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The Frequencies of Six Important Thrombophilic Mutations in a Population of the Czech Republic

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Summary

The primary aim was to determine frequencies of mutations related to risk of venous thrombosis in healthy Caucasians in Central Bohemia. In a cohort of 1527 healthy individuals the frequency of risk alleles for the mutations FV Leiden and FII 20210G>A was 4.5 % and 1.3 %, respectively. Frequency of 4G PAI-1 allele was 55.5 %. Genotype frequencies were: GG 91.03 %, GA 8.91 %, and AA 0.07 % for FV Leiden; GG 97.45 %, GA 2.49 %, and AA 0.07 % for FII 20210G>A; 4G/4G 30.26 %, 4G/5G 50.56 %, and 5G/5G 19.19 % for PAI-1. Frequency of the risk allele A in polymorphism SERPINC1 (IVS +141G >A) was 11.3 %, and frequencies of genotypes were as follows: GG 78.36 %, GA 20.66 %, and AA 0.98 %. Frequency of the risk allele T for polymorphism GP6 13254T>C was 87.7 %, and frequencies of genotypes were as follows: TT 77.14 %, TC 21.15 %, and CC 1.70 %. Frequency of the risk allele A in polymorphism CYP4V2 (Lys259Gln) was 65.2 %, and frequencies of genotypes were: CC 12.25 %, CA 45.12 %, and AA 42.63 %. All observed genotypes and alleles frequencies were without gender differences. Their occurrences confirm a relatively high prevalence of hereditary thrombophilia predisposition in the Czech Republic.

Key words

Hereditary thrombophilia • Genotypes • Allele • Frequencies • Czech Republic

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Introduction

Venous thromboembolism (VTE) is a multifactorial disorder (Rosendaal 1999) and it is a result of interaction between different environmental factors such as trauma, hormonal therapy, pregnancy, etc., and genetic factors (Margaglione *et al.* 2011). The largest meta-analytic study so far (Gohil *et al.* 2009), may be used when determining risk of venous thromboembolism related to genetic mutations. The analysis included 173 studies conducted in approximately 126,000 cases with VTE and 184,000 controls, in whom 28 polymorphisms in 21 genes related to venous thrombophilia were tested. Only FV Leiden (FVL), FII 20210G>A, and polymorphism of a gene for inhibitor of plasminogen activator PAI-1 4G/5G (SERPINE1) complied with the criteria for moderate risk of VTE, with odds ratio greater than 1.5 (Manolio 2010).

Results of genome-wide association studies (GWAS) have been published in the last three years, involving examinations of tens- to hundreds of thousands

of known single nucleotide polymorphisms (SNP) in cohorts containing several thousands of individuals who suffered from venous thrombosis, and healthy controls (Bezemer 2008). New examination technology called DNA microarray was used for this purpose (Manolio 2010).

The aim of our study was to determine frequency of the three already known thrombophilic mutations with clinically significant risk of VTE (FVL [Arg534Gln, rs6025] causing activated protein C resistance (Bertina *et al.* 1994), prothrombin F2 [20210G>A, rs1799963] associated with elevated plasma prothrombin levels (Poort *et al.* 1996), and PAI-1 /SERPINE1/ [4G/5G, rs1799889]) inhibiting the fibrinolysis activation (Eriksson *et al.* 1995) as well as of three other newly detected polymorphisms related to VTE that were established in GWAS, GP6 [Ser219Pro, rs1613662] encoding the receptor glycoprotein (GP) VI that has a major role in collagen-induced platelet signaling (Riba *et al.* 2005), SERPINC1 [IVS +141G>A, rs2227589] associated with mildly reduced antithrombin activity (de la Morena-Barrio *et al.* 2012), and cytochrome 450 (CYP) family gene CYP4V2 [Lys259Gln, rs13146272] which maps close to F11 gene coding for coagulation Factor XI level (Nakan *et al.* 2009) in a population of healthy, middle-aged individuals in the Czech Republic.

Methods

Selection of healthy population sample within the age group 18-60 years: 1,527 healthy individuals were randomly enrolled in the study; of those, 1,450 were anonymous blood donors at the Blood Bank of the General Faculty Hospital in Prague and 77 were healthy volunteers. All examinations were performed in scope of the project of the Ministry of Health, Czech Republic, No.: NT 11176-5, which has been approved by the ethics committee of the 1st Medical Faculty of the Charles University and General Faculty Hospital in Prague. All individuals were Europeans residing in Prague or the Central Bohemia region. Other demographic data regarding this cohort are presented in Table 1.

