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TO THE EDITOR:

Archeogenetics of *F11* p.Cys38Arg: a 5400-year-old mutation identified in different southwestern European countries

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Factor XI (FXI) is a key element for the amplification of thrombin generation, which participates in the contact pathway. This explains why FXI deficiency has minor physiological relevance but protects against thrombotic events, supporting FXI as an excellent target for antithrombotic treatments.[1,2]

FXI deficiency (MIM #612416) has been considered a rare disorder that might reach relatively high prevalence in certain populations. The best example is within the Ashkenazi Jews, demonstrating an incidence of 8% of heterozygous individuals for 2 mutations: p.Glu117Ter and p.Phe283Leu, which account for 98% of alleles.[3] So far, 220 different causative mutations have been identified throughout the FXI gene (*F11*) (http://www.factorix.org/). Recently, the exome-based data obtained from >60 000 individuals (Exome Aggregation Consortium) have revealed new information regarding genetic variation in *F11*, showing (a) profound differences in heterozygous frequency among populations, and (b) evidence of recurrent and ethnic-specific mutations: (1) p.Phe223Leu in Africans (23.5% of all mutated alleles); (2) p.Gln263Ter and p.Leu424CysfsTer in East Asians (28.2% and 20.5%, respectively); and (3) p.Ala412Thr in Latinos (25%).[4]

Table 1. *F11* haplotype of carriers of the p.Cys38Arg gene variation

dbSNP ID	rs4253398	rs3822057	rs4241823	rs4253405	rs4241824	rs566328623	rs2036914	p.Cys38Arg (rs121965069)	rs4253409	rs2055916	rs4253416	rs4253417	rs3756011	rs2289252
chr4*	187188061	187188152	187189294	187190810	187191787	187191859	187192481	187192873	187194685	187196510	187197994	187199005	187206249	187207381
HGVSc†	c.-1-229T>C	c.-1-138A>C	c.55+949T>A	c.56-1953A>G	c.56-976G>A	c.56-904T>A	c.56-282T>C	c.166T>C	c.325+354C>T	c.486-431G>A	c.755+450C>T	c.755+1461T>C	c.1305-543C>A	c.1481-188C>T
Type	Intron 1	Intron 1	Intron 2	Intron 2	Intron 2	Intron 2	Intron 2	Exon 3	Intron 4	Intron 5	Intron 7	Intron 7	Intron 11	Intron 12
Frequency‡	0.211	0.462	0.461	0.294	0.413	0.007	0.393	0.00002	0.263	0.515	0.594	0.297	0.321	0.319
Allele	C	A	T	G	G	A	T	C	T	A	T	C	A	T

Localization of intragenic polymorphic markers associated to this mutation. The MAF (data from 1000 Genomes Project) and associated alleles are shown.
*NC_000004.11.
†NM_000128.3.
‡The allele frequency from all populations of 1000 genomes data, April 2012 version 3.

The screenings of FXI deficiency for 20 years in Yecla, a small town in the southeast of Spain, have revealed a recurrent point mutation, c.166T>C p.Cys38Arg, identified in 24 out of 46 unrelated cases (52%), and reached a frequency of 2% in the general population.[5] This mutation was initially described in the French Basque country as the most prevalent genetic defect causing FXI deficiency (8 out of 12 cases: 66.7%) and also with high frequency in the general population (1%).[6] The same mutation was identified in French Brittany in 3 out of 12 cases (25%).[7] One Portuguese patient also had this mutation.[8] Here, we detected this mutation in 14 out of 55 (25.5%) unrelated cases with FXI deficiency from Barcelona (in the northeast of Spain but 487 km away from Yecla). However, it has never been described in patients with FXI deficiency from non-European populations[9-11] and was also absent from large UK or Italy cohorts of patients (supplemental Figure 1, available on the *Blood* Web site).[12,13]

Because p.Cys38Arg mutation was thought to be related to a founder effect in the French Basque country,[6] the present study was performed to confirm a potential common founder effect and to estimate its occurrence time.

