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

* Unknown effect.

Table 1. Characteristics of the different polymorphisms analyzed

POLYMORPHISM S	CHOROTEGA		GUATUSO		GUAYMI		CABECAR		BRIBRI		HUETAR		CR INDIANS Σ		GUANACAST E		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	100.00	29	100.00	157	100.00	149	100.00	110	99.09	152	99.34	730	99.72	179	100.00	110	99.09	289	99.65	392	97.19	170	98.80
	133	-	29	-	157	-	149	-	109	1	151	0.66	728	2	-	-	109	1	288	1	11	2.81	168	1.20
	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	20210 GA	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
20210 AA	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
f(G) f(A)	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	0.003*	1	0.005*	1	0.002*	11	0.014*	2	0.006*
FVL	132	100.00	29	100.00	156	100.00	149	100.00	110	100.00	153	96.73	724	99.31	179	99.44	113	98.23	292	98.97	392	97.70	1172	92.91
	132	-	29	-	156	-	149	-	110	-	148	3.27	724	5	1	0.56	111	1.77	289	3	9	2.30	1089	7.00
	-	-	-	-	-	-	-	-	-	-	5	-	5	0.69	-	-	2	-	3	1.03	-	-	82	0.09
	1691 AA	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	0.09
f(G) f(A)	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	52.63	23	52.17	156	80.77	149	55.03	110	40.91	153	72.55	724	61.60	178	77.53	114	90.35	292	82.54	377	80.37	358	86.03
	70	39.10	10	43.48	126	17.95	61	40.94	45	48.18	111	26.14	446	33.70	138	19.66	103	6.14	241	14.38	303	19.10	308	13.97
	52	8.27	1	4.35	28	1.28	6	4.03	53	10.91	40	1.31	244	4.70	35	0.56	-	-	42	0.34	72	0.53	50	-
	R2R2 R1R3	-	-	-	-	-	-	-	-	-	-	-	-	-	4	2.25	4	3.51	8	2.74	-	-	-	-
f(R1) f(R2) f(R3)	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	97.74	25	96.00	157	99.36	149	99.33	109	99.08	153	94.77	726	97.52	179	92.18	114	81.57	293	88.05	94	93.61	170	85.90
	130	2.26	24	4.00	156	0.64	148	0.67	108	0.92	142	5.23	708	18	14	7.82	93	18.43	258	11.95	88	6.39	146	14.10
	3	-	1	-	1	-	1	-	1	-	11	-	18	2.48	14	-	21	-	35	-	6	-	24	-
	D1D1 D1D2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
f(D1) f(D2)	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	%		
FVIIINS7 (37bp repeat)	125		28	135		134	101	98	621	145	109	254	229	115												
	46	1.60	-	-	-	-	-	-	-	-	-	-	-	-	-	3	1.18	-	1	0.44	-	-	-	-		
	47	0.80	-	-	-	-	-	-	-	-	-	-	-	-	-	1	0.39	-	-	0.44	-	-	-			
	55	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
	56	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
	57	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
	58	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
	66	23.20	23	82.14	72	53.33	69	46.94	279	44.93	35	32.11	106	46.28	37	32.17	35	32.11	93	36.61	106	46.28	37	32.17		
	67	48.80	5	17.86	48	35.55	54	44.90	254	40.90	59	40.69	108	42.53	101	44.10	54	40.69	108	42.53	101	44.10	54	40.69		
	77	24.00	-	-	15	11.12	11	8.16	82	13.21	22	15.17	19	17.43	18	7.86	18	7.86	41	16.15	18	7.86	18	15.65		
86	1.60	-	-	-	-	-	-	2	0.32	4	3.67	6	2.36	1	0.44	4	3.67	6	2.36	1	0.44	4	3.48			
87	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	0.39	-	1	0.39	-	-	1	0.87		
96	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	0.92	1	0.39	-	-	1	0.87			
f(4) f(5) f(6) f(7) f(8) f(9)	3	0.012*	-	-	-	-	-	-	3	0.002*	3	0.010*	1	0.002*	1	0.002*	4	0.005*	4	0.008*	3	0.007*	-	-	-	-
	123	0.492*	51	0.911*	192	0.716*	123	0.609*	817	0.658*	180	0.621*	124	0.569*	304	0.598*	124	0.569*	304	0.598*	133	0.578*	133	0.578*		
	122	0.488*	5	0.089*	78	0.289*	76	0.386*	419	0.337*	104	0.359*	88	0.403*	192	0.378*	88	0.403*	192	0.378*	139	0.303*	91	0.396*		
	2	0.008*	-	-	-	-	-	-	2	0.002*	3	0.010*	4	0.018*	7	0.014*	4	0.018*	7	0.014*	1	0.002*	5	0.022*		
	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
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	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
FVII73G>A 73GG 73GA 73AA	123	73.17	27	1.00	152	96.71	84	89.36	592	88.85	104	218	51	72	22	75.44	49	47.12	135	61.93	34	66.67	53	73.60		
