GENETIC RISK FACTORS FOR INHIBITOR DEVELOPMENT IN A BRAZILIAN SEVERE HEMOPHILIA A POPULATION

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INTRODUCTION

The formation of inhibitory alloantibodies against factor VIII (FVIII) is a severe complication of the replacement therapy in patients with hemophilia A (HA). Approximately 20-25% of patients with severe HA develop inhibitors. Both genetic and environmental factors influence the susceptibility of patients to develop inhibitors. The ethnicity is a known risk factor for the development of inhibitor, with a high prevalence among African descents.

Brazil has a highly heterogeneous population, and the Brazilian population has a great influence of the African ethnic group. In Brazil more than 95% of HA patients receive exclusively plasma-derived FVIII.

OBJECTIVE

The aim of this study is to investigate genetic factors that could influence the risk of inhibitor development in a multiracial population receiving similar FVIII concentrates.

METHODS

We invited to participate in this study, patients from six centers from distinct geographic regions in Brazil, with the influence of different ethnic backgrounds according to each region, Caucasians, African descents and Indigenous from Amazon (figure 1). To define race we considered physical traits and ancestry ethnic background at the last three generations. The inhibitory antibodies has been quantified according to the Bethesda modified assay and the Nijmegen. Inhibitor was defined by Bethesda titers > 0.6 BU/mL in at least 2 tests with a minimum interval of 6 months. This study evaluated genetic risk factors for the development of inhibitor including, FVIII genotype, and polymorphisms in genes encoding immunoregulatory citokines, such as interleukin 10 (IL10), tumor necroses factor alpha (TNFA) and cytotoxic T-lymphocyte antigen 4 (CTLA-4)

RESULTS

327 severe HA patients (268 unrelated families) from Brazil were enrolled in this study. In this population 52% were non-Caucasians, based on physical features and ancestry, with 141 (43%) African-Brazilian, and 28 (9%) Indigenous (table 1). Inhibitor was present in 66/327 (20%) with 84% high-responding inhibitor patients. 39/66 (59%) inhibitor patients were black, whereas in 102/261 (39%) of the non-inhibitor patients were black (*P*=0.005; OR 1.51, 95% CI 1.18-1.94). In contrast, all 28 indigenous descents were inhibitor negative (*P*=0.002; OR 0, infinity) (figure 2). The FVIII mutation was determined in 130 patients. The prevalence of nonsense mutation was statistically higher among inhibitor patients (33% vs. 9%, *P*=0.02; OR 5.0, 95% CI 1.33-18.82). The prevalence of inhibitors among patients with FVIII gene intron 1 and intron 22 inversions was 15% (10/66). The analysis of the SNPs in IL10 gene (-1082 G>A), TNFA gene (-308 G>A), and CTLA-4 gene (-318 C>T, and -49 A>G) did not show significant difference regard the presence of inhibitor.

Table 1. Prevalence of inhibitors in severe hemophilia A patients from Brazil.

	All (327 / 268 families)		African-Brazilians (141 / 94 families)		Caucasians (158 / 119 families)		Indigenous (28 / 16 families)	
	Inhibitor†		Inhibitor		Inhibitor		Inhibitor	
	Yes N (%)	No N (%)	Yes N (%)	No N (%)	Yes N (%)	No N (%)	Yes N (%)	No N (%)
	66 (20)	261 (80)	39 (28)	102 (72)	27 (17)	131 (83)	0	28 (100)
Mean age, y [range]	23.8 [2-61]	26.6 [2-77]	21.5 [5-61]	22.3 [2-65]	26.4 [2-51]	25.2 [3-77]	-	23.2 [10-45]
FVIII mutation t ype§								
High-risk for inhibitor	27 (41)	103 (41)	14 (36)	42 (41)	13 (48)	37 (28)	-	24 (86)
Low-risk for inhibitor	1 (1)	4 (4)	1 (3)	4 (4)	0	17 (13)	-	1 (4)
Not determined¶	38 (58)	56 (55)	24 (61)	56 (55)	14 (52)	77 (59)	-	3 (10)

† Inhibitor was defined by Bethesda titers > 0.6 BU/mL in at least 2 tests with a minimum interval of 6 months.

§ 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.