This study was conducted in 64 subjects with the p.Cys38Arg mutation (30 from Yecla; 27 from Barcelona; 3 from the French Brittany; and 4 from the French Basque Country) well characterized by molecular, functional, and biochemical methods previously described.[5] In addition, 20 unrelated noncarrier family trios from Yecla were enrolled as controls. All subjects gave their informed consent to enter the study, which was performed according to the Declaration of Helsinki (Edinburgh 2000) (see supplemental Materials for additional information).

The whole *F11* (23 Kpb) was sequenced by next-generation sequencing (supplemental Materials).[5] All carriers shared a unique intragenic haplotype. The selection of single-nucleotide polymorphisms with minor allele frequency (MAF) < 0.6 revealed the common *F11* haplotype containing 13 polymorphisms, rs566328623 (MAF 0.007) being the most informative variant linked to the p.Cys38Arg mutation (Table 1).

Interestingly, rs4253413 c.486-361C>T (MAF 0.217) was exclusively detected in all carriers from Yecla, but was absent from all other subjects.

Four microsatellite markers covering 1.7 Mbp upstream and 1.8 Mbp downstream of *F11* (supplemental Figure 2; supplemental Materials) were also evaluated.

Extragenic haplotypes were established from homozygous cases and by allele segregation among family. In cases without information, we chose the allele associated with the lowest number of recombination events.

Microsatellite analysis revealed at least 23 potential different extragenic haplotypes among carriers (Table 2), none present in any of the 60 healthy subjects from the family trios coming from Yecla (Fisher's exact test, $P < .0001$).

The extragenic diversity was lower among carriers from small or isolated populations as Yecla and Brittany than in carriers from the big city of Barcelona (Table 2), as also the linkage of

Table 2. Haplotypes defined by *F11* extragenic microsatellites markers identified among carriers of the *F11* p.Cys38Arg mutation

D4S3047	D4S2924	*F11*p.Cys38Arg	D4S3051	D4S2921	Allele number	Origin
7 (240 pb)	4 (220 pb)	+	1 (244 pb)	3 (161 pb)	3	Barcelona
−1*	4	+	1	7(171 pb)	1	
7	4	+	1	7	1	
4 (234 pb)	4	+	2 (246 pb)	3	1	
7	4	+	2	7	2	
4	4	+	1	5 (167 pb)	1	French Brittany
4	4	+	1	7	1	
7	4	+	1	5	1	
7	6 (224 pb)	+	1	6 (169 pb)	1	Barcelona
3 (232 pb)	6	+	2	3	1	
−1	7 (226 pb)	+	1	7	1+1 (Brittany)	
−1	7	+	2	−1	1	French Basque
4	8 (228 pb)	+	1	3	1	Yecla
4	8	+	1	7	2	
6 (238 pb)	8	+	1	7	1	
7	8	+	1	3	2	
7	8	+	1	7	18+1 (Barcelona)	
8 (242 pb)	8	+	1	3	1	
8	8	+	1	6	1	
8	8	+	1	7	1	Barcelona
3	8	+	2	10 (177 pb)	1	
7	8	+	2	3	1	
9 (244 pb)	8	+	2	3	1	
					47	Total

*It was not possible to be established; the mutated allele could be 4 (234 bp) or 7 (240 bp).

disequilibrium analysis showed (supplemental Table 1; supplemental Materials).

Although the extragenic haplotype was only partially determined in carriers from the Basque Country, microsatellite data showed a remarkable genetic diversity, particularly in the markers closer to *F11* (supplemental Table 2).