	90	26.02	-	-	147	96.71	8	8.51	63	10.64	45	43.27	34	53	31.65	24	21.05	45	43.27	69	31.65	16	19	26.40		
	1	0.81	-	-	5	3.29	2	2.12	3	0.51	4	3.51	10	9.61	14	6.42	10	9.61	14	6.42	1	1.96	-	-		
	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
f(G) f(A)	212	0.862*	54	1.00*	299	0.984*	265	0.974*	1115	0.942*	109	0.908*	143	0.688*	196	0.860*	143	0.688*	339	0.778*	84	0.824*	125	0.868*		
	34	0.138*	-	-	5	0.016*	7	0.026*	69	0.058*	11	0.092*	65	0.312*	32	0.140*	65	0.312*	97	0.222*	18	0.176*	19	0.132*		
FVII Arg353Gln ArgArg M1M1 ArgGln M1M2 GlnGln M2M2	117	-	27	151	-	132	108	92	627	150	108	258	235	96	77.52	122	81.33	200	77.52	50	19.38	175	74.47	71	73.95	
	88	75.21	27	100.00	148	98.01	96	88.89	552	88.04	74	80.43	78	72.22	122	81.33	78	72.22	200	77.52	57	24.25	22	22.92		
	29	24.79	-	-	3	1.99	12	11.11	75	11.96	18	19.57	27	25.00	23	15.33	27	25.00	50	19.38	3	1.28	3	3.13		
	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
f(Arg353) M1 f(Gln353) M2	205	0.876*	54	1.00*	299	0.990*	251	0.951*	1179	0.940*	166	0.902*	183	0.847*	267	0.890*	183	0.847*	450	0.872*	407	0.866*	164	0.854*		
	29	0.124*	-	-	3	0.010*	13	0.049*	75	0.060*	18	0.098*	33	0.153*	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	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%										
EXII 46C>T 46 CC 46 CT 46 TT	127	48.82	26	46.15	153	56	36.60	106	24	22.64	95	51.58	84	30	35.71	591	33	35.48	49	11	22.45	142	30.99	44	24	43.63	55	24	43.63	97	69.07																	
	62	34.65	13	50.00	70	45.75	62	58.49	40	42.11	39	46.43	30	35.71	233	39	42	33	22	44.90	58	40.85	29	52.74	24	24	52.74	67	24	24.74	67	69.07																
	44	16.53	1	3.85	27	17.65	20	18.87	6	6.31	15	17.86	90	15.23	268	45	36	36	16	32.65	2	28.16	58	40.85	2	3.63	6	6.19	6	6.19	24	24.74																
	21	0.660*	37	0.710*	182	0.590*	110	0.520*	138	0.730*	99	0.590*	734	0.620*	102	0.548*	448	0.380*	84	0.452*	54	0.551*	138	0.486*	33	0.300*	36	0.186*	158	0.814*																		
f(C) f(T)	86	0.340*	15	0.290*	124	0.410*	102	0.480*	52	0.270*	69	0.410*	84	0.452*	54	0.551*	138	0.486*	33	0.300*	36	0.186*	158	0.814*	36	0.186*	158	0.814*	36	0.186*	158	0.814*	36	0.186*														
	133	81.95	25	36.00	157	120	76.43	141	77	54.61	153	89	58.17	114	70	61.40	165	56.70	210	55.12	99	51.03	194	51.03	194	51.03	194	51.03	194	51.03	194	51.03	194	51.03														
	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	140	36.74	83	42.78	140	36.74	83	42.78	140	36.74	83	42.78												
	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	5.80	31	8.14	12	6.19	31	8.14	12	6.19	31	8.14	12	6.19	31	8.14	12	6.19												
f(Val34) f(Leu34)	241	0.910*	29	0.590*	269	0.860*	205	0.730*	114	0.710*	229	0.750*	1087	0.790*	262	0.740*	178	0.780*	50	0.220*	142	0.244*	202	0.266*	202	0.266*	202	0.266*	202	0.266*	202	0.266*	202	0.266*	202	0.266*												
	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*	202	0.266*	202	0.266*	202	0.266*	202	0.266*	202	0.266*	202	0.266*	202	0.266*												
	133	59	44.36	17	68.00	92	58.60	103	68.67	47	42.73	32	20.91	728	48.08	38	21.23	14	12.39	52	17.80	101	28.77	101	28.77	101	28.77	101	28.77	101	28.77	101	28.77	101	28.77	101	28.77											
	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	163	46.44	163	46.44	163	46.44	163	46.44	163	46.44	163	46.44	163	46.44	163	46.44										
f(I) f(D)	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*	141	0.624*	315	0.539*	365	0.461*	337	0.480*	337	0.480*	337	0.480*	337	0.480*	337	0.480*	337	0.480*	337	0.480*										
	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*	365	0.461*	337	0.480*	337	0.480*	337	0.480*	337	0.480*	337	0.480*	337	0.480*	337	0.480*	337	0.480*										
	133	13.53	1	3.45	9	5.73	5	3.40	10	9.09	21	13.73	64	8.78	74	66.67	74	66.67	74	66.67	74	66.67	74	66.67	74	66.67	74	66.67	74	66.67	74	66.67	74	66.67	74	66.67	74	66.67										
