Origins and dynamics of the Brazilian population and sickle cell mutations reveal unexpected diversity

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Introduction

Sickle Cell Disease (SCD)

SCD is relatively common in Brazil (approximately 1:700). Several disease-causing mutations within the HBB gene, specifically the 1 base pair (bp) apart Hemoglobin S mutation (HbS) and Hemoglobin C mutation (HbC), reach relatively high frequency probably due to founding effects of the Brazilian Population and balancing positive selection from the protection they appear to provide against certain types of malaria.

Transatlantic Slave Trade

From the 16th to the 19th centuries, enslaved African people were transported by slave traders from Africa to the Americas. It was estimated that 4.9 million slaves from Africa were brought to Brazil during the period from 1501 to 1866.

Hemoglobin Mutation Allele Frequency

The hemoglobin allele frequencies differ markedly across Africa, with rates of HbC ranging from 12.5% (Burkina Faso and Ghana) to less than 1% (Angola and Mozambique) and HbS from 18% (Angola) to about 2% (other Malaria endemic regions across Africa). There are at least 4 known HbS haplotypes (Benin, Bantu, Senegal, and Cameroon).

Methods

Study Population

As part of the Recipient Epidemiology and Donor evaluation Study-III (REDS-III), a Brazilian sickle cell disease cohort (SCDC) was established with enrollment of ~2,800 sickle cell patients from six geographically diverse sites within Brazil.

Hemoglobin Mutation and Haplotype Typing

Patients enrolled in the study has been genotyped with a genome wide Affymetrix Axiom genotyping array. The specific hemoglobin mutation was determined by both array based genotyping and single-strand conformation polymorphism (SSCP) typing. Both genotype clustering and probe affinity as measured by signal intensity were used to call HbS and HbC alleles, because they are 1bp apart. Array based genotyping result is in general congruent with SSCP typing (93% concordance rate). Haplotypes were constructed using 1,516 markers spanning >2 MB around HBB.

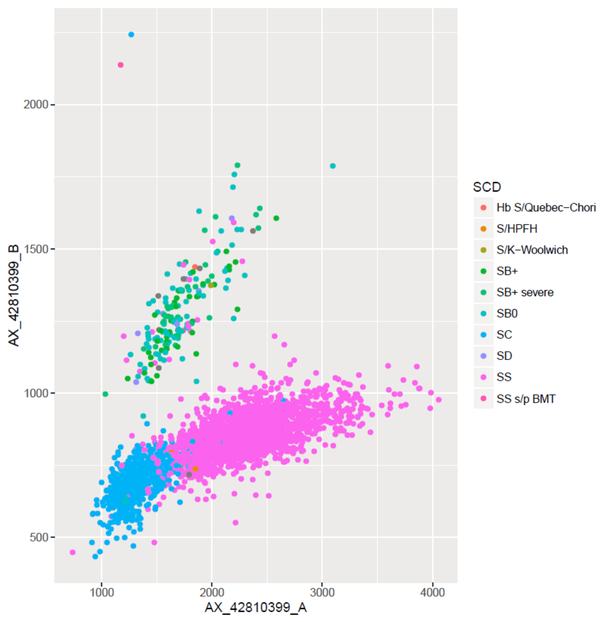


Fig. 1 Plotting of an example probe in the array designed to type HbS/C alleles in reference to the clinical diagnosed SCD type. HbSC patients show lower probe affinity comparing to other SCD patients due to the 1bp separation of the HbS and HbC alleles.

