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Geographic and Ethnic Differences in the Prevalence of Thrombophilia

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1. Introduction

Cardiovascular diseases and venous thromboembolism are multifactorial diseases. Risk factors result from genetics, environment and behavior. The concept of the multicausal disease has received much attention in recent years. One of the reasons is that some of the genetic risk factors concerning single point mutations are quite common in the general population. There are known molecular factors which increase the relative risk for disease, and others with protective effects. The genetic background is given by the combination of all these molecular markers.

Several genetic variants are currently identified as risk factors for venous and arterial thrombosis (myocardial infarction and deep venous thrombosis)(Table 1). Activated protein C (APC) resistance due to the factor V Leiden mutation (FVL) and the 20210 G>A mutation in the factor II (FII, Prothrombin) gene are well established causes of thrombophilia. Concerning the risk of myocardial infarction the results are different (Ozmen F et al., 2009).

The 677C>T mutation in the methylentetrahydrofolate reductase gene (MTHFR 677C>T), which causes a mild hyperhomocysteinemia, is considered to be a risk factor for coronary heart disease (Kluijtmans et al., 1997; Morita et al., 1997), venous thromboembolism and stroke (Frosst et al., 1995; Arruda et al., 1997; Margaglione et al., 1998, Khandanpour et al., 2009, Tug E et al., 2011), but the results are controversial.

New polymorphic markers of the FV gene were described in the last years (Lunghi et al., 1996; Bernardi et al.,1997; Castoldi et al., 1997; Castoldi, 2000). A specific factor V gene haplotype (HR2) was defined by five restriction polymorphisms in exon 13 and a sequence variation located in exon 16. The exon 13 markers include the Rsa I polymorphic site, the rare allele of which (R2) has been previously found to be associated with partial FV deficiency in the Italian population (Lunghi et al., 1996). The nucleotide change 4070 G>A underlying the R2 allele gives rise to an amino acid change His to Arg at position 1299. Bernardi et al. (1997) demonstrated that the FV gene marked by the HR2 haplotype, which was invariably found to underlie the R2 marker, is both able to contribute to a mild APC resistance phenotype and to interact synergistically with the FVL mutation Arg506Gln to produce a severe APC resistance phenotype. Carriers of the R2 allele are more frequent among patients of carotid endarterectomy (Marchetti et al., 1999) and the carriership of the R2 allele is associated with an increased risk for coronary artery disease (Hoekema et al., 1999; Hoekema et al., 2001) and venous thromboembolism (Bernardi et al., 1997; Faioni et al., 1999; Alhenc-Gelas et al., 1999).

For some new variants of clotting factors FVII, FXII and FXIII associations with venous and arterial thrombosis were reported. Within the FVII gene eight polymorphisms are known (Herrmann et al., 1998; Herrmann et al., 2000) and three of them influence the level of FVII activity: the insertion polymorphism of the promotor (Marchetti et al., 1993), a tandem repeat unit polymorphism within intron 7 (Marchetti et al., 1991; de Knijff et al., 1994; Mariani et al., 1994; Pinotti et al., 2000) and the Arg353Gln polymorphism of exon 8 (Green et al., 1991). Iacoviello et al. (1998) demonstrated in patients with myocardial infarction and family history of cardiovascular diseases, that the Gln353 allele of the Arg353Gln polymorphism and the 7(a) allele of the tandem repeat unit polymorphism of the hypervariable region 4 within intron 7 might have a protective effect on the risk of myocardial infarction. These alleles independently showed an effect in reducing the risk and both were associated with lower levels of FVII (Green et al., 1991; Mariani et al., 1994; Iacoviello et al., 1998; Domenico et al., 2000).

For severe factor XII deficiency, an increased predisposition to venous thromboembolic diseases and myocardial infarction has been reported. Some cohort studies have shown a high prevalence of slightly reduced FXII levels in patients of deep venous thrombosis or coronary heart diseases (Mannhalter et al., 1987; Halbmayer et al., 1994; Franco et al., 1999; Zito et al., 2000), but more association studies in this field are necessary. The C>T mutation at nucleotide 46 in the 5´untranslated region of FXII (FXII 46C>T) is associated with a diminished plasma FXII level (Kanaji et al., 1998; Kohler et al., 1999; Zito et al., 2000) and the role of this polymorphism as a thrombophilic risk factor is under discussion.

The G>T transition in exon 2 of the FXIII A subunit gene was reported to provide a protective effect against myocardial infarction (Kohler et al., 1998; Franco et al., 2000) and venous thrombosis (Catto et al., 1999; Franco et al., 1999; Rosendaal et al., 1999; Alhenc-Gelas et al., 2000; Franco et al., 2001), but also an increased predisposition to primary intracerebral hemorrhage (Catto et al., 1998; Reiner et al., 2001).

Many epidemiological studies have been performed to associate the presence (insertion, I) or absence (deletion, D) of a 287bp Alu repeat element in intron 16 of the ACE (Angiotensin Converting Enzyme) gene with the level of the circulating enzyme or cardiovascular pathophysiology. Some reports have found that the D allele confers increased susceptibility to cardiovascular diseases and myocardial infarction, others found no such association or even a beneficial effect (Rieder et al., 1999; Agerholm-Larsen et al., 2000). The same is true for cerebrovascular diseases, stroke or stenosis of carotids and venous thrombosis (Philipp et al., 1998; Della Valle et al., 2001). Markus et al. (1995) reported that the DD genotype is a risk factor for lacunar stroke but not for carotid atheroma. However, the precise role of the I/D polymorphism is not clear, so more association studies are necessary.

A series of studies have been carried out to elucidate the mechanisms of the athero-thrombotic pathology in the middle-age and older adults. However, few studies have examined the joint effect of interaction of environmental factors and molecular markers in the risk of thrombosis particularly among the young. However, these claims have been challenged. Based upon in this observation it was considered important to study the role of the risk factors and molecular markers for thrombosis in Hispanics living in Costa Rica, Central America. In the population of Costa Rica (CR) and its different ethnic groups the prevalence of molecular risk and protective factors are few reports until now. In order to estimate the role of these factors in this population it is necessary to know their prevalence and it will be interesting to compare with one Caucasian population as NE Germany, see Figure 1.