	18	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	180	45.92	180	45.92	180	45.92	180	45.92	180	45.92	180	45.92	180	45.92	180	45.92										
f(C) f(T)	110	0.414*	16	0.276*	56	0.178*	68	0.231*	74	0.336*	121	0.395*	445	0.308*	191	0.534*	177	0.797*	45	0.203*	368	0.634*	390	0.497*	390	0.497*	390	0.497*	390	0.497*	390	0.497*	390	0.497*	390	0.497*	390	0.497*	390	0.497*								
	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*	394	0.503*	212	0.366*	394	0.503*	394	0.503*	394	0.503*	394	0.503*	394	0.503*	394	0.503*	394	0.503*	394	0.503*	394	0.503*								

*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) demonstrated 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; Bernardi 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 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 intracerebral 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 et 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 complications 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/17th 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 polymorphisms 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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4. References

Agerholm-Larsen B, Nordestgaard BG, Tybjaerg-Hansen A. ACE gene polymorphism in cardiovascular disease: meta-analyses of small and large studies in whites. *Arterioscler Thromb Vasc Biol* 2000; 20: 484-492.

- Anwar R, Gallivan L, Edmonds SD, Markham AF. Genotype/phenotype correlations for coagulations factor XIII: specific normal polymorphisms are associated with high or low factor XIII specific activity. *Blood* 1999; 93:897-905.
- Arruda VR, Siqueira LH, Goncalves MS, Von Zuben PM, Soares MCP, Menezes R, Annichino Bizzacchi JM, Costa FF. Prevalence of the mutation C677T in the Methylene Tetrahydrofolate reductase gene among distinct ethnic groups in Brazil. *Am J Med Genet* 1998; 78:322-335.
- Attié-Castro F, Zago AM, Lavinha J, Elion J, Rodriguez-Delfin L, Gerreiro JF, Franco R. Ethnic heterogeneity of the factor XIII Val34Leu polymorphism. *Thromb Haemost* 2000; 84: 601-603.
- Balleisen L, Bailey J, Epping P-H, Schulte H, van de Loo J. Epidemiological study on factor VII, factor VIII and fibrinogen in an industrial population: I. baseline data on the relation to age, gender, body-weight, smoking, alcohol, pill-using, and menopause. *Thromb Haemost* 1985; 54: 475-479.
- Balogh I, Póka R, Pfiegler G, Dékány M, Bereczky Z, Muszbek L. Prevalence of genetically determined major thrombosis risk factors in Eastern-Hungary. *Thromb Haemost* 1999; 82 (suppl) 667.
- Barrantes R, Smouse PE, Mohrenweiser HW, Gershowitz H, Azofeifa J, Arias TD, Neel JV. Microevolution in Lower Central America: Genetic characterization of the Chibcha-speaking groups of Costa Rica and Panama, and a consensus taxonomy based on genetic and linguistic affinity. *Am J Hum Genet* 1990; 46: 63-84.
- Barrantes R. Desarrollo y perspectivas de la genética humana en Costa Rica. *Acta Med Cost* 1998; 12: 87-94.
- Bernardi F, Faioni EM, Castoldi E, Lunghi B, Castaman G, Sacchi E, Mannucci PM. A factor V genetic component differing from factor V R506Q contributes to the activated Protein C Resistance phenotype. *Blood* 1997; 90:1552-1557.
- Bernardi F, Aricieri P, Bertina RM, Chiarotti F, Corral J, Pinotti M, Prydz H, Samama M, Sandset PM, Strom R, Vincente Garcia V, Mariani G. Contribution of factor VII genotype to activated FVII levels. Differences in genotype frequencies between Northern and Southern european populations. *Arterioscler Thromb Vasc Biol* 1997a; 17: 2548-2553.
- Bloem LJ, Manatunga AK, Pratt JH. Racial difference in the relationship of an angiotensin I-converting enzyme gene polymorphism to serum angiotensin I-converting enzyme activity. *Hypertension* 1996; 27:62-66.
