odds of DVT development when present with either FV-Leiden or PRT G20210A. This was in agreement with previous studies which documented lack of difference in the T allele frequency between DVT patients and controls [22,33], thereby prompting the conclusion that homozygous MTHFR 677T/T variant is not a risk factor for DVT [20,21,34]. In spite of its lack of association with DVT, MTHFR 677T/T apparently increased the risk associated with FV-Leiden or with PRT G20210A [20].

This was in agreement with studies which suggested that MTHFR C677T is a risk factor for DVT only when combined with thrombophilia risk factors [21], including FV-Leiden [20], and in disagreement with other studies which indicated that MTHFR C677T is not a genetic risk factor for DVT, irrespective of FV-Leiden genotype [34], and that the incidence of VTE was comparable in patients with FV-Leiden and MTHFR 677 T/T genotype and those with only FV-Leiden mutation [22]. Furthermore, it was shown that the presence of the MTHFR C677T did not enhance the risk imparted by PRT G20210A [20]. While higher plasma Hcy levels were seen in MTHFR 677 T/T [patients, 19.56 ± 5.65 μmol/L; controls, 16.84 ± 5.10 μmol/L], but not C/T [patients, 11.47 ± 5.35 μmol/L; controls, 10.48 ± 5.01 μmol/L] carriers, no association was seen between plasma homocysteine levels and DVT (data not shown), in agreement with previous results [21].

To consolidate these findings, we estimated the attributed risks of DVT by a logistic regression model adjusting for age (younger or older than 45 years of age), smoking, and gender. Among patients with DVT only, carriers of one or more gene variants exhibited a significantly higher associated risk, and the highest risk was exerted by the combined presence of FV-Leiden and PRT G20210A (OR, 85.198). Patients carrying FV Leiden individually (OR, 10.418), and in combination with PRT G20210A (OR, 85.198), or homozygous MTHFR C677T (OR, 81.133), had a very high estimated odds, while the calculated odds in carriers of the PRT G20210A and homozygous MTHFR C677T (OR, 20.812), was notably lower. This was in agreement with previous reports documenting the synergistic interaction between FV-Leiden and other prothrombotic SNPs [35], and enhanced risk of VTE in FV-Leiden when associated with PRT G2010A [36,37], or homozygous MTHFR C677T [20].

VTE is a multifactorial disease in which inherited and acquired risk factors are involved [1]. It is noteworthy that the prevalence of inherited prothrombotic risk factors, and hence their association with thrombotic disorders, varies significantly in different populations. This was highlighted by the virtual absence of FV-Leiden and PRT G20210A from Africans, Orientals, and native Americans bearing neither FV-Leiden [38,39] nor PRT G20210A [40,41], and their high prevalence in Lebanon [5,23], and southern Sweden [42]. It remains to be seen whether carriers of inherited prothrombophilic risk factors are more likely to develop DVT, and is an important issue that deserves to be addressed.

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