Subjects

Blood samples analyzed in this study were obtained from 732 CR-Indians belonging to six different tribes. Samples were collected from 133 Chorotega of the Matambu Indian locality; 157 Guaymi of the south area (San Vito, Coto Brus, Abrojo localities) and of the Pacific area (Osa); 150 Cabecar of the Atlantic Talamanca area (Chirripo, Amubri localities) and of the Pacific (Ujarras Indian locality); 110 Bribri of the Talamanca area (Bribi and Suretka localities); 153 Huetar of Quitirrisi and Zapaton Indian localities, as well as 29 Guatuso of the Guatuso Indian locality (figure 1).

In order to compare the results with European Caucasians blood samples were analyzed from 170 blood donors from northeastern Germany (NE-Germany).

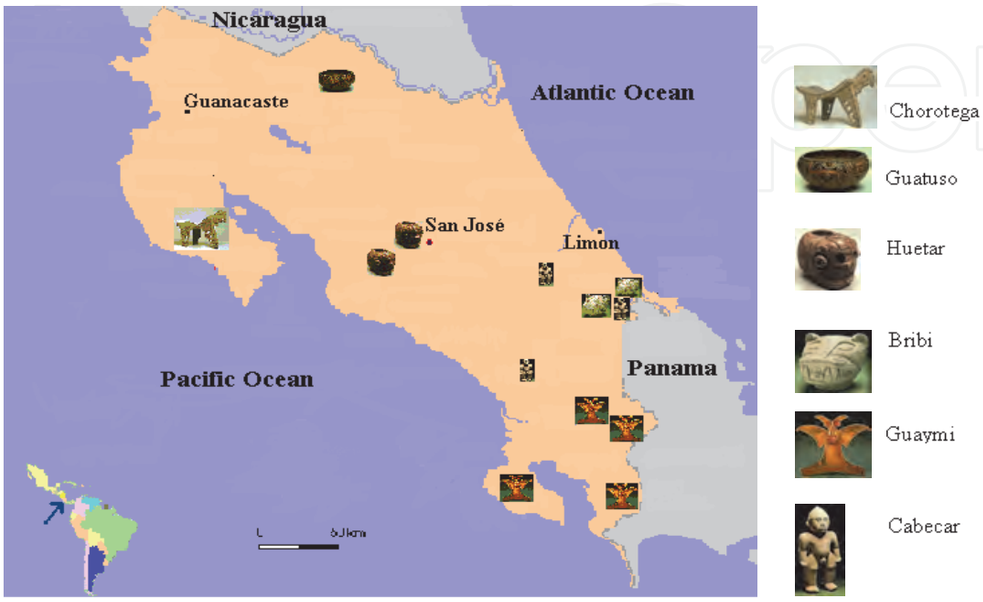

Fig. 1. The approximate geographic locations of the six tribes of CR Amerindians

2. A brief history of Costa Rican population

The current population of Costa Rica presents an ancestral gene combination of Amerindians (30%), Africans (10-15%) and Caucasians (50-60%) (Barrantes, 1998). In the pre-Columbian period, the human population in this area was composed of Amerindian tribes descending from the Na-dene and North-American Eskimos (Torroni et al., 1994). Four of the tribes studied (Guatuso, Guaymi, Cabecar, Bribri) belong to Chibcha-speaking tribes of lower Central America (Thompson et al., 1992; Barrantes, 1998). The Chibcha, which have been separated biologically and linguistically from other groups of this region, show differences in some aspects when compared to other North and South American groups of Indians (Barrantes et al., 1990; Thompson et al., 1992) and also have rare genetic variants and private polymorphisms.

The Chorotega, another tribe included in the present study (Figure 1), belong to the Mesoamerican culture with strong influences from the Aztec and Maya culture (Ibarra, 2001). At present, this tribe is located in the western Pacific area of the country.

The Huetar tribe inhabited the North-Central area of Costa Rica during the time of the Spanish Conquest. At the present time, they are located in the southwest of the country (Figure 1). During colonization, the admixture between Spanish colonizers, mostly from the south of Spain, and indigenous women began (Thiel, 1977; Ibarra, 2001).

In the 16th and 17th centuries Africans were firstly brought to Costa Rica by the transatlantic slave trade from western and Central Africa. The first settlement of Africans in Costa Rica

was in the Pacific area (Meléndez and Duncan, 1989). From the beginning, this ethnic group participated in the admixture process with the Amerindians. The second important African migration to Costa Rica was into the Caribbean Area during the 18th and 20th centuries. This group of Africans migrated from the Antilles, principally from Jamaica, and settled in "Cahuita" in the Limon province at the Atlantic coast (Palmer, 2000).

Genotype prevalence and allele frequencies of the eleven molecular markers in Costa Rica Indians from six different tribes and Cr-Africans as well as blood donors from Costa Rica and NE Germany

The results of the prevalence of these molecular markers in this ethnic context are summarized in Table 1, 2, 3 and 4.

2.1 FII 20210G>A

The 20210A allele of the factor II polymorphism was extremely rare in CR-Indians (Table 2). Only one allele was detected in the Bribri and one in the Huetar Indians. In CR-Africans, the 20210A allele frequency was also extremely low (1 out of 578 alleles). In a cooperative study including more than 5500 healthy subjects from nine European and American countries, the overall prevalence of heterozygous FII carriers was estimated to be 2% (Rosendaal et al., 1998). In the same study a very low prevalence of the prothrombin mutation was reported for Africans and subjects of Asian descent (Rosendaal et al., 1998). Therefore, we conclude that the FII mutation found in CR-Indians and CR-Africans is of Caucasian origin, as suggested for FVL.

2.2 FV gene : FVL, FVHR2, FV IVS16

The factor V Leiden mutation is a known risk factor for venous thrombosis in Caucasians and has been discussed as a risk factor for arterial thrombosis. This mutation was rare in CR-Indians, with only five heterozygous FVL carriers detected among the Huetar. In the CR-Indian tribes without FVL, the frequency of the R2 allele of the HR2 haplotype was extremely high. It has been shown that this allele is associated with partial FV deficiency and acts synergistically with FVL (Bernardi et al., 1997; Lunghi et al., 1998). In various populations the R2 allele frequency ranged from 0.04 to 0.08; [Netherlands 0.040 (De Visser et al., 2000); England 0.055 (Luddington et al., 2000); Italy, India, Somalia 0.080 (Bernardi et al., 1997; Faioni et al., 1999;); Germany 0.070 (Hermann et al., 2001 and this study)]. The extremely high frequency of the R2 allele and the R1R2 and R2R2 genotypes in Bribri Indians is the highest reported so far. In the same CR Indian tribes with a high prevalence of the R2 allele, the D2 allele of FV IVS16 polymorphism was very rare.