- Castaman G, Ruggeri M, Tosetto A, Rodeghiero F. Heterogeneity of activated Protein C resistance phenotype in subjects with compound heterozygosity for HR2 haplotype and FV Leiden mutation (R506Q) in factor V gene. *Thromb Haemost* 2000; 84:357-358.
- Castoldi E, Lunghi B, Mingozzi F, Ioannou I, Marchetti G, Bernardi F. New coagulation factor V gene polymorphisms define a single and infrequent haplotype underlying the Factor V Leiden mutation in mediterranean populations and indians. *Thromb Haemost* 1997; 78:1037-1041.
- Castoldi E. Molecular bases of APC-resistance and factor V deficiency in thrombophilia. Ph.D thesis, University of Ferrara, Italy. 2000

- Catto AJ, Kohler HP, Bannan S, Stickland M, Carter A, Grant PJ. Factor XIII Val34Leu. A novel association with primary intracerebral hemorrhage. *Stroke* 1998; 29: 813-816.
- Catto AJ, Kohler HP, Coore J, Mansfield MW, Stickland MH, Grant PJ. Association of a common polymorphism in the factor XIII gene with venous thrombosis. *Blood* 1999; 93:906-908.
- Della Valle CJ, Issack PS, Baitner A, Steiger DJ, Fang C, Di Cesare PE. The relationship of the factor V Leiden mutation or the deletion-deletion polymorphism of the angiotensin converting enzyme to postoperative thromboembolic events following total joint arthroplasty. *BMC Musculoskelet Disord* 2001; 2:1.
- de Maat MPM, Green F, de Knijff P, Jespersen G, Kluft C. Factor VII polymorphisms in populations with different risk of cardiovascular disease. *Arterioscler Thromb Vasc Biol* 1997; 17: 1918-1923.
- de Visser MCH, Guasch JF, Kamphuisen PW, Vos HL, Rosendaal FR, Bertina RM. The HR2 haplotype of factor V: Effects on factor V levels, normalized activated protein C sensitivity ratios and the risk of venous thrombosis. *Thromb Haemost* 2000; 83: 577-582.
- Di Castelnuovo A, D'Orazio A, Amore C, Falanga A, Kluft C, Donati MB, Iacoviello L. Genetic modulation of coagulation factor VII plasma levels: contribution of different polymorphism and gender-related effects. *Thromb Haemost* 1998; 80: 592-597.
- Domenico G, Carla R, Ferraresi P, Olivieri O, Pinotti M, Friso S, Manzato F, Mazzucco A, Benardi F, Corrocher R. Polymorphisms in the factor VII gene and the risk of myocardial infarction in patients with coronary artery disease. *N Engl J Med* 2000; 343: 774-780.
- Faioni EM, Franchi f, Bucciarelli P, Margaglione M, de Stefano V, Castaman G, Finazzi G, Casorelli I, Mannucci PM. The HR2 haplotype in the factor V gene confers an increased risk of venous thromboembolism to carriers of factor V R506Q. *Thromb Haemost* 1999; 82(suppl): 418.
- Faioni EM. Factor V HR2: An ancient haplotype out of Africa - reasons for being interested. *Thromb Haemost* 2000; 83: 358-359.
- Foy CA, McCormack LJ, Knowler WC, Barret JH, Catto A, Grant PJ. The angiotensin-I converting enzyme (ACE) gene I/D polymorphism and ACE levels in Pima Indians. *J Med Genet* 1996; 33: 336-337.
- Franco RF, Reitsma PH, Lourenco D, Maffei FH, Morelli V, Tavella MH, Araújo AG, Piccinato CE, Zago MA. Factor XIII Val34Leu is a genetic factor involved in the aetiology of venous thrombosis. *Thromb Haemost* 1999; 81: 676-679.
- Franco RF, Reitsma PH. Genetic risk factors of venous thrombosis. *Human Genet* 2001; 109: 369-384.
- Frosst P, Blom HJ, Milos R, Goyette P, Sheppard CA, Matthews RG, Boers GJ, den Heijer M, Kluijtmans LAJ, van den Heuvel LP, Rozen R. A candidate genetic risk factor for vascular diseases: a common mutation in methylenetetrahydrofolate reductase. *Nat Genet* 1995; 10: 111-113.

- Green F, Kelleher C, Wilkes H, Temple A, Meade T, Humphries S. A common genetic polymorphism associated with lower coagulation factor VII level in healthy individuals. *Arterioscler Thromb* 1991; 11: 540-546.