Genome DNA was extracted from their leukocytes in peripheral blood and isolated using the MagNA Pure LC Nucleic Acid Extraction system™ with the MagNA Pure DNA Isolation Kit I™. DNA was isolated according to the MagNA Pure High-Performance DNA Extraction™ protocol (all products supplied by Roche Diagnostics, Mannheim, Germany).

Table 1. Baseline characteristics of the study population.

Characteristic	
Caucasian origin – no. of the individuals (%)	1527 (100)
***Age**, years*	
Mean (SD)	35.1 (9.7)
Median	33.0
Interquartile range	28.0 - 41.0
***Weight**, kg*	
Mean (SD)	79.8 (14.3)
Median	80.0
Interquartile range	70.0 - 89.0
***Height**, cm*	
Mean (SD)	177.0 (9.0)
Median	177.0
Interquartile range	170.0 - 183.0
***Body mass index**, kg/m^2*	
Mean (SD)	25.5 (3.7)
Median	25.1
Interquartile range	22.8 - 27.7
***Male sex** – no. of the individuals (%)*	1008 (66.0)
***Female sex** – no. of the individuals (%)*	519 (34.0)
***Systolic blood pressure**, mm Hg*	
Mean (SD)	119.1 (10.9)
Median	120.0
Interquartile range	110.0 - 130.0
***Diastolic blood pressure**, mm Hg*	
Mean (SD)	75.4 (8.7)
Median	70.0
Interquartile range	70.0 - 80.0
***Blood groups** – no. of the individuals (%)*	
A	610 (40.8)
B	272 (18.2)
AB	106 (7.1)
0	495 (34.0)
***Smoking status** – no. of the individuals (%)*	
Smoker	353 (23.3)
Ex-smoker	28 (1.9)
Non-smoker	1135 (74.9)

Mutations were determined using PCR in a process called FRET (Fluorescence Resonance Energy Transfer). Tests were performed using the LightCycler® 480 System with LC® 480 Genotyping Master kits (all products supplied by Roche Diagnostics, Mannheim, Germany). Specific primers and fluorescently labelled probes were designed in cooperation with TIB MOLBIOL (Berlin, Germany), where they were custom made. Table 2

presents sequences of used primers and probes.

The chi square test was used to determine the deviation from Hardy-Weinberg equilibrium ($p>0.05$) and the differencies in genotypes and alleles between males and females. The Fisher exact test was used in case of low representation of homozygous mutations. Wald's method was used to calculate a 95 % confidence interval. The statistical program SAS, version 9.2 (SAS Institute, NC, USA) with tools for population genetics was used for calculations.

Table 2. The primers and probes used for thrombophilic polymorphisms investigation.

Factor V Leiden		
Primers	FVR	5'-TgCCCAgTgCTTAACAAgACCA-3'
	FVL	5'-CTTgAAggAAATgCCCCATTA-3'
Probes	Sensor wt	5'-ggCgAggAATACAggTAT-FL-3'
	FV Anchor	5'-LCRed640-TgTCCTTgAAgTAACCTTTCAgAAATTCTg-PH-3
Factor II 20210G>A		
Primers	F2F	5'-CCgCTggTATCAAATggg-3'
	F2R	5'-CCAgTAgTATTACTggCTCTTCCTg-3'
Probes	F2 wt	5'-CTCAgCgAgCCTCAATg-FL-3'
	F2 640	5'-LCRed640- TCCCAgTgCTATTCATgggC-PH-3'
SERPINE1 (PAI-1) 4G/5G		
Primers	PAI-1 F	5'-AgCCAgACAAggTTgTTgACAC-3'
	PAI-1 R	5'-CAgAggACTCTTggTCTTTCCC-3'
Probes	PAI-1 Probe	5'-TgACTCCCCCACgTgTCC-FL-3'
	PAI-1 Anchor	5'-LCRed640-CCTgCTACCgAggAAggTgg-PH-3'
GP6 rs1613662		
Primers	GP6_F	5'-CAAATCTgTgAAAgAACCAACT-3'
	GP6_A	5'-gATTTCCCAggAACCTCTgT-3'
Probes	rs1613662_Anc	5'-gCACCAgAATggACCCTgCAgAACCT-FL–3'
	rs1613662_[A]	5'-LCRed640-CCTgCTACCgAggAAggTgg-PH-3'
SERPINC1 (antithrombin) rs2227589		
Primers	rs2227589 F	5'-ggATgACATCCCCCTTgT-3'
	rs2227589 R	5'-CTCCAAAggACTCACAggAAT-3'
Probes	rs2227589 C	5'-gCACTTgAAATgACgTCTTCC-FL-3'
	Anc rs2227589	5'-LCRed640-AACAggTCTTTgACTgTAACTACCAgggA-PH-3'
CYP4V2 rs13146272		
Primers	rs13146272 S	5'-ggCTTgATCTCTggTACCTTATgTTT-3'
	rs13146272 A	5'-CATCgTgAATgCACTTAATACCACC-3'
Probes	rs13146272 C	5'-AAAgAgCCTTCAgATCCTACATACTT-FL-3'
	Anc rs13146272	5'-LCRed640-ACCAACAgTgTAAgTCCCTgACTTTTACAA-PH-3'