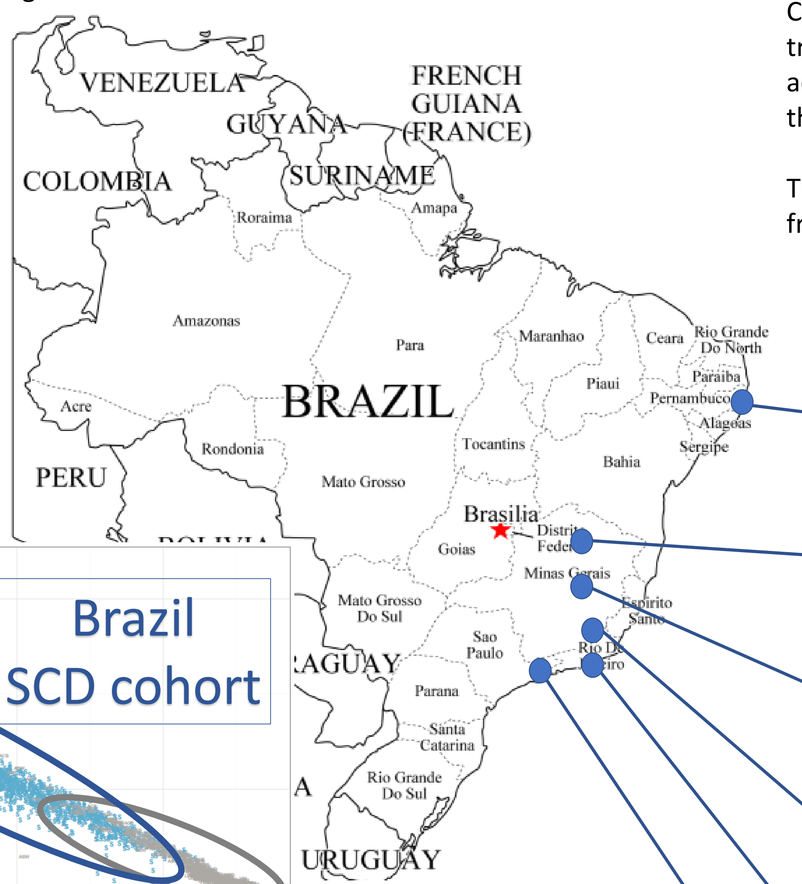
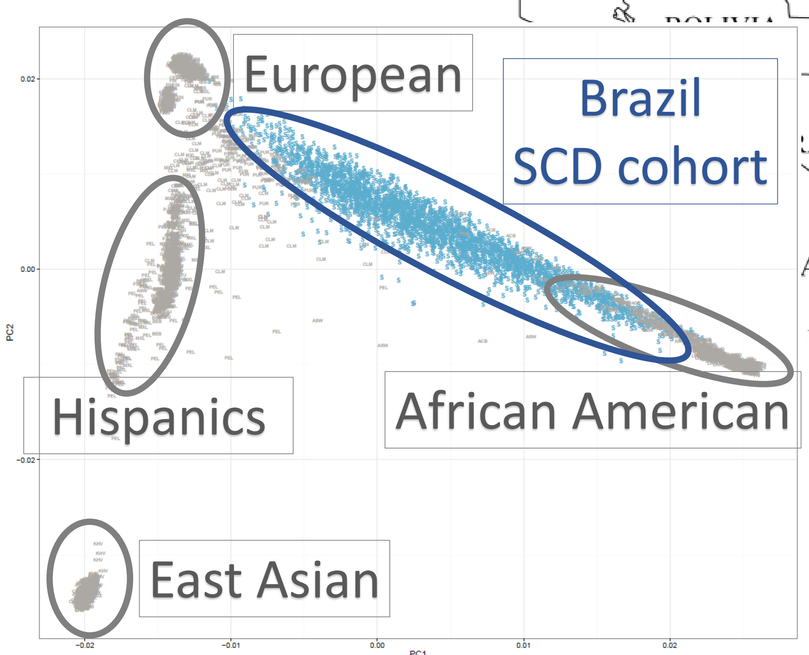


Fig. 3 Population genetics of the Brazilian SCD cohort. Blue dots on the map indicates the six study sites. Distribution of African ancestry as measured by the first principle component, proportion of HbC mutation, and proportion of the Benin HbS haplotype were shown for each site respectively. Bottom left insert shows the 1st and 2nd principle component from the PCA using 1000 genomes as reference. Gray letters labels 1000 genome subjects, while blue letter S labels Brazil SCD cohort patients.



Results

SCD haplotypes

A single HbC haplotype that is congruent with the previously identified West African HbC, and two HbS haplotypes that represents the Benin and the Bantu types that were identified among Brazilian SCD patients(Figure 2).

The Bantu and Benin haplotypes accounted for over 95% of the HbS chromosome in Brazil. The Benin haplotype averages over 1.4 MB in length, the Bantu haplotype around 1.6 Mb, and the HbC around 700 kb in length.