The FVL mutation was likewise rare in the other CR groups analyzed (subpopulations of CR-Africans and in the CR blood donors). The R2 frequency of the HR2 haplotype was lower in the CR-Africans than in CR-Indians and CR-blood donors. However, in CR-Africans the rare R3 allele (His1254Arg) was also detected. This allele was first described in subjects from Somalia and in Greek Cypriotes and mimics the R2 polymorphism (His1299Arg) in subjects of African origin (Lunghi et al., 1998). The FVL mutation was not found in combination with the R2 or R3 allele in CR-Africans or CR-blood donors .

In the German group of 170 blood donors, 11 heterozygous FVL genotypes were detected. Eight of them had the R1R1 genotype and only three FVL heterozygotes had the R1R2 genotype. All the eleven FVL heterozygous subjects were also heterozygous for the D2

Polymorphism	Mutation	Localization	Genotype	Symbol	Phenotype Effect	References
Factor II Gene	20210 G >A	Chromosome 11	GG (wild type)	GG	normal FII	Poort et al. (1996)
20210 G>A		3'-untranslated region	GA (heterozygous)	GA	moderate increased FII	
			AA (homozygous)	AA	increased FII	
Factor V Gene	R506Q	Chromosome 1	GG (wild type)	GG	normal	Bertina et al. (1994)
FV Leiden	1691G>A	Exon 10	GA (heterozygous)	GA	mild APC resistance	
			AA (homozygous)	AA	APC resistance	
FV HR2	H1299R	Exon 13	AA (wild type)	R1R1	normal	Lunghi et al. (1996)
	4070A>G		AG (heterozygous)	R1R2	mild APC resistance	Bernardi et al. (1997)
			GG (homozygous)	R2R2	mild APC resistance	Faioni et al. (1999)
	H1254R		AG (heterozygous)	R1R3	*	
	3935A>G					
FV IVS 16	IVS16+12 G>A	Intron 16	GG (wild type)	D1D1	*	Castoldi et al. (1997)
			GA (heterozygous)	D1D2	*	
			AA (homozygous)	D2D2	*	
Factor VII Gene	repeat 37 bp	Chromosome13	66	bb	normal FVII: C	Marcheti et al. (1991)
	HVR4	Intron 7	67	ba	reduced FVII: C	Bernardi et al. (1993)
FVII IVS 7			77	aa	strong reduced FVII:C	
			rare allele	rare allele		
			4	4	increased FVII:C	
			5	5	*	
			8	8	*	
			9	9	*	
FVII Arg353 Gln	Arg 353 Gln	Exon 8	GG (wild type)	M1M1	normal FVII: C	Green et al. (1991)
	10975 G>A		GA (heterozygous)	M1M2	reduced FVII: C	
			AA (homozygous)	M2M2	strong reduced FVII:C	
FVII IVS 1a			GG (wild type)	GG	*	Herrmann et al. (1998);
FVII 73 G>A	73 G>A	Intron 1a	GA (heterozygous)	GA	*	Wulff et al. (2000)
			AA (homozygous)	AA	*	
Factor XII Gene		Chromosome 5	CC (wild type)	CC	normal FXII: C	Kanaji et al. (1998)
FXII 46 C> T	46 C >T	5'-untranslated	CT (heterozygous)	CT	reduced FXII: C	
		region	TT (homozygous)	TT	strong reduce FXII:C	
Factor XIII Gene	Val 34 Leu	Chromosome 6			Transglutaminase	
FXIII Val34Leu	G>T	Exon 2	GG (wild type)	ValVal	normal activity	Catto et al. (1999)
		(XIII A-Subunit)	GT (heterozygous)	ValLeu	mild activity	Rosendaal et al. (1999)
			TT (homozygous)	LeuLeu	increased activity	
MTHFR Gene	Ala >Val	Chromosome 1			Homocysteine level	Kang et al. (1991)
MTHFR 677C>T	677C>T		CC (wild type)	CC	normal	Frosst et al. (1995)
			CT (heterozygous)	CT	normal	Kluijtmans et al. (1999)
			TT (homozygous)	TT	mild increased	

* Unknown effect.