Results

Determined genotypes and frequencies of the alleles FVL, FII 20210G>A, PAI-1 4G/5G, *GP6* (Ser219Pro, rs1613662), SERPINC1 (IVS +141G>A, rs2227589), and CYP4V2 (Lys259Gln, rs13146272) in the whole population and then separately in females and males are presented in Table 3, 4 and 5. All results met the criteria of Hardy-Weinberg equilibrium. There was no gender difference ($p <0.05$) between these frequencies.

Table 3. The prevalence of genotypes and alleles frequencies in a population of healthy individuals in the Czech Republic.

Chromo-zome	Gene	SNP	dbSNP ID	Genotype (%) (n = 1527)			Risk allele	Allele frequency (95 % confidence interval)		HWE
								p	q	
1q23	F5 (Leiden)	Arg534Gln	rs6025	GG 91.03	GA 8.91	AA 0.07	A	G = 0.955 (0.947-0.962)	A = 0.045 (0.038-0.053)	P = 0.3564
11p11-12q	F2	20210G>A	rs1799963	GG 97.45	GA 2.49	AA 0.07	A	G = 0.987 (0.982-0.991)	A = 0.013 (0.009-0.018)	P = 0.2325
7q21.3-q22	SERPINE1	4G/5G	rs1799889	5G5G 18.97	5G4G 50.34	4G4G 30.69	4G	4G = 0.555 (0.540-0.574)	5G = 0.445 (0.426-0.460)	P = 0.3550
19q13.4	GP6	Ser219Pro	rs1613662	TT 77.14	TC 21.15	CC 1.70	T	T = 0.877 (0.866-0.889)	C = 0.123 (0.111-0.134)	P = 0.4794
1q23-q25.1	SERPINC1	IVS +141G>A	rs2227589	GG 78.36	GA 20.66	AA 0.98	A	G = 0.887 (0.875-0.898)	A = 0.113 (0.102-0.125)	P = 0.2494
4q35.2	CYP4V2	Lys259Gln	rs13146272	AA 42.63	AC 45.12	CC 12.25	A	A = 0.652 (0.635-0.669)	C = 0.348 (0.331-0.365)	P = 0.8214

Table 4. The prevalence of genotypes and alleles frequencies in a population of healthy males in the Czech Republic.

Males								
Gene	SNP	dbSNP ID	Genotype (%) (n = 1008)			Allele frequency (95 % confidence interval)		HWE
						p	q	
F5 (Leiden)	Arg534Gln	rs6025	GG 91.07	GA 8.83	AA 0.10	G = 0.955 (0.945-0.964)	A = 0.045 (0.036-0.055)	P = 0.7183
F2	20210G>A	rs1799963	GG 97.52	GA 2.48	AA 0.00	G = 0.988 (0.983-0.992)	A = 0.012 (0.008-0.017)	P = 1.0000
SERPINE1	4G/5G	rs1799889	5G5G 19.15	5G4G 50.69	4G4G 30.16	4G = 0.555 (0.534-0.576)	5G = 0.445 (0.424-0.466)	P = 0.4031
GP6	Ser219Pro	rs1613662	TT 76.19	TC 21.53	CC 2.28	T = 0.870 (0.855-0.884)	C = 0.131 (0.116-0.145)	P = 0.1046
SERPINC1	IVS +141G>A	rs2227589	GG 77.73	GA 21.17	AA 1.09	G = 0.883 (0.870-0.897)	A = 0.117 (0.103-0.130)	P = 0.4051
CYP4V2	Lys259Gln	rs13146272	AA 41.47	AC 45.44	CC 13.10	A = 0.642 (0.621-0.663)	C = 0.358 (0.337-0.380)	P = 0.7101

Table 5. The prevalence of genotypes and alleles frequencies in a population of healthy females in the Czech Republic.