- Halbmayer WA, Haushofer A, Radek J, Schön R, Deutsch M, Fischer M. Prevalence of factor XII (Hageman Factor) deficiency among 426 patients with coronary heart disease awaiting cardiac surgery. *Coron Artery Dis* 1994; 5: 451-454.
- Heinrich J, Balleisen L, Schulte H, Assmann G, van de Loo J. Fibrinogen and factor VII in the prediction of coronary risk. Results from the PROCAM study in healthy men. *Arterioscler Thromb* 1994; 14: 54-59.
- Herrmann FH, Koesling M, Schröder W, Altman R, Jimenez Bonilla R, Lopaciuk S, Perez-Requejo JL, Singh JR. Prevalence of factor V Leiden mutation in various populations. *Genet Epidemiol* 1997; 14: 403-411.
- Herrmann FH, Schröder W, Altman R, Jimenez Bonilla R, Perez-Requejo JL, Singh JR. Zur Prävalenz des G20210A-Prothrombin-Polymorphismus, der C677T-Mutation des MTHFR-Gens und der Faktor V-Leiden Mutation in Nordostdeutschland, Argentinien, Venezuela, Costa Rica und Indien. In: I. Scharrer/W. Schramm (Hrsg.) 28. Hämophilie-Symposium Hamburg 1997. Springer-Verlag Berlin Heidelberg 1999: 305-309.
- Herrmann FH, Wulff K, Auberger K, Aumann V, Bergmann F, Bergmann K, Bratanof E, Franke D, Grundeis M, Kreuz W, Lenk H, Losonczy H, Maak B, Marx G, Mauz-Körholz C, Pollmann H, Serban M, Sutor A, Syrbe G, Vogel G, Weinstock N, Wenzel W, Wolf K. Molecular biology and clinical manifestation of hereditary factor VII deficiency. *Semin Thrombos Hemost* 2000; 26: 393-400.
- Herrmann FH, Salazar-Sanchez L, Wulff K, Grimm R, Schuster G, Jimenez-Aru, Chavez M, Schröder W. Prevalence of common mutations and polymorphisms of the genes of FII, FV, FVII, FXIII, MTHFR and ACE. Identified as risk factors for venous and arterial thrombosis in Germany and different ethnic groups (Indians, Blacks) of Costa Rica. In: I. Scharrer/W. Schramm (Hrsg.) 30. Hämophilie-Symposium Hamburg 1999. Springer-Verlag Berlin Heidelberg 2001: 240-257.
- Hoekema L, Castoldi E, Tans G, Manzato F, Bernardi F, Rosing J. Characterization of blood coagulation factor V (a) encoded by the R2-gene. *Thromb Haemost* 1999; 82 (Suppl.): 684.
- Hoekema L, Castoldi E, Tans G, Girelli D, Gemmati D, Bernardi F, Rosing J. Functional properties of factor V and factor Va encoded by the R2-gene. *Thromb Haemost* 2001; 85: 75-81.
- Hong Y, Pedersen NL, Egberg N, de Faire U. Genetic effects for plasma factor VII levels independent of and in common with triglycerides. *Thromb. Haemost* 1999; 81: 382-386.
- Humphries SE, Lane A, Green FR, Cooper J, Miller GJ. Factor VII coagulant activity and antigen levels in healthy men are determined by interaction between factor VII genotype and plasma triglyceride concentration. *Arterioscler Thromb Vasc Biol.* 1994; 14: 193-198.

- Iacoviello L, Di Castelnuovo A, De Knijff P, D'Orazio A, Amore C, Arboretti R, Kluft C, Donati MB. Polymorphisms in the coagulation factor VII gene and the risk of myocardial infarction. *N Engl J Med* 1998; 338: 79-85.
- Ibarra E. Fronteras étnicas en la conquista de Nicaragua y Nicoya. Entre la solidaridad y el conflicto 200 d.c.-1544. Editorial Universidad de Costa Rica. San José, Costa Rica. 2001.
- Kain K, Catto A, Kohler HP, Grant PJ. Haemostatic risk factors in healthy white and south asian populations in U.K. *Thromb Haemost* 1999; 82 (suppl.) 185.
- Kanaji T, Okamura T, Osaki K, Kuroiwa M, Shimoda K, Hamasaki N, Niho Y. A common genetic polymorphism (46C to T substitution) in the 5'-untranslated region of the coagulation factor XII gene is associated with low translation efficiency and decrease in plasma factor XII level. *Blood* 1998; 91: 2010-2014.
- Kario K, Narita N, Matsuo T, Kayaba K, Tsutsumi A, Matuso M, Miyata T, Shimada K. Genetic determinants of plasma FVII activity in the Japanese. *Thromb Haemost* 1995; 73: 617-622.