Table 1. Characteristics of the different polymorphisms analyzed

POLYMORPHISMS	CHOROTEGA		GUATUSO		GUAYMI		CABECAR		BRIBRI		HUETAR		CR INDIANS Σ		GUANACASTE		LIMON		CR AFRICANS Σ		CR BLOOD DONORS		NE-GERMANY Caucasians	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
FII G>A 20210	133		29		157		149		110		152		730		179		110		289		392		170	
20210 GG	133	100.00	29	100.00	157	100.00	149	100.00	109	99.09	151	99.34	728	99.72	179	100.00	109	99.09	288	99.65	381	97.19	168	98.80
20210 GA	-		-		-		-		1	0.91	1	0.66	2	0.28	-		1	0.91	1	0.35	11	2.81	2	1.20
20210 AA	-		-		-		-		-		-		-		-		-		-		-		-	
f(G)	266	1.00*	58	1.00*	314	1.00*	298	1.00*	219	0.995*	303	0.997*	1458	0.998*	358	1.00*	219	0.995*	577	0.998*	773	0.986*	338	0.994*
f(A)									1	0.005*	1	0.003*	2	0.002*			1	0.005*	1	0.002*	11	0.014*	2	0.006*
FVL	132		29		156		149		110		153		729		179		113		292		392		172	
1691 GG	132	100.00	29	100.00	156	100.00	149	100.00	110	100.00	148	96.73	724	99.31	178	99.44	111	98.23	289	98.97	383	97.70	1089	92.91
1691 GA	-		-		-		-		-		5	3.27	5	0.69	1	0.56	2	1.77	3	1.03	9	2.30	82	7.00
1691 AA	-		-		-		-		-		-		-		-		-		-		-		1	0.09
f(G)	264	1.00*	58	1.00*	312	1.00*	298	1.00*	220	1.00*	301	0.984*	1453	0.996*	357	0.997*	224	0.991*	581	0.995*	775	0.988*	2260	0.964*
f(A)											5	0.016*	5	0.004*	1	0.003*	2	0.009*	3	0.005*	9	0.012*	84	0.036*
FV-HR2																								
(His1299Arg)	133		23		156		149		110		153		724		178		114		292		377		358	
R1R1	70	52.63	12	52.17	126	80.77	82	55.03	45	40.91	111	72.55	446	61.60	138	77.53	103	90.35	241	82.54	303	80.37	308	86.03
R1R2	52	39.10	10	43.48	28	17.95	61	40.94	53	48.18	40	26.14	244	33.70	35	19.66	7	6.14	42	14.38	72	19.10	50	13.97
R2R2	11	8.27	1	4.35	2	1.28	6	4.03	12	10.91	2	1.31	34	4.70	1	0.56	-		1	0.34	2	0.53	–	
R1R3	–		–		–		–		–		–		–		4	2.25	4	3.51	8	2.74	–		–	
f(R1)	192	0.720*	34	0.739*	280	0.897*	225	0.755*	143	0.650*	262	0.856*	1136	0.785*	315	0.885*	217	0.952*	532	0.910*	678	0.899*	666	0.930*
f(R2)	74	0.278*	12	0.261*	32	0.103*	73	0.245*	77	0.350*	44	0.144*	312	0.215*	37	0.104*	7	0.031*	44	0.076*	76	0.101*	50	0.070*
f(R3)															4	0.011*	4	0.017*	8	0.014*				
FV-IVS16	133		25		157		149		109		153		726		179		114		293		94		170	
D1D1	130	97.74	24	96.00	156	99.36	148	99.33	108	99.08	142	94.77	708	97.52	165	92.18	93	81.57	258	88.05	88	93.61	146	85.90
D1D2	3	2.26	1	4.00	1	0.64	1	0.67	1	0.92	11	5.23	18	2.48	14	7.82	21	18.43	35	11.95	6	6.39	24	14.10
f(D1)	263	0.989*	49	0.980*	313	0.997*	297	0.997*	217	0.995*	295	0.964*	1434	0.988*	344	0.961*	207	0.908*	551	0.940*	182	0.968*	316	0.929*
f(D2)	3	0.011*	1	0.020*	1	0.003*	1	0.003*	1	0.005*	11	0.036*	18	0.012*	14	0.039*	21	0.092*	35	0.060*	6	0.032*	24	0.071*

*Allele frequency

Table 2 Prevalence of polymorphisms in the FII and FV genes in the different ethnic groups studied

POLYMORPHISMS		CHOROTEGA		GUATUSO		GUAYMI		CABECAR		BRIBRI		HUETAR		CR INDIANS Σ		GUANACASTE		LIMON		CR AFRICANS Σ		CR BLOOD DONORS		NE-GERMANY Caucasians	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
FVII IVS7 (37bp repeat)		125		28		135		134		101		98		621		145		109		254		229		115	
46	4b	2	1.60	-	-	-	-	-	-	-	-	-	-	2	1. 60	3	2. 07	-	-	3	1. 18	1	0. 44	-	-
47	4a	1	0.80	-	-	-	-	-	-	-	-	-	-	1	0. 80	-	-	1	0. 92	1	0. 39	-	-	-	-
55	5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	0. 44	-	-
56	5b	-	-	-	-	-	-	-	-	1	0. 99	-	-	1	0. 16	-	-	-	-	-	-	-	-	-	-
57	5a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	0. 44	-	-
66	bb	29	23.20	23	82.14	72	53. 33	69	51. 49	40	39. 61	46	46. 94	279	44. 93	58	40. 00	35	32 11	93	36. 61	106	46. 28	37	32. 17
67	ab	61	48.80	5	17.86	48	35. 55	54	40. 30	42	41. 58	44	44. 90	254	40. 90	59	40. 69	49	44. 95	108	42. 53	101	44. 10	54	46. 96
77	aa	30	24.00	-	-	15	11. 12	11	8. 21	18	17. 82	8	8. 16	82	13. 21	22	15. 17	19	17. 43	41	16. 15	18	7. 86	18	15. 65
86	8b	2	1.60	-	-	-	-	-	-	-	-	-	-	2	0. 32	2	1. 38	4	3. 67	6	2. 36	1	0. 44	4	3. 48
87	8a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	0. 69	-	-	1	0. 39	-	-	1	0. 87
96	9b	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	0. 92	1	0. 39	-	-	1	0. 87
	f(4)	3	0.012*	-	-	-	-	-	-	-	-	-	-	3	0. 002*	3	0. 010*	1	0. 005*	4	0. 008*	1	0. 002*	-	-
	f(5)	-	-	-	-	-	-	-	-	1	0. 005*	-	-	1	0. 001*	-	-	-	-	-	-	3	0. 007*	-	-
	f(6)	123	0.492*	51	0.911*	192	0. 711*	192	0. 716*	123	0. 609*	136	0. 694*	817	0. 658*	180	0. 621*	124	0. 569*	304	0. 598*	314	0. 686*	133	0. 578*
	f(7)	122	0.488*	5	0.089*	78	0. 289*	76	0. 284*	78	0. 386*	60	0. 306*	419	0. 337*	104	0. 359*	88	0. 403*	192	0. 378*	139	0. 303*	91	0. 396*
	f(8)	2	0.008*	-	-	-	-	-	-	-	-	-	-	2	0. 002*	3	0. 010*	4	0. 018*	7	0. 014*	1	0. 002*	5	0. 022*
	f(9)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	0. 005*	1	0. 002*	-	-	1	0. 004*
FVII 73G>A		123		27		152		136		94		60		592		114		104		218		51		72	
	73GG	90	73.17	27	1.00	147	96.71	129	94.85	84	89.36	49	81.67	526	88.85	86	75.44	49	47.12	135	61.93	34	66.67	53	73.60
	73GA	32	26.02	-	-	5	3.29	7	5.15	8	8.51	11	18.33	63	10.64	24	21.05	45	43.27	69	31.65	16	31.37	19	26.40
	73AA	1	0.81	-	-	-	-	-	-	2	2.12	-	-	3	0.51	4	3.51	10	9.61	14	6.42	1	1.96	-	
	f(G)	212	0.862*	54	1.00*	299	0.984*	265	0.974*	176	0.936*	109	0.908*	1115	0.942*	196	0.860*	143	0.688*	339	0.778*	84	0.824*	125	0.868*
	f(A)	34	0.138*	-	-	5	0.016*	7	0.026*	12	0.064*	11	0.092*	69	0.058*	32	0.140*	65	0.312*	97	0.222*	18	0.176*	19	0.132*
FVII Arg353Gln		117		27		151		132		108		92		627		150		108		258		235		96	
ArgArg	M1M1	88	75.21	27	100.00	148	98.01	119	90.15	96	88.89	74	80.43	552	88.04	122	81.33	78	72.22	200	77.52	175	74.47	71	73.95
ArgGln	M1M2	29	24.79	-	-	3	1.99	13	9.85	12	11.11	18	19.57	75	11.96	23	15.33	27	25.00	50	19.38	57	24.25	22	22.92
GlnGln	M2M2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	5	3.34	3	2.78	8	3.10	3	1.28	3	3.13
f(Arg353) M1		205	0.876*	54	1.00*	299	0.990*	251	0.951*	204	0.944*	166	0.902*	1179	0.940*	267	0.890*	183	0.847*	450	0.872*	407	0.866*	164	0.854*
f(Gln353) M2		29	0.124*	-	-	3	0.010*	13	0.049*	12	0.056*	18	0.098*	75	0.060*	33	0.110*	33	0.153*	66	0.128*	63	0.134*	28	0.146*

