

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Santos A, Annichino-Bizzacchi JM, Ozelo MC. Inhibitors of factor VIII in hemophilia. *N Engl J Med* 2009;361:309-10.

Table 1. Factor VIII haplotype frequencies and the prevalence of inhibitors in severe hemophilia A patients from Brazil.

	FVIII haplotypes*										P value‡
	All		H1		H2		H1+H2		H3		
	Inhibitor†		Inhibitor		Inhibitor		Inhibitor		Inhibitor		
	Yes no. (%)	No no. (%)	Yes no. (%)	No no. (%)	Yes no. (%)	No no. (%)	Yes no. (%)	No no. (%)	Yes no. (%)	No no. (%)	
African-Brazilians (n= 77 from 51 families)											
	24 (31)	53 (69)	16 (21)	32 (41)	7 (9)	13 (17)	23 (30)	45 (58)	1 (1)	8 (11)	0.26
Mean age, yrs [range]	22.4 [4-61]	19.1 [2-45]	24.6 [4-61]	19.9 [2-45]	18.7 [5-37]	20.8 [6-43]	20.2 [4-61]	20.2 [2-45]	13 [13]	12.9 [6-21]	
FVIII mutation type§											
High-risk for inhibitor	14 (18)	37 (48)	10 (13)	23 (30)	3 (4)	8 (10)	13 (17)	31 (40)	1 (1)	6 (8)	0.66
Low-risk for inhibitor	0	1 (1)	0	1 (1)	0	0	0	1 (1)	0	0	
Not determined¶	10 (13)	15 (20)	6 (8)	8 (10)	4 (5)	5 (7)	10 (13)	13 (17)	0	2 (3)	0.50
Caucasians (n= 71 from 52 families)											
	14 (20)	57 (80)	9 (13)	47 (66)	5 (7)	10 (14)	14 (20)	57 (80)	0	0	
Mean age, yrs [range]	24.3 [5-71]	24.8 [3-69]	27.8 [5-71]	24.7 [3-69]	18 [9-36]	25 [7-45]	24.3 [5-71]	24.8 [3-69]			
FVIII mutation type§											
High-risk for inhibitor	11(15)	34 (48)	6 (8)	29 (41)	5 (7)	5 (7)	11 (15)	34 (48)			
Low-risk for inhibitor	0	6 (8)	0	3 (4)	0	3 (4)	0	6 (8)			
Not determined¶	3 (5)	17 (24)	3 (5)	15 (21)	0	2 (3)	3 (5)	17 (24)			

* Of all six possible factor VIII haplotypes (H1 to H6) only H1, H2, and H3 were identified.

† Inhibitor was defined by Bethesda titers of 0.6 BU/mL or higher.

‡ Two-sided Fisher's exact test was used to compare the two groups (H1+H2) and H3 for the presence of inhibitor.

§ Factor VIII gene mutations identified according to the risk for inhibitors development. High-risk: factor VIII intron 22 and intron 1 inversions, nonsense mutations, and small deletion non-A run. Low-risk: missense mutations at A1 or A3 domain, and small insertion A-run.

¶ Among the cases that the mutation were not determined, both factor VIII intron 22 and intron 1 inversions were excluded.