- Kelleher CC, Mitropoulos KA, Imeson J, Meade TW, Martin JC, Reeves BEA, Hughes LO. Hageman factor and risk of myocardial infarction in middle-aged men. *Atherosclerosis* 1992; 97: 67-73.
- Khandanpour N, Willis G, Meyer FJ, Armon MP, Loke YK, Wright AJ, Finglas PM, Jennings BA. Peripheral arterial disease and methylenetetrahydrofolate reductase (MTHFR) C677T mutations: A case-control study and meta-analysis. *J Vasc Surg*. 2009 Mar;49(3):711-8.
- Kluijtmans LAJ, Kastelein JJP, Lindemans J, Boers GHJ, Heil SG, Bruschke AVG, Jukema JW, van den Heuvel LPWJ, Trijbels JMF, Boerma GJM, Verheugt FWA, Willems F, Blom HJ. Thermolabile methylenetetrahydrofolate in coronary artery disease. *Circulation* 1997; 96: 2573-2577.
- Kohler HP, Stickland MH, Ossei-Gerning N, Carter A, Mikkola H, Grant PJ. Association of a common polymorphism in the factor XIII gene with myocardial infarction. *Thromb Haemost* 1998; 79: 8-13.
- Kohler HP, Futers TS, Grant PJ. FXII (46 C→T) polymorphism and in vivo generation of FXII activity. *Thromb Haemost* 1999; 81: 745-747.
- Koster T, Rosendaal FR, Briet E, Vandenbroucke JP. John Hageman's factor and deep vein thrombosis: Leiden Thrombophilia Study. *Br J Haematol* 1994;87: 422-424.
- Lämmle B, Wuillemin WA, Huber I, Krauskopf M, Zürcher C, Pflugshaupt R, Furlan M. Thromboembolism and bleeding tendency in congenital factor XII deficiency-A study on 74 subjects from 14 Swiss families. *Thromb Haemost* 1991; 65: 117-121.
- Lane A, Cruickshank JK, Mitchell J, Henderson A, Humphries S, Green F. Genetic and environmental determinants of factor VII coagulant activity in ethnic group at differing risk of coronary heart disease. *Atherosclerosis* 1992; 94: 43-50.
- Lane A, Green F, Scarabin PY, Nicaud V, Bara L, Humphries S, Evans A, Luc G, Cambou JP, Arveiler D, Cambie F. Factor VII Arg/Gln353 polymorphism determines factor VII coagulant activity in patients with myocardial infarction (MI) and control subjects in Belfast and France but is not a strong indicator of MI risk in the ECTIM study. *Artherosclerosis* 1996; 119: 119-127.

- Lane DA, Grand PJ. Role of hemostatic gene polymorphisms in venous and arterial thrombotic disease. *Blood* 2000; 95: 1517-1532.
- Lunghi B, Iacoviello L, Gemmati D, DiLasio MG, Castoldi E, Pinotti M, Castaman G, Redaelli R, Mariani G, Marchetti G, Bernardi F. Detection of new polymorphic markers in the factor V gene: Association with factor V levels in plasma. *Thromb Haemost* 1996; 75: 45-48.
- Lunghi B, Castoldi E, Mingozzi F, Bernardi F. A new factor V gene polymorphism (His1254Arg) present in subjects of African origin mimics the R2 polymorphism (His1299Arg). *Blood* 1998; 91: 364-365.
- Mannhalter C, Fischer M, Hopmeier P, Deutsch E. Factor XII activity and antigen concentrations in patients suffering from recurrent thrombosis. *Fibrinolysis* 1987; 1: 259-263.
- Marchetti G, Gemmati D, Patracchini P, Pinotti M, Bernardi F. PCR detection of a repeat polymorphism within the F7 gene. *Nucleic Acids Res* 1991; 19: 4570.
- Marchetti G, Petracchini P, Papacchini M, Ferrati M, Bernardi F. A polymorphism in the 5' region of coagulation factor VII gene (F7) caused by an inserted decanucleotide. *Hum Genet* 1993; 90: 575-576.
- Marchetti G, Ferraresi P, Quaglio S, Taddia C, Chiozzi A, Cataldi A, Bernardi F, Mascoli F. Study of FV genetic markers in carotid artery disease. *Thromb Haemost* 1999; 82 (suppl.): 450.
- Margaglione M, D'Andrea G, d'Addetta M, Giuliani N, Cappucci G, Iannaccone L, Vecchione G, Grandone E, Brancaccio V, Di Minno G. The methylenetetrahydrofolate reductase TT677 genotype is associated with venous thrombosis independently of the coexistence of the FV Leiden and the prothrombin A²⁰²¹⁰ mutation. *Thromb Haemost* 1998; 79: 907-911.