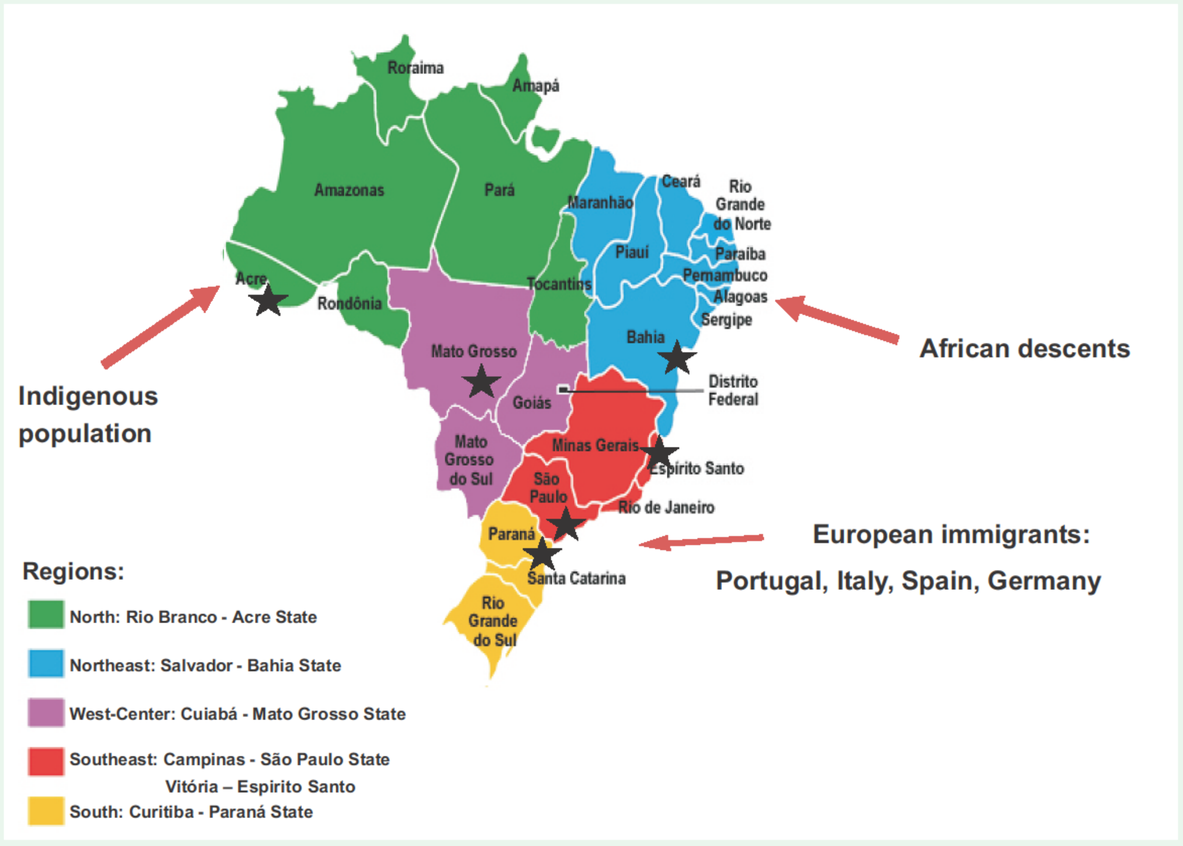

Figure 1. Centres participants localization. The six centres involved in this study are from distinct geographic regions in Brazil, with the influence of different ethnic backgrounds according to each region.

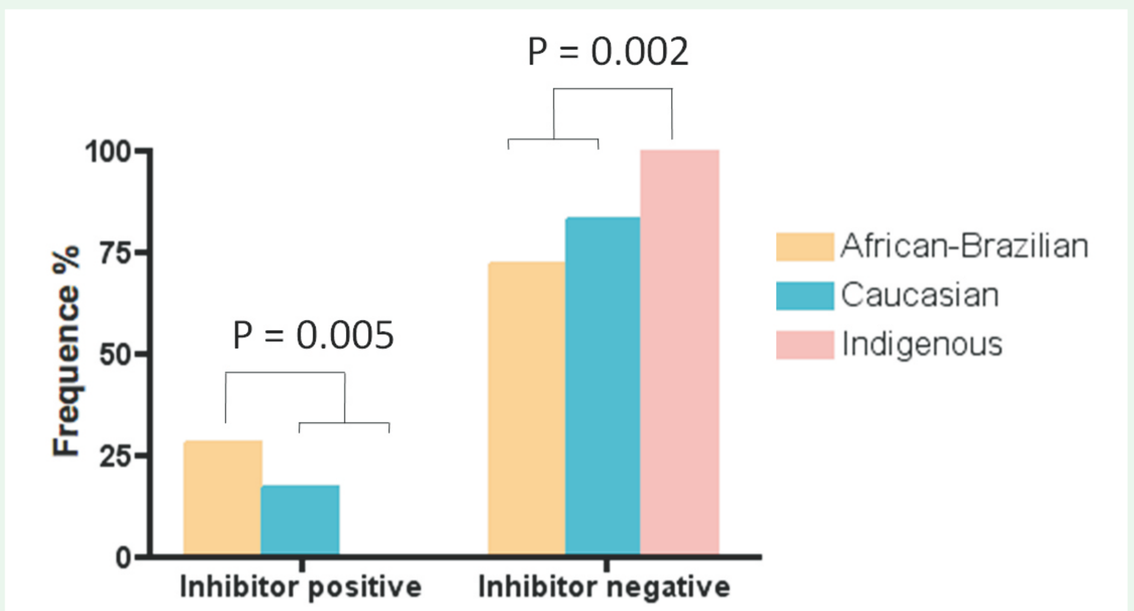

Figure 2. Inhibitor frequency according to the ethnic backgrounds. African-Brazilian had higher frequency of inhibitor, whereas all patients with Indigenous background were inhibitor negative.

CONCLUSION

The prevalence of inhibitor in the Brazilian severe HA patients analyzed in this study was higher among black patients. The FVIII mutation analysis revealed higher prevalence of nonsense mutation among inhibitor patients. Furthermore, the preliminary analysis of polymorphisms in immunoregulatory citokines genes did not demonstrate to be related to inhibitor development in these patients.

Acknowledgments:

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