Females								
Gene	SNP	dbSNP ID	Genotype (%) (n = 519)			Allele frequency (95 % confidence interval)		HWE
						p	q	
F5 (Leiden)	Arg534Gln	rs6025	GG 90.94	GA 9.06	AA 0.00	G = 0.955 (0.942-0.966)	A = 0.045 (0.034-0.058)	P = 0.6247
F2	20210G>A	rs1799963	GG 97.30	GA 2.50	AA 0.19	G = 0.986 (0.978-0.993)	A = 0.015 (0.007-0.022)	P = 0.0950
SERPINE1	4G/5G	rs1799889	5G5G 19.27	5G4G 50.29	4G4G 30.44	4G = 0.556 (0.529-0.589)	5G = 0.444 (0.411-0.471)	P = 0.6734
GP6	Ser219Pro	rs1613662	TT 79.00	TC 20.42	CC 0.58	T = 0.892 (0.874-0.911)	C = 0.108 (0.089-0.126)	P = 0.1653
SERPINC1	IVS +141G>A	rs2227589	GG 79.58	GA 19.65	AA 0.77	G = 0.894 (0.877-0.912)	A = 0.106 (0.088-0.123)	P = 0.3969
CYP4V2	Lys259Gln	rs13146272	AA 44.89	AC 44.51	CC 10.60	A = 0.672 (0.642-0.701)	C = 0.329 (0.299-0.358)	P = 0.8404

Discussion

It is well known that prevalence of FVL and FII 20210G>A mutations in a population is mainly established by ethnic origin. A large epidemiologic study conducted in the USA presented a 5.27 % incidence of heterozygous FVL mutation in European individuals, 2.21 % in Latinos, 1.23 % in Afro-Americans, 1.25 % in American Indians, and only 0.45 % in Asians. Similarly, low or zero incidence of the FII 20210G>A mutation was found in non-European population (Ridker *et al.* 1997). European incidence of FVL heterozygotes varies between 2-15 % (Lucotte *et al.* 2001), and between 1-5 % in the case of FII 20210G>A (Bertina 1998). Relatively high differences in various European regions are probably due to past migration of population. FVL heterozygotes have prevalence of 4 % in the Slovak Republic and thus similar composition to the Czech Republic's population can be assumed (Honzak 1999). Germany has 7.8 % prevalence of FVL, and 3.5 % of FII 20210G>A heterozygotes (Hoppe *et al.* 2006). In the north-south axis, an uneven geographic incidence of FVL should be expected (Schwender 1997). If a more appropriate epidemiologic parameter – the frequency of mutated alleles – is used, the ranges are 1.6-4 % for *F5* 1691A allele, and 1 % for *F2* 20210A allele in the neighbouring states (Renner *et al.* 2000, Adler *et al.* 2010). The first data regarding FVL mutation prevalence in healthy population of the Czech Republic were presented in 1998 with a prevalence of heterozygotes of 6.5 % (8.2 % of females and 4.92 % of males) and a total frequency of mutated allele 4.1 % (Matyskova *et al.* 1999). In 1999, the first data on FII 20210G>A mutation in the Czech population were presented by Hrachovinova *et al.* (1999) with a prevalence of heterozygotes of 3.4 %. Incidence of the homozygous PAI-1 4G/4G mutation is rather high in the European population. For example, in Germany the distribution of 4G/4G homozygotes is 29.4 %, 4G/5G heterozygotes 48.2 %, and wild type genotype 5G/5G 22.3 %, with frequency of the variant allele 4G up to 57.6 % (Hoppe *et al.* 2006). Data on prevalence of PAI-1 polymorphism in the Czech Republic were published in two studies so far. Buckova *et al.* (2002) presented the following genotype frequencies in healthy individuals: PAI-1 4G/4G 28.5 %, PAI-1 4G/5G 44.6 %, and PAI-1 5G/5G 26.9 %. Hubacek *et al.* (2010) observed the incidence of 4G/4G, 4G/5G and 5G/5G genotypes in 29.7 %, 49.7 %, and 20.6 % of healthy males and in 31.8 %, 46.6 % and 21.6 % of females, respectively. Our data suggest that prevalence of FVL as well as FII 20210G>A and PAI-1 in healthy individuals in Prague and Central Bohemian regions does not differ significantly from that in neighbouring Germany and Austria. FVL prevalence, however, seems to be somewhat lower in the Slovak Republic and in Poland. Lower FVL prevalence in healthy population (3.5 % heterozygotes) was detected even farther east, in Ukraine (Tatarskyy *et al.* 2010). The PAI-1, however, is an acute phase protein, and, apart from the influence of this mutation, its synthesis is affected by other factors that include the activity of a variety of hormones, cytokines (IL-1 beta, TNF-alpha, or IL-6), and the time of day (Kruithof 2008).