Estimation of the p.Cys38Arg mutation age was carried out using the Bayesian method proposed by Rannala and Reeve[14] and implemented by Disease Mapping Linkage disEquilibrium software (DMLE+2.3).[15] The applied map distance, obtained from deCODE map,[16] was 3.1 cM/Mb. The growth population rate (r) was obtained from the census results in Yecla during the last 551 years (in 1450, the population was 1400; in 2001, the population was 30 824), considering 25 years for a generation and according to the following formula: $r = (\mathrm{Ln}P_1 - \mathrm{Ln}P_0)/g$ (P = population, g = generations). Thus, Yecla's population growth rate was estimated to be 0.14. For Europe, we used the growth population rate of the last 2000 to 3000 years (r = 0.034) described elsewhere.[17]

The proportion of disease-bearing chromosomes, f = 0.1% in Europe and f = 4% in Yecla, was calculated by (1) estimating the frequency of the p.Cys38Arg mutation (in Europe 1/35 000 [http://exac.broadinstitute.org/variant/4-187192873-T-C], and in Yecla 2/100[5]); (2) considering population sizes (Europe: 700×10^6 and Yecla: 35 000); and (3) the number of chromosomes analyzed (46 for the European cohort and 27 for Yecla).

The density peaked at 216 generations (95% confidence interval: 149-317) when estimating a proportion of 0.2% for the mutated allele according to data from the Exome Aggregation Consortium. The estimated age of this mutation was ~5400 years. The estimated time of mutation occurrence in Yecla was ~30 generations

(95% confidence interval: 19-50), which represents 625 years (supplemental Figure 3).

FXI deficiency denomination as hemophilia C has certainly contributed to broaden the conclusions on the rarity of this disorder. Textbooks on general medicine, clinical hematology, and hemostasis still report a low prevalence for FXI deficiency (1/10 000-50 000) in the general population. However, increasing evidence from epidemiological studies,[5,11,13] the limitation of current diagnostic methods to identify FXI deficiency,[18] the clinical mildness of bleeding in even cases with severe FXI deficiency,[19] and our current study strongly suggest that the incidence of this disorder might be underestimated.

Our study shows new hot spots of FXI deficiency in Europe raised by a new recurrent and significantly older mutation than that found in the Ashkenazi Jews. The recurrent Ashkenazi's p.Glu117Ter and the p.Phe283Leu mutations, deriving from relatively few founders that have maintained rather high endogamous rates over time,[3,20] were dated back from 120 to 185 and 31 to 100 generations ago, respectively.[20,21] We estimated that the p.Cys38Arg variant occurred ~149 to 317 generations ago. The remarkable extragenic genetic diversity observed in the French Basque Country suggests that this variant might have appeared in this population. Then, it was spread out to the north (reaching the French Brittany) and to the south (arriving to Spain and Portugal). Our study reveals that this variant arrived to Yecla in the thirteenth century, probably during the Christian Reconquest of Southern Spain, with a new intragenic marker. It is also important to consider possible positive selection mechanisms to explain the high prevalence of this mutation in certain populations (Yecla or the French Basque Country), as it has been described for other hemostasis genetic disorders.[22] Resistance to infection, hemostasis, or iron conservation has been interpreted as an adaptive profile that might positively select certain gene variations.[23] Within this framework, we think that this potential positive selection might not be explained by the antithrombotic protective effect of FXI deficiency.[2] A real positive selection could be based on the evidence supporting that FXI deficiency may confer a survival advantage in sepsis by altering the cytokine response to infection and blunting activation of the contact system.[24] Alternatively, drift hypothesis cannot be ruled out, because these regions were geographically isolated, with low inward migration and a high degree of consanguinity, as it has been described for other founder mutations involved in different diseases.[25]

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Authorship

Contribution: M.E.d.l.M.-B. and S.S.-A. performed research, analyzed data, wrote, and reviewed the paper; P.C., B.d.l.M.-B., L.M.-F., F.V., and J.C. performed genetic research and analyzed the data; J.P. and A.M. carried out biochemical and genetic analysis. J.E., P.G., F.B., C.A., and R.P. recruited patient samples, designed the research, and reviewed the paper; P.C., J.C., F.B., and V.V. designed the research, analyzed the data, wrote, and reviewed the paper.

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Footnotes

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