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POSTER ABSTRACTS

322.DISORDERS OF COAGULATION OR FIBRINOLYSIS: CLINICAL AND EPIDEMIOLOGICAL

Native American Ancestry Is Associated with Successful Immune Tolerance Induction in Admixed Brazilians with Hemophilia a

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Immune tolerance induction (ITI) is the treatment of choice for eradicating neutralizing antibodies (inhibitors) against factor VIII (FVIII) in patients with hemophilia A (PwHA). Previous studies have investigated the association of ethnicity with inhibitor development with conflicting results. However, to our concern, studies targeting the role of ethnicity on ITI outcomes are still missing. Since unfavorable ITI response occurs in 30%-40% of these patients, establishing predictors of ITI response is needed.

To evaluate genetic determinants of ITI outcome beyond FVIII genotype, we investigated the association of genomic ancestry and ITI response by analyzing the exomes of PwHA from the Brazilian Immune Tolerance Study (Camelo et al. 2021). PwHA were enrolled in 15 hemophilia treatment centers from all Brazilian regions. We collected clinical data and blood samples for DNA extraction. ITI was carried out using a single protocol, regardless of selection based on "good" or "bad" risk of ITI outcome. Inclusion criteria comprised patients with severe and moderately-severe (FVIII<2%) HA with high-responding inhibitors who completed a first course of ITI. Since the characteristics of PwHA who responded with partial and complete success yielded similar results, these groups were analyzed together. Exomes were obtained with high quality using the xGen Exome Research Panel v2 (Illumina). Quality control filters evaluated average coverage and deep coverage, phred score, genomic position, sex, heterozygosity, and duplicated SNPs. In a multiple regression analysis, we used geographic location, inhibitor levels, presence or absence of null mutations (i.e., frameshift, deletions, nonsense, and inversions; Oldenburg et al., 2002), and kinship coefficients as explanatory variables. Inhibitor levels were evaluated as historical inhibitor peak, titer immediately before the start of ITI, and inhibitor peak during ITI.

We included 150 PwHA, of whom 136 (91%) had severe (FVIII<1%) HA, median age 0.9 years [IQR, 0.5,1.4] at diagnosis of HA. A total of 44 (29%) PwHA had ITI failure, 60 (40%) had partial success, and 46 (31%) had complete ITI success. Functional annotation showed that most SNPs were intronic (48%) and exonic (29%). We identified 808,706 variants, of which 90,075 were not reported in the dbSNP. Average ancestries of European, African, and Native American were 79.4% [IQR:75.4,83.4], 17.3% [IQR:17.0,17.6], and 3.3% [IQR:2.6,4.0], respectively (Table 1). There was an association between a higher Native American ancestry in patients with successful ITI (2% [IQR:1.95,2.05] ancestry mean) when compared with patients who failed ITI (1% [IQR:0.97,1.03] ancestry mean). A 1% increase in the Native American ancestry proportion was associated with a rise of ~10% in the probability of successful ITI (*odds ratio* [OR], 10.43 [95% CI,7.45,13.41], p = 0.040 (Table 2). Neither European nor African ancestry was associated with ITI outcome.

In conclusion, Native American ancestry was associated with successful ITI. To our concern, this is the first study to evaluate genomic ancestry as a predictor of ITI response and the first to enroll an admixed population of HA. Identifying ancestry as a predictor of ITI outcome may elicit different therapeutic approaches for inhibitor eradication. However, our findings may not apply to other populations due to a particular characteristic of admixture of the Brazilian population.

REFERENCES

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TABLE 1 Characteristics of the study population

Characteristics	n=150
Diagnosis	
Age, in years, median (IQR)	0.9 (0.5,1.4)
Ethnicity, n (%)	
White	77 (51.0)
Pardo	60 (39.7)
Black	14 (9.3)
Genomic Ancestry, median (IQR)	
African	17.3 (17,17.6)
European	79.4 (75.4,83.4)
Native American	3.3 (2.6,4.0)
Hemophilia A severity, n (%)	
Severe (FVIII activity < 1% IU/dL)	136 (90.6)
Moderately-severe (FVIII activity 1-2% IU/dL)	14 (9.3)
Immune tolerance induction (ITI) outcome, n (%)	
Failure	44 (29.3)
Partial success	60 (40.0)
Complete success	46 (30.7)
F8 variant type, n (%)	
Presence of null mutation*	104 (69.3)
Absence of null mutation*	47 (30.7)
Inhibitor characteristics	
Age at inhibitor diagnosis, in years, median (IQR)	2.0 (1.2,5.6)
Age at ITI start, in years, median (IQR)	6.5 (2.1,18.6)
Interval between diagnosis of hemophilia A and inhibitor development, in years, median (IQR)	0.9 (0.4,3.5)
Historic inhibitor peak, in BU/mL, median (IQR)	41.6 (15.2,96.0)
Inhibitor titer immediately before ITI, in BU/mL, median (IQR)	6.0 (2.9,12.8)
Inhibitor peak during ITI, in BU/mL, median (IQR)	25.6 (6.3,138.9)
ITI duration, in years, median (IQR)	2.6 (1.8,3.3)

F8 null mutations are defined as frameshift, deletions, nonsense and inversions according to Oldenburg et al, 2002; BU, Bethesda Units; *F8*, factor VIII gene; FVIII, factor VIII; IQR, interquartile range; ITI, immune tolerance induction; IU, International Units.

TABLE 2 *Odds ratios* for the association of Native American ancestry and immune tolerance induction outcome

Genomic Ancestry	ITI outcome		OR (95% CI)				
	Success* (n = 106)	Failure (n = 44)	Crude**	Adjusted†	Adjusted&	Adjusted#	Adjusted@
Native American	70.7%	29.3%	4.35 (1.17,7.53)	11.90 (5.6,18.2)	10.90 (6.94,14.86)	7.90 (3.70,12.10)	10.43 (7.45,13.41)

*Success represents the sum of total and partial successes.
** Model with the intercept only
† Adjusted for geographical region and kinship coefficients
& Adjusted for inhibitor level (pre-ITI, historical peak, and peak during ITI) and kinship coefficients
# Adjusted for null mutations and kinship coefficients
@ Full model, adjusted for geographical region, inhibitor level, null mutations, and kinship coefficients
ITI, immune tolerance induction; OR, *odds ratio*.

Figure 1

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