According to GWAS, the additional three polymorphisms associated with venous thrombosis have a rather low odds ratio. Antithrombin gene polymorphism (SERPINC1, IVS +141G>A, rs2227589) is related to a very small increase in risk of venous thromboembolism (estimated odds ratios for minor allele A were 1.42, 1.24, and 1.29, respectively, in case-control studies LETS, MEGA-1, and MEGA-2) (Bezemer *et al.* 2008). But other case-control studies, however, did not confirm this correlation (Austin *et al.* 2011). The presence of risk allele A is related to mild prothrombogenic functional defect in its carriers – lower inhibition of F Xa (genotype AA 94.6±8.4 %) and concentration of antithrombin (AA 94.8±5.6 %) than in individuals with genotype GG (97.0±7.3 % and 99.5±5.8 respectively). Frequency of SERPINC1 IVS +141G>A genotype was 80.5 % GG, 18.1 % GA, and 1.3 % AA, with frequency of allele A 12 % in healthy individuals of European origin in Spain (Antón *et al.* 2009). The MEGA-2 study in Netherlands presented the following rates: 82 % GG, 17 % GA, and 1 % AA, with frequency of allele A 11 % (Bezemer *et al.* 2008). Frequency of the minor allele in healthy American Caucasians was determined to be 11 %, with frequency of genotype CC 79.82 %, CT 19.13 %, and TT 1.05 % (Watkins *et al.* 2006). Our study detected similar frequency (11.3 %) of the minor risk allele A. The platelet receptor for collagen glycoprotein VI (*GP6*) is found in human thrombocytes and megakaryocytes, but not in other human cells (Clemetson *et al.* 1999). Functional differences were described between the incidence of major (a) and minor (b) haplotype that encodes isoforms of GP6 with amino acids SKTQH or PEALN at sites 219, 237, 249, 317, and 322 (mutations GP6 655T>C, 709A>G, 745A>G, 950A>T, and 964C>A, respectively) (Takagi *et al.* 2002). Incidence of minor

allele *GP6* (haplotype b) or its representative GP6 mutation 655T>C (Ser219Pro, 13254T>C, rs1613662) was investigated mainly in relation to atherothrombosis or myocardial infarction, however, with contradictory findings (Croft *et al.* 2001, Bray *et al.* 2007, Motovska *et al.* 2010). However, another large study, SMILE (Snoep *et al.* 2010), did not confirm the correlation of GP6 mutation with heart attack, recurrence of cardiovascular events, or a higher mortality. According to *in vitro* tests, a minor variant of GP6 results in reduction of platelet reactivity with the agonist (collagen); this was attributed to lower expression of this receptor on platelet surface (Joutsi-Korhonen *et al.* 2003) and to functional defect on the level of constitutionally activated Src-tyrosine kinase Fyn/Lyn in immunoreceptor tyrosine-based activation motif (ITAM) (Trifiro *et al.* 2009). GWAS also described a somewhat protective effect of the *GP6* 13254T>C mutation (specifically, its haplotype b) in regard of venous thromboembolism incidence, with odds ratio 0.80-0.87 (Tregouet *et al.* 2009). Risk of venous thromboembolism should be related to incidence of the major haplotype a and allele T (odds ratio 1.36-1.5). However, this assumption was not confirmed by a repeated case-control study conducted by Austin *et al.* (2011) in Americans of European origin, where the odds ratio for this major allele was only 1.04. Watkins *et al.* (2006) determined the incidence of T allele as 85 %, and C allele as 15 % in Europeans. Caucasian Americans had similar frequency of the major allele (84 %), with genotype frequency TT 71.04 %, TC 29.40 %, and CC 2.56 %. Our study in healthy Czech corresponds with frequencies in European population, with slight dominance of the major allele and lower frequency of the minor allele.