*Allele frequency

Table 3. Prevalence of polymorphisms in the FVII gene in the different ethnic groups studied

POLYMORPHISMS	CHOROTEGA		GUATUSO		GUAYMI		CABECAR		BRIBRI		HUETAR		CR INDIANS Σ		GUANACASTE		LIMON		CR AFRICANS Σ		CR BLOOD DONORS		NE-GERMANY Caucasians	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
FXII 46C>T	127		26		153		106		95		84		591		93		49		142		55		97	
46 CC	62	48.82	12	46.15	56	36.60	24	22.64	49	51.58	30	35.71	233	39.42	33	35.48	11	22.45	44	30.99	24	43.63	67	69.07
46 CT	44	34.65	13	50.00	70	45.75	62	58.49	40	42.11	39	46.43	268	45.35	36	38.71	22	44.90	58	40.85	29	52.74	24	24.74
46 TT	21	16.53	1	3.85	27	17.65	20	18.87	6	6.31	15	17.86	90	15.23	24	25.81	16	32.65	40	28.16	2	3.63	6	6.19
f(C)	168	0.660*	37	0.710*	182	0.590*	110	0.520*	138	0.730*	99	0.590*	734	0.620*	102	0.548*	44	0.448*	146	0.514*	77	0.700*	158	0.814*
f(T)	86	0.340*	15	0.290*	124	0.410*	102	0.480*	52	0.270*	69	0.410*	448	0.380*	84	0.452*	54	0.551*	138	0.486*	33	0.300*	36	0.186*
FXIII Val34Leu	133		25		157		141		80		153		689		177		114		291		381		194	
Val34Val34	109	81.95	9	36.00	120	76.43	77	54.61	40	50.00	89	58.17	444	64.44	95	53.67	70	61.40	165	56.70	210	55.12	99	51.03
Val34Leu34	23	17.29	11	44.00	29	18.47	51	36.17	34	42.50	51	33.33	199	28.88	72	40.68	38	33.34	110	37.80	140	36.74	83	42.78
Leu34Leu34	1	0.76	5	20.00	8	5.10	13	9.22	6	7.50	13	8.50	46	6.68	10	5.65	6	5.26	16	5.50	31	8.14	12	6.19
f(Val34)	241	0.910*	29	0.580*	269	0.860*	205	0.730*	114	0.710*	229	0.750*	1087	0.790*	262	0.740*	178	0.780*	440	0.756*	560	0.734*	281	0.724*
f(Leu34)	25	0.040*	21	0.420*	45	0.140*	77	0.270*	46	0.290*	77	0.250*	291	0.210*	92	0.260*	50	0.220*	142	0.244*	202	0.266*	107	0.256*
ACE	133		25		157		150		110		153		728		179		113		292		351		194	
II	59	44.36	17	68.00	92	58.60	103	68.67	47	42.73	32	20.91	350	48.08	38	21.23	14	12.39	52	17.80	101	28.77	44	22.68
ID	68	51.13	7	28.00	56	35.67	43	28.67	56	50.91	83	54.25	313	42.99	108	60.34	57	50.44	165	56.51	163	46.44	91	46.91
DD	6	4.51	1	4.00	9	5.73	4	2.66	7	6.36	38	24.84	65	8.93	33	18.43	42	37.17	75	25.69	87	24.79	59	30.41
f(I)	186	0.670*	41	0.820*	240	0.764*	249	0.830*	150	0.682*	147	0.480*	1013	0.696*	184	0.514*	85	0.376*	269	0.461*	365	0.520*	179	0.461*
f(D)	80	0.330*	9	0.180*	74	0.236*	51	0.170*	70	0.318*	159	0.520*	443	0.304*	174	0.486*	141	0.624*	315	0.539*	337	0.480*	209	0.539*
MTHFR 677 C>T	133		29		157		147		110		153		729		179		111		290		392		170	
677 CC	18	13.53	1	3.45	9	5.73	5	3.40	10	9.09	21	13.73	64	8.78	48	26.82	74	66.67	122	42.00	107	27.30	84	49.94
677 CT	74	55.64	14	42.28	38	24.20	58	39.45	54	49.09	79	51.63	317	43.48	95	53.07	29	26.13	124	42.80	180	45.92	73	42.29
677 TT	41	30.83	14	48.25	110	70.07	84	57.15	46	41.82	53	34.69	348	44.74	36	20.11	8	7.20	44	15.20	105	26.78	13	7.70
f(C)	110	0.414*	16	0.276*	56	0.178*	68	0.231*	74	0.336*	121	0.395*	445	0.305*	191	0.534*	177	0.797*	368	0.634*	390	0.497*	241	0.709*
f(T)	156	0.587*	42	0.724*	258	0.822*	226	0.769*	146	0.664*	185	0.605*	1013	0.695*	167	0.466*	45	0.203*	212	0.366*	394	0.503*	99	0.291*

*Allele frequency

Table 4. Prevalence of polymorphism in the FXII, FXIII, ACE and MTHFR genes in the different ethnic groups studied

allele. On the other hand, only 45.80% of the D1D2 heterozygous subjects also had the heterozygous FVL genotype (Herrmann et al., unpublished).