- Mariani G, Marchetti G, Arcieri P, Bernardi F. The role of factor VII gene polymorphism in determining FVII activity and antigen plasma level. *Blood* 1994; 84 (suppl)1: 86a.
- Markus HS, Barley J, Lunt R, Bland JM, Jeffery S, Carter ND, Brown MM. Angiotensin-converting enzyme gene deletion polymorphism - A new risk factor for lacunar stroke but not carotid atheroma. *Stroke* 1995; 26: 1329-1333.
- McCormack LJ, Kain K, Catto AJ, Kohler HP, Stickland MH, Grant PJ. Prevalence of FXIII V34L in populations with different cardiovascular risk. *Thromb Haemost* 1998; 80: 523-524.
- Meade TW, Brozovic M, Chakrabarti RR, Haines AP, Imeson JD, Mellows S, Miller GJ, North WRS, Stirling Y, Thompson SG. Haemostatic function and ischaemic heart disease: principal results of the Northwick Park Heart Study. *Lancet* 1986; 2: 533-537.
- Meléndez C, Duncan Q. El Negro en Costa Rica durante la colonia. Editorial Costa Rica, San José, Costa Rica. 1989.
- Mennen LJ, Schouten EG, Grobbee DE, Kluft C. Coagulation factor VII dietary fat and blood lipids: a review. *Thromb Haemost* 1996; 76: 492-499.
- Mikkola H, Syrjälä M, Rasi V, Vahtera E, Hämläinen E, Peltonen I, Paotie A. Deficiency in the A-subunit of coagulation factor XIII: two novel point mutations demonstrate different effects on transcript levels. *Blood* 1994; 84: 517-525.

- Miller GJ, Martin JC, Mitropoulos KA, Reeves BE, Thompson RL, Meade TW, Cooper JA, Cruickshank JK. Plasma factor VII is activated by postprandial triglyceridemia, irrespective of dietary fat composition. *Atherosclerosis* 1991; 86: 163-171.
- Morita H, Taguchi H, Kurihara H, Kitaoka M, Kaneda H, Kurihara Y, Maemura K, Shindo T, Minamino T, Ohno M, Yamaoki K, Ogasawara K, Aizawa T, Suzuki S, Yazaki Y. Genetic polymorphism of 5,10-methylenetetrahydrofolate reductase (MTHFR) as a risk factor for coronary artery disease. *Circulation* 1997; 95: 2032-2036.
- Muszbek L. Deficiency causing mutations and common polymorphisms in the factor XIII-A gene. *Thromb Haemost* 2000; 84: 524-527.
- Niccoli G, Iacovello L, Cianflone D, Crea F. Coronary risk factors: new perspectives. *Int J Epidemiol* 2001; 30: S41-S47.
- Ozmen F, Ozmen MM, Ozalp N, Akar N. The prevalence of factor V (G1691A), MTHFR (C677T) and PT (G20210A) gene mutations in arterial thrombosis. *Ulus Travma Acil Cerrahi Derg (Turkish J Trauma & Emergency Surgery)* 15: 113-119, 2009
- Palmer P. Wa'apin man: la historia de la costa talmanquena de Costa Rica, según sus protagonistas. 2ed. Editorial de la Universidad de Costa Rica, San José, Costa Rica. 2000: 13-110.
- Pandita D, Steen P, Potti A. Risk factors for deep venous thrombosis of the upper extremities. *Ann Int Med* 1997; 127: 1129.
- Philipp CS, Dilley A, Saidi P, Evatt B, Austin H, Zawadsky J, Harwood D, Ellingsen D, Barnhart E, Phillips DJ, Craig W. Deletion polymorphism in the angiotensin-converting enzyme gene as a thrombophilic risk factor after hip arthroplasty. *Thromb Haemost* 1998; 80: 869-873.
- Pinotti M, Toso R, Girelli D, Bindini D, Ferraresi P, Papa ML, Corrocher R, Marchetti G, Bernardi F. Modulation of factor VII levels by intron 7 polymorphisms: population and in vitro studies. *Blood* 2000; 95: 3423-3428.
- Rees DC, Cox M, Clegg JB. World distribution of factor V Leiden. *Lancet* 1995; 346:1133-1134.
- Reiner A, Schwartz S, Frank M, Longstreth WT, Hindorff LA, Teramura G, Rosendaal FR, Gaur LK, Psaty BM, Siscovick D. Polymorphisms of coagulation factor XIII subunit A and risk of nonfatal hemorrhagic stroke in young white women. *Stroke* 2001a; 32: 2580-2587.
- Rieder M, Scott LT, Clark AG, Nickerson DA. Sequence variation in the human angiotensin converting enzyme. *Nature Genetics* 1999; 22: 59-62.
