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An Arab selective gradient in the distribution of factor V G1691A (Leiden), prothrombin G20210A, and methylenetetrahydrofolate reductase (MTHFR) C677T

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Venous thrombosis (VTE) is a multi-factorial disease resulting from the interaction of genetic and environmental risk factors. Among the inherited factors are factor V (FV) G1691A (FV Leiden) [1], prothrombin (PRT) G20210A [2], and methylenetetrahydrofolate reductase (MTHFR) C677T [3] single nucleotide polymorphisms (SNPs). In FV Leiden, an arginine is substituted by glutamine at amino acid residue 506, which renders FVa resistant to degradation by activated protein C [1]. The PRT G20210A SNP, a G to A transition in the 3′ untranslated region of the PRT gene, is associated with increased PRT levels [2]. While both FV Leiden and G20210A SNPs are present at varying rates in Caucasians [4], and are virtually absent from Africans and Asians [5], the MTHFR C677T is found in many populations with a marked heterogeneity in its distribution, exemplified by its low incidence in Africa and Indian subcontinent [6], and higher rates in North America, Europe [7], and Japan. Insofar as the incidence of FV Leiden, PRT G20210A, and MTHFR C677T SNPs among Arabs is poorly defined, we assessed the incidence of these three SNPs in four distinct Arab communities: Lebanon, Tunisia, Bahrain, and Saudi Arabia.

Study subjects comprised 698 Lebanese (288 males and 410 females), 313 Tunisian (129 males and 184 females), 193 Bahraini (150 males and 43 females), and 149 Saudi (69 males and 80 females) healthy subjects. Genotyping was carried out by PCR-RFLP analysis using *Mnl*I, *Hin*dIII, and *Hinf*I digestion for detecting FV Leiden, PRT G20210A and MTHFR C677T, respectively. Allele frequencies were determined using the gene counting method, and Wright's F_{ST} calculations were made using GENALEX software. Additional statistical was performed with SPSS version 12.0.1.

The distribution of the three SNPs genotypes was in Hardy–Weinberg equilibrium. The frequencies of FV Leiden (A) and PRT G20210A mutant (A) alleles, together with the G/A and A/A genotypes of FV Leiden, were highest among Lebanese, while Tunisians, Bahraini and Saudi Arabian participants had lower frequencies (Table 1). Higher incidence of FV Leiden was seen among Lebanese compared with other populations ($P < 0.001$), while the difference between Tunisians and Bahraini ($P = 0.157$) or Saudi ($P = 0.073$) subjects was not different. All PRT G20210A SNP carriers were in the heterozygous state (G/A); no PRT G20210A SNP carrier was found among Saudi participants (Table 1). With the exception of Lebanese–Saudi ($P = 0.038$), the distribution of PRT G20210A was similar among study communities. The distribution of the C677T alleles varied; high incidence of the T allele and the T/T genotype was found in Lebanon and Tunisia, and lower rates among Saudi and Bahraini subjects (Table 1). While the incidence of T/T genotype was similar between Lebanese and Tunisian ($P = 0.542$), and Saudi and Bahraini ($P = 0.470$) subjects, higher incidence of T/T genotype was seen among Lebanese vs. Bahraini ($P < 0.001$) and Saudi ($P = 0.014$), and between Tunisian and Bahraini ($P = 0.005$) subjects.

Table 1 Factor V Leiden and PTR G20210A genotype and allele distribution

	Genotype			Allele	
	G/G	G/A	A/A	G	A
FV Leiden					
Lebanese*	85.2†	13.8	1.0	0.92 ± 0.01‡	0.08 ± 0.01
Tunisian*	93.6	5.8	0.6	0.96 ± 0.01	0.04 ± 0.01
Bahraini*	96.9	3.1	0.0	0.98 ± 0.01	0.02 ± 0.01
Saudi Arabian*	98.0	2.0	0.0	0.99 ± 0.01	0.01 ± 0.00
PRT G20210A					
Lebanese*	96.4†	3.6	0.0	0.99 ± 0.00‡	0.01 ± 0.00
Tunisian*	97.4	2.6	0.0	0.99 ± 0.00	0.01 ± 0.00
Bahraini*	99.0	1.0	0.0	0.99 ± 0.00	0.01 ± 0.00
Saudi Arabian*	98.0	0.0	0.0	0.98 ± 0.01	0.02 ± 0.01
	C/C	C/T	T/T	C	T
MTHFR C677T					
Lebanese*	50.2†	38.7	11.0	0.70 ± 0.01‡	0.30 ± 0.01
Tunisian§	50.8	40.1	9.1	0.71 ± 0.02	0.29 ± 0.02
Bahraini*	77.0	20.9	2.1	0.87 ± 0.02	0.13 ± 0.02
Saudi Arabian*	74.5	21.5	4.0	0.85 ± 0.02	0.15 ± 0.02

*Study subjects included 697 Lebanese, 313 Tunisian, 191 Bahraini, and 149 Saudi Arabian healthy subjects of both sexes.
†Percent of total within population.
‡Analyzed by HLA STAT2000 software.
§$n = 197$.

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The varied incidence of these SNPs in the four Arab communities was consistent with previous reports documenting the geographical heterogeneity in their distribution [5,6,8]. To avoid epidemiologic bias, non-Arab nationals (Armenians in Lebanon, Berbers in Tunisia, or Iranians in Bahrain) were excluded from the study. Lebanon had the highest, while Saudi Arabia had the lowest incidence of the three SNPs. The high incidence rate of FV Leiden in Lebanon was matched with similar high rates in neighboring Syria [9], Jordan [10], Turkey [9], Cyprus [9], and among Israeli Arabs [11], suggesting that the FV Leiden mutation has occurred as a single mutational event in the Eastern Mediterranean basin [9]. The incidence of FV Leiden was also high in Tunisia in sharp contrast to the low rates in neighboring Algeria and Morocco [4,9], due to the relatedness of Lebanese and Tunisians brought about by the admixture of ancient Lebanese (Phoenicians) with Carthaginians (ancestors of present-day Tunisians). In addition, the incidence of the T/T genotype in Lebanon and Tunisia was higher than the rates of Bahrain and Saudi Arabia, and was closely comparable with southern European communities, including Spain, France, and Italy [7], together with Jordan [10], hereby indicating that MTHFR C677T may have occurred on a founder haplotype [6].

The low incidence FV Leiden and PRT G20210A in Bahrain and Saudi Arabia suggest a genetic influence of Asian non-Caucasian evidenced by the low rates established for India [12] and Thailand [0%; 5]. There was a progressive decline in the incidence rates of the three SNPs moving eastward from Lebanon to Jordan, on to Bahrain and Saudi Arabia and onward to the Indian subcontinent where they were virtually absent, thereby pointing to an Asian gradient in the distribution of these SNPs, similar to the north–south MTHFR C677T incidence gradient described for North America and Europe.

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Prolonged prothrombin time is not common in bird flu infection: a summary from Thailand

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Bird flu or avian flu, caused by H5N1 virus, is a new emerging infectious disease. There has been a worldwide situation regarding avian influenza infections in poultry since 1997. Recently, H5N1 caused severe disease with high mortality in