The similar high frequency of the FV D2 allele in CR-Africans and in German Caucasians supports the hypothesis that this is a very old ancestral mutant allele (Bernardi et al., 1997; Castoldi et al., 1997), dating back to a time prior to the human migration out of Africa. The absence of FVL in native populations of Africa, eastern Asia, Australasia and in CR Indians is well known (Rees et al., 1995; Herrmann et al., 1997; Herrmann et al., 1999 and this study). The different distribution of the FVL and of the FVHR2 haplotypes supports the hypothesis that the HR2 haplotype is also older than FVL and represents an ancient set of mutations (Bernardi et al., 1997; Faioni, 2000). Both the R2 and the D2 mutations seem to have originated in a single mutation event in different ancestral wildtype alleles of the FV gene. The high frequency of the R2 allele in CR-Indians without FVL as well as the extremely low frequency of the D2 allele in the same Indian tribes (< 0.50%) seems to indicate that the R2 His1254Arg polymorphism is older than the FV IVS 16 polymorphism.

The „out of Africa" model of the origin of *Homo sapiens sapiens* provides a plausible explanation for the observed differences in the distribution of the three polymorphisms of FV gene among the different ethnic groups studied. This model suggests that non-African human populations were descended from an anatomically modern *H. sapiens* ancestor that evolved in Africa approximately 100,000 to 200,000 years ago and then spread and diversified throughout the rest of the world (Tishkoff et al., 1996; Zivellin et al., 1997). The ancestral population of Africans is characterized by the FV haplotypes of HR2 with the mutant alleles R2 and R3 and the FV-IVS16 polymorphism. We found these haplotypes in CR-Africans, who reached the Costa Rican area in the post-Columbian time, coming from the sub-Saharan African population (Ibarra, 2001). The similarity in the frequency of D2 and R2 in Africans and in Caucasoid subpopulations outside of Africa, including Europeans, Jews, Israeli Arabs and from India (Zivellin et al., 1997; Herrmann et al., 2001) is consistent with the migration of modern humans out of northeast Africa into the Middle East and Europe and out of southeast Africa to Asia, the Pacific Islands and the New World. Studies of both mitochondrial and nuclear DNA have suggested that the ancestral population leaving Africa towards the Southeast around 60,000 years ago was small (Tishkoff et al., 1996). The migration to Asia and the New World was accompanied by a further reduction of the rare D2 allele, probably by random genetic drift. This assumption provides a possible explanation for the absence or extremely low frequency of the D2 allele in the CR-Indians. Further studies of other populations descended from the Southeast migrators are needed in order to confirm this speculation.

Schröder et al. (2001) demostrated in German patients with deep venous thrombosis that FVL in Caucasians was always combined with the D2 allele. The investigation of 25 homozygous FVL thrombotic patients from Germany also showed homozygosity for D2D2, indicating that both mutations (FVL and D2) are localized as double mutations in the same allele (Herrmann et al., unpublished data). These results support a single origin hypothesis (Castoldi et al., 1997; Zivellin et al., 1997), indicating that the FVL mutation in European Caucasians has its ancestral origin in a D2 marked allele of the FV gene of a modern Caucasoid subpopulation, now widespread among the Indo-European group.

The FVL mutation is estimated to have arisen ca. 21,000 to 34,000 years ago, i.e. after the evolutionary divergence of Africans from non-Africans and of the Caucasoid from the Mongoloid subpopulation (Zivellin et al., 1997). The three FVL mutation carriers found in

CR-Africans are compound-heterozygous for FVL and D2 (D1D2, FVL/FVwt), and probably have a European/Caucasian origin caused through racial admixture in the past.

2.3 FVII gene: FVII IVS7, FVII R353Q and FVII IVS1a polymorphism

Epidemiological studies have shown that high blood levels of FVII are associated with an increased risk of ischaemic heart disease (Meade et al., 1986; Heinrich et al., 1994; Benardi et al., 1997). Environmental and biochemical factors influence the plasma level of FVII. Age, gender, BMI, insulin resistance and the use of oral contraceptives have been associated with FVII levels (Balleisen et al.,1985). Dietary fats and blood lipids are important determinants of FVII levels (Miller et al.,1991; Mennen et al.,1996). Several studies have demonstrated that three polymorphisms of the FVII gene can directly influence the FVII levels and also modulate its response to environmental stimuli (Lane et al., 1992; Humphries et al., 1994; Hong et al., 1999)

The Gln353 variant of the FVII gene has consistently been associated with lower levels of FVII in white Europeans (Humphries et al., 1994), Gujarati Indians (Lane et al., 1992), Afrocaribbean Britains (Lane et al., 1992; Temple et al., 1997) and Japanese (Kario et al., 1995). Individuals with the GlnGln genotype have a decreased risk for MI, and they have a lower level of FVII activity and FVII antigen in comparison to the ArgGln and homozygous Arg genotypes (Iacovello et al., 1998).

The Gln allele frequencies of the Arg353Gln polymorphism in NE Germany, CR-blood donors and CR-Africans were similar to those described in other studies (Bernardi et al., 1997; Di Castelnuovo et al., 1998). The Gln allele frequencies of the Arg353Gln polymorphism in NE Germany and various ethnic groups in Costa Rica ranged from 0.010 to 0.153 (Table 3). Significant differences in the allele frequencies in the Costa Rican groups were found. Among 627 CR-Indians, the homozygous GlnGln form was not found. The frequency of the mutant allele was lower in the CR-Indian groups (0.060) than in the North European populations (0.100) (Lane et al., 1992; de Maat et al., 1997). Smoking is a known risk for MI, but Iacoviello et al. (1999) and Niccoli et al. (2001) showed a decreased in the risk of MI in smokers subjects carrying the Gln353 allele.