Third polymorphism – CYP4V2 rs13146272 (Lys259Gln, substitution of alleles A>C) – is also associated with the risk of venous thromboembolism. So far, however, there is no known association of this gene with blood coagulation or function of platelets. Previously known mutations of CYP4V2 result in metabolic disorder of fatty acids called the Bietti progressive crystal dystrophy of the cornea and retina (Li *et al.* 2004). Three association studies (Bezemer *et al.* 2008, Tregouet *et al.* 2009, Austin *et al.* 2011) confirmed that minor allele C of the new gene polymorphism CYP4V2 registered in the SNP database as rs13146272 (Lys259Gln) is found in smaller number of individuals with venous thrombosis than in the control population. The major allele A is considered a risk of venous thrombosis, with odds ratio 1.24. It can be related to the activity of coagulation factor XI with its gene located close to gene CYP4V2 (Morange *et al.* 2011). Li *et al.* (2009) in a wide haplotype study confirmed that two polymorphisms of the gene *F 11* rs2289252 and rs2036914 related to higher level of FXI are also present in haplotypes that contain risk allele A of polymorphism CYP4V2 rs13146272. Thus, the mutation CYP4V2 (Lys259Gln) is only a marker for higher risk in development of VTE. Control population samples containing European individuals without venous thromboembolism detected following frequencies of the major allele A (rs13146272 CYP4V2): in Dutch individuals 64-65 %, with frequency of the minor allele 35-36 %, and genotype frequency (MEGA-2 study) CC 13 %, CA 45 %, and AA 42 %; in French individuals 63-67 % frequency of the risk allele A, and 33-37 % frequency of the minor allele C (odds ratio 0.84); in Caucasian Americans 62 % frequency of the allele A and 38 % frequency of the allele C, with genotype incidence CC 15.43 %, CA 45.84 %, and AA 38.73 % (Bezemer *et al.* 2008, Tregouet *et al.* 2009, Austin *et al.* 2011). In our population, the following results were obtained: frequency of the major risk allele A was 65.2 %; frequency of the minor allele C was 34.8 %; genotype frequency of CC was 12.25 %, of CA 45.12 %, and of AA 42.63 %. These results are very similar to those in other monitored European populations.

Conclusions

The data presented in our study showed in healthy Czech population a prevalence of well known thrombophilia mutations, conferring a moderate risk of thrombosis, Factor V Leiden and Factor II 20210G>A of 4.5 % and 1.3 %, respectively. These figures are comparable with data from other countries in the Central European region. In accordance with published results we found a high prevalence of polymorphisms of PAI-1 as well as of the three novel susceptibility genes for VTE (GP6, SERPINEC1 and CYP4V2), suggesting these polymorphisms to confer only a modest increase in the risk of VTE. The risk is probably increased in individuals with concurrent presence of several these polymorphisms. The clinical importance of their laboratory detection, however, should be documented by future studies in subjects with VTE.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

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Abbreviations

SNP – single nucleotide polymorphism; dbSNP ID – database of SNPs identification; rs – reference SNP ID; p – "major"allele frequency; q – "minor"allele frequency; HWE – Hardy-Weinberg equilibrium; F5 – coagulation factor V, FV; FVL – Factor V Leiden; F2 – coagulation factor II, FII, prothrombin; PAI-1 – plasminogen activator inhibitor type 1; F11 – coagulation factor XI, FXI; SERPINE1 – serpin peptidase inhibitor, clade E (plasminogen activator inhibitor type 1, PAI-1), member 1; SERPINC1 – serpin peptidase inhibitor, clade C (antithrombin), member 1; GP6 – glycoprotein VI; CYP4V2 – cytochrome P450, family 4, subfamily V, polypeptide 2; PCR – Polymerase Chain Reaction; VTE – venous thromboembolism; OR – odds ratio; GWAS – genome wide association study; LD – linkage disequilibrium; SMILE – Study of Myocardial Infarctions in Leiden.

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