- Rosendaal FR, Doggen CJ, Zivelin A, Arruda VR, Aiach M, Siscovick DS, Hillarp A, Watzke HH, Bernardi F, Cumming AM, Preston FE, Reitsma PH. Geographic distribution of the 20210 G to A prothrombin variant. *Thromb Haemost* 1998; 79: 706-708.
- Rosendaal FR, Grant PJ, Ariens RAS, Poort SR, Bertina RM. Factor XIII Val34Leu, factor XIII antigen and activity levels and risk of venous thrombosis. *Thromb Haemost* 1999; 82 (suppl.) 508.
- Rotimi C, Puras A, Cooper R, McFarlane-Anderson N, Forrester T, Ogunbiyi O, Morrison L, World R. Polymorphisms of renin-angiotensin genes among Nigerians, Jamaicans, and African Americans. *Hypertension* 1996; 27: 558-563.
- Sagnella GA, Rothwell MJ, Onipinla AK, Wicks PD, Cook DG, Cappuccio FP A population study of ethnic variations in the angiotensin-converting enzyme I/D

- polymorphism: relationships with gender, hypertension and impaired glucose metabolism. *J Hypertens* 1999; 17: 657-664.
- Salazar-Sánchez L, Schröder W, Vizcaino G, Perez-Resquejo JL, Jiménez G, Grimm R, Herrmann FH The prevalence of three molecular risk factors (G20210A, Prothrombin, C677T MTHFR, factor V Leiden) in various ethnic groups in Costa Rica and Venezuela. *Thromb Haemost* 1999; 82 (suppl): 275.
- Schröder W, Konrad H, Grimm R, Schuster G, Herrmann FH. Factor V variants- FV Leiden, FV R2 polymorphism (ex13), FV Dde-I polymorphism (Int 16). Risk factors for venous thrombosis? Results of a Pilot Study. 30th Hemophilia Symposium Hamburg 1999. Scharrer, Schramm (eds), Springer-Verlag, Berlin, 2001; 261-265.
- Thiel BA. Monografía de la población de la República de Costa Rica en el siglo XIX, 2d Ed. Editorial Costa Rica, San José, Costa Rica. 1977; 15-72.
- Thompson EA, Neel JV, Smouse PE, Barrantes R Microevolution of the Chibcha-speaking peoples of lower Central America: rare genes in an Amerindian complex. *Am J Hum Genet* 1992; 51: 609-626.
- Tishkoff SA, Dietzsch E, Speed W, Pakstis AJ, Kidd JR, Cheung K, Bonn-Tamir B, Santachiara-Benerecetti AS, Moral P, Krings M, Pbo S, Watson E, Risch N, Jenkins T, Kidd KK Global patterns of linkage disequilibrium at the CD4 Locus and modern human origins. *Science* 1996; 271: 1380-1387.
- Torroni A, Neel JV, Barrantes R, Schurr TG, Wallace DC. Mitochondrial DNA "clock" for the Amerinds and its implications for timing their entry into North America. *Proc Natl Acad Sci USA* 1994; 91: 1158-1162.
- Tug E, Aydin H, Kaplan E, Dogruer D. Frequency of genetic mutations associated with thromboembolism in the Western Black Sea Region. *Intern Med*. 2011;50(1):17-21.
- Vizcaino G, Diez-Ewald M, Herrmann FH, Schuster G, Perez-Resquejo JL. Relationships between homocysteine, folate and vitamin B12 levels with the methylenetetrahydrofolate reductase polymorphism in Indians from Western Venezuela. *Thromb Haemost* 2001; 85: 186-187.
- Zago MA, Silva Jr WA, Tavella MH, Santos SEB, Guerreiro JF, Figueiredo MS Interpopulational and intrapopulational genetic diversity of Amerindians as revealed by six VNTRs. *Human Hered* 1996; 46: 274-289.
- Zeerleder S, Schloesser M, Redondo M, Wuillemin WA, Engel W, Furlan M, B Lmle. Revaluation of the incidence of thromboembolic complications in congenital factor XII deficiency. *Thromb Haemost* 1999; 82: 1240-1246.
- Zito F, Drummond F, Bujac S, Esnouf P, Morrissey J, Humphries SE, Miller GJ. Epidemiological and genetic associations of activated factor XII concentration with factor VII activity, fibrinopeptide A concentration, and risk of coronary heart disease in Men. *Circulation* 2000;102: 2058-2062.
- Zivellin A, Griffin JH, Xu X, Pabinger I, Samama M, Conrad J, Brenner B, Eldor A, Seligsohn U. A single genetic origin for a common Caucasian risk factor for venous thrombosis. *Blood* 1997; 89: 397- 402.

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-gynecologists 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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