Concerning the FVII IVS7 polymorphism, it is known that the 5 monomers genotypes are associated with the highest risk for MI, followed in descending order by the 66, 67 and 77 genotypes (Iacoviello et al., 1998; Niccoli et al., 2001). The frequency of the 7 allele was similar in German and CR-African population and slightly lower in CR-blood donors and CR-Indians. The prevalence of the 77 genotype was higher in the Chorotega (24.00%) and Bribri (17.82%) Indian groups, followed by CR-Africans (16.15%), in comparison with CR-blood donors (7.86%). In Chorotegas Indians, the potentially higher risk caused by the absence of the protective homozygous Gln353 genotype seems to be compensated by the high prevalence of the 77 genotype. The 5 monomers with a high risk for MI were only found in CR-groups. Moreover, the 4, 8 and 9 monomers were detected for first time in CR-ethnic groups.

The influence on FVII activity of the recently described polymorphism within the promotor region of the FVII, the G>A transition at nucleotide 73 in the intron 1a, is not yet known (Herrmann et al., 2000). In this study, we report the lowest frequency of the rare mutant allele in the CR- Indian group (0.058) and the highest in the CR-Africans (0.222). In the NE-Germans and the CR-blood donors, the frequency of the rare mutant allele was not significantly different.

2.4 FXII 46C>T

There are several reports of severe FXII deficiency in subjects with thrombotic events or MI, cohort as well as case control studies have reported an increased predisposition to vascular thrombosis, (Mannhalter et al., 1987; Halbmayer et al., 1994; Pandita et al., 1997). Other authors did not find a decrease of FXII to be a determinant of thrombosis (Lämmle et al., 1991; ; Koster et al., 1994) or CVD (Kelleher et al.,1992; Kohler et al., 1999).

The FXII 46 C>T mutation was found to be associated with diminished plasma FXII levels in homozygous and heterozygous carriers in comparison with normal individuals, principally in the homozygous form. These low plasma FXII levels were caused by the decreased translation efficiency of the mutant messenger RNA (Kanaji et al., 1998). The FXII 46C>T mutation exhibits an ethnic variability that might contribute to the racial differences observed in FXII plasma levels. In Orientals, the FXII level is lower than in Caucasians (Kanaji et al., 1998). The allele frequency of 46C/T was estimated to be 0.270/0.730 in Orientals and 0.800/0.200 in Caucasians. Franco et al. (1999) reported an allele 46T frequency of 0.250 in Whites and 0.320 in Blacks (n 19) and Mulattos (n15).

In the present study, the 46T allele frequency in NE Germany (0.186) was in the range of other Caucasians reports [(Kanaji et al., 1998, (0.200); Kohler et al., 1999, (0.280)]. In Costa Rica the frequency of the FXII 46T allele in CR- blood donors (0.300) was significantly higher than in the German population. The highest frequency was observed in the CR-African group (0.486) and more than 30 % of the CR-Africans from Limon were homozygotes for the T allele (Table 4). This is the highest rate reported in any population to date.

Among 1182 alleles, 734 T alleles were detected in the CR-Indians (allele frequency 0.620), but the frequency differed between the various tribes. the prevalence of the homozygous wild type and heterozygous genotypes was higher than expected. In the 591 CR-Indians, the prevalence of the TT genotype was significantly higher (15.23%) than in Germans (6.19%).

The role of this mutation as a risk factor in these populations is unclear and further studies are necessary. Franco et al. (1999) discussed that this mutation alone is probably not a major risk factor for venous thrombotic disease. Zeerleder et al. (1999) have shown that hereditary partial and probably severe FXII deficiency does not constitute a thrombophilic condition. The possibility of interactive effects of the FXII mutation with other genetic effects associated with vascular thrombosis and coronary artery disease need to be investigated.

2.5 FXIII Val34Leu

The FXIII Val34Leu was shown to confer protection for arterial and venous thrombosis and to predispose to intracerebreal hemorrhage (Kohler et al., 1998; Catto et al., 1998; Catto et al., 1999; Franco et al., 1999; Rosendaal et al., 1999). These findings support the hypothesis that the factor XIII Leu34 is involved in the production of weaker fibrin structures which might protect against clot formation (Kohler at al., 1998; Catto et al., 1999). The mechanism underlying this protective effect is still unclear. The FXIII Leu34 variant gives rise to increased FXIII specific transglutaminase activity. Anwar et al. (1999) and Rosendaal et al. (1999) reported activities for FXIII ValVal of 96%, FXIII ValLeu:131% and FXIII LeuLeu: 152% .

The factor XIII Val34Leu polymorphism was originally described in a Finnish population with a Leu34 allele frequency of 0.230 in 600 normal controls (Mikkola et al.,1994). A frequency from 0.245 to 0.288 was reported for other Caucasian populations from three continents (Balogh et al., 1999; Muszbek, 2000). In healthy South Asians, the Leu34 allele

frequency was less frequent (0.130) than in Whites (0.289) (McCormack et al.,1998; Kain et al., 1999). The allele frequency was also low in Brazilian Blacks (0.140) and African Blacks from Cameroon (0.118) and Angola (0.188) (Attie Castro et al., 2000). In the Japanese population the lowest frequency has been described (0.013) (Attie Castro et al., 2000).
In the CR-Indians with a Chibcha origin (Cabecar, Bribri, Guaymi and Guatuso), the Leu34 allele frequency (0.280) was similar to South Amerindians from Brazil and Peru (0.293) (Attie Castro et al., 2000). In contrast, the frequency of the mutant allele was lower (0.040) in the Chorotegas with Mesoamerican origin.
The mutant allele frequency in CR-Africans (0.244) was similar to Africans (0.243) from Zaire (Attie Castro et al., 2000).

2.6 MTHFR 677C>T

The 677C>T mutation in the MTHFR gene was very frequent in CR groups, particularly in the CR-Indians (Table 4). The mutant allele frequency of 0.822 and the prevalence of 70% homozygous subjects found in Guaymi Indians is the highest reported in the literature to date. For comparison, in Yupka Indians from western Venezuela an allele frequency of 0.45 (homozygosity 15%) was determined (Salazar-Sánchez et al., 1999; Vizcaino et al., 2001). In five Brazilian Amazonian tribes of Indians, Franco et al. (1998) found an allele frequency of 0.240 (homozygosity 7.8%). Arruda et al. (1998) described in Amazonian Tupy Indians a frequency of 0.114 (homozygosity 1.2%). It seems that intertribal heterogeneity exists, which might be caused by isolation of small subpopulations and a high degree of consanguinity, as well as by genetic drift (Zago et al., 1996). This might also be an explanation for the deviations from the Hardy-Weinberg equilibrium we found in Guaymi Indians and CR-Africans from Limon. The extremely high prevalence of the homozygous mutant allele (TT) in CR-Indians is remarkable, particularly considering that homozygosity has been discussed as a risk factor for cardiovascular diseases (CVD) caused by mild homocysteinemia.
The relationship between homocysteine, folate, vitamin B12 levels and the MTHFR 677C>T was studied in Indians from Western Venezuela by Vizcaino et al. (2001). An elevated homocysteine level was detected in the homozygous TT group which could be partially explained by the folate deficiency found in this group. The implication for an increased risk of thrombotic events in the Yupka Indians from Venezuela does not appear to be relevant since the life expectancy in this population is relatively short and a high incidence of coronary complicactions has not been described (Diez-Ewald et al., 1999; Salazar-Sanchez et al., 2006). Clinical studies are necessary to determine the influence of this genotype on the prevalence of CVD in different ethnic groups and the relation with different life styles, e.g. folate level or vitamin B12 intake.
In CR-Africans from Limon, the TT genotype and T allele frequency were similar to that of Caucasians. The higher frequencies of the T allele in the Guanacaste CR-Africans can probably be explained by admixture with Indians in this area since the 16th/17 th century (Ibarra, 2001).

2.7 ACE

The frequency of the D allele of the ACE polymorphism and the prevalence of the DD genotype were lower in CR-Indians than in CR-blood donors, CR-Africans or Germans (Table 4). Foy et al. (1996) reported a similar low frequency of the D allele in Pima Indians. CR-Africans had the same frequencies of the ACE DD genotype or D allele as Caucasians.

This was also reported for individuals from Nigeria, Jamaica and the United States (Rotimi et al., 1996). However, it is still not clear and results are conflicting, whether there is an association between the I/D polymorphism of the ACE gene (Rotimi et al., 1996; Sagnella et al., 1999) and serum ACE activity in people of African descent (Bloem et al., 1996). All these results clearly suggest that ethnic origin should be carefully considered in association studies between ACE genotype and disease etiology.

Comparing the Indian tribes of this study, it appears that the Huetar Indians are a distinct group of CR-Indians. In Huetar Indians, the frequency of the FVL and ACE D-alleles was significantly higher and the R2-allele frequency of FV HR2 haplotype was lower than in the other tribes. These results are probably due to a higher degree of admixture with Europeans in the past, compared to other CR-Indian tribes (Barrantes et al., 1998; Ibarra, 2001). Concerning the frequencies of FV IVS16 and MTHFR polymorphisms, Chorotega Indians were different from Guatuso, Guaymi, Cabecar and Bribri, indicating their different origins. The similarity of the prevalence of the ACE polymorphism in the Chorotega and Bribri Indians is remarkable, but more markers should be studied before conclusions can be drawn. Note that in Chorotega Indians and CR-Africans from Guanacaste, ACE genotypes were not distributed as expected by the Hardy-Weinberg; the same although not significant tendency also occurred in Bribri Indians. One reason might be a higher degree of admixture with Caucasians, especially in the Chorotega, compared to the others tribes investigated in this study

In conclusion, the present study has shown that genetic polymporphisms may vary appreciably within and between racial groups. Clear differences in the prevalence of studied polymorphisms were found between the different subpopulations in Costa Rica. These results indicate the importance of considering more than one molecular risk factor for determination of the risk or predisposition for a given disease. It is necessary to analyze a panel of molecular factors to determine the genetic background of a subject or population in order to estimate the genetical predisposition to disease. It was demonstrated that the prevalence of some established risk factors was lower in CR Indians than in Caucasians (D allele of ACE) or absent (FVLeiden, FII 20210G>A polymorphisms). Concerning the FVII polymorphism the protective 77 genotype was frequent only in the Chorotegas Indians, but the protective homozygous Gln353 genotype was absent in all CR-Indian groups.

Knowledge of the prevalence of the studied polymorphisms in the Costa Rican populations provides the basis for follow studies of thrombosis in latinamerican populations.

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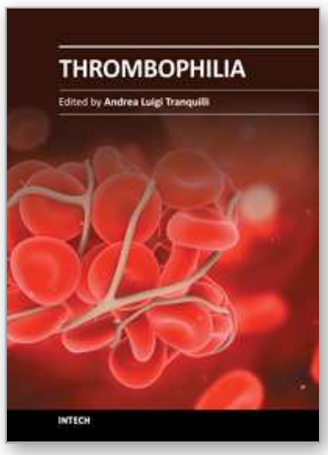

Thrombophilia

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Thrombophilia(s) is a condition of increased tendency to form blood clots. This condition may be inherited or acquired, and this is why the term is often used in plural. People who have thrombophilia are at greater risk of having thromboembolic complications, such as deep venous thrombosis, pulmonary embolism or cardiovascular complications, like stroke or myocardial infarction, nevertheless those complications are rare and it is possible that those individuals will never encounter clotting problems in their whole life. The enhanced blood coagulability is exacerbated under conditions of prolonged immobility, surgical interventions and most of all during pregnancy and puerperium, and the use of estrogen contraception. This is the reason why many obstetricians-gynecologysts became involved in this field aside the hematologists: women are more frequently at risk. The availability of new lab tests for hereditary thrombophilia(s) has opened a new era with reflections on epidemiology, primary healthcare, prevention and prophylaxis, so that thrombophilia is one of the hottest topics in contemporary medicine.

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