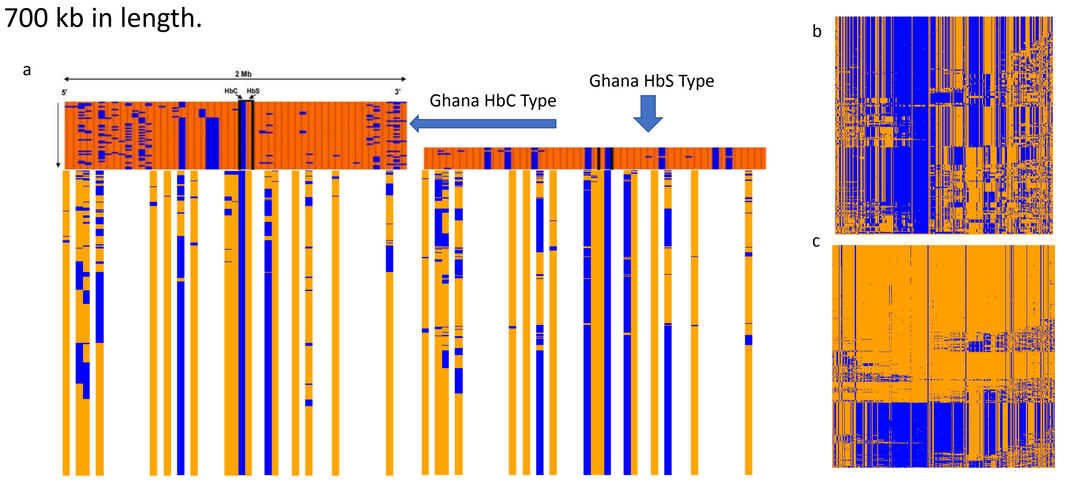


Fig. 2 a)SCD haplotypes showing a single HbC haplotype and two HbS haplotype – the Benin type and the Bantu type. b) and c) show HbC and HbS haplotype defined with dense SNPs.

Comparison with transatlantic slave trade data

Principal components analysis (PCA) using 1000 genomes as reference support the finding that most of the African ancestry in Brazil is related to Luhya (Bantu) as opposed to the West Africa like in US African-Americans. Slave trade data from (www.slavevoyages.org) supports this, as many as 85% of slaves brought to Brazil were from West Central Africa (modern Angola) but there were regional differences. 46% of slaves who were brought to Bahia/Minas Gerias were from Ghana/Bight of Benin while for the rest of the county, the rate is around 10%.

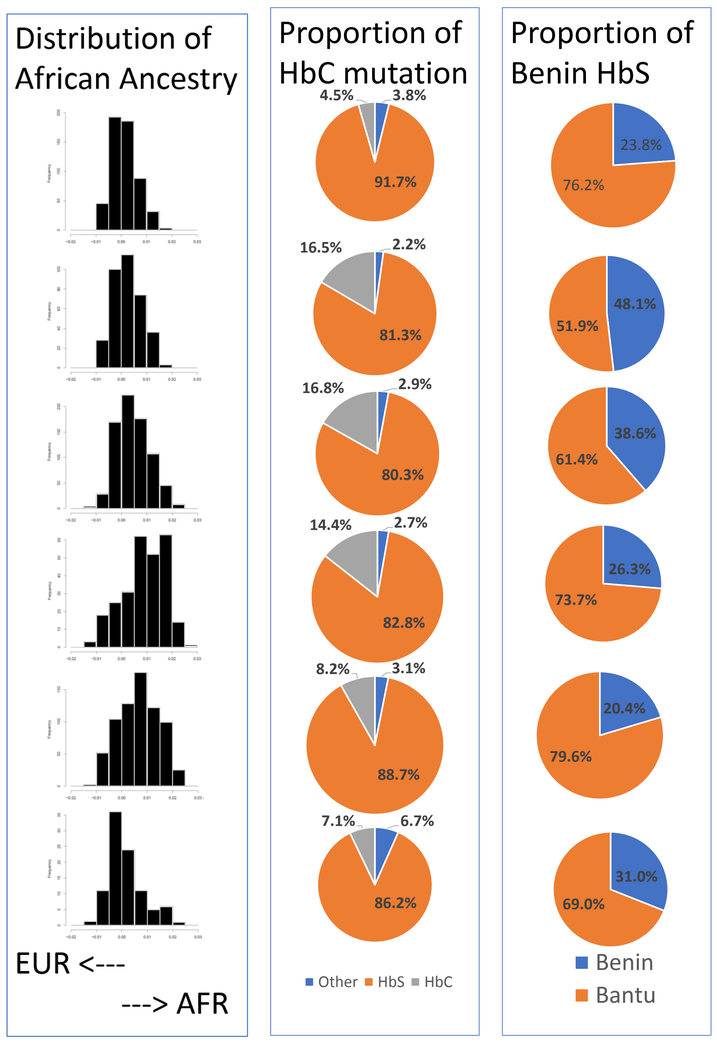
As many as 33% of the sickle cell patients from the 3 sites in Minas Gerias (Montes Claros, Belo Horizonte, and Juiz De For) has a frequency of HbC and the Benin type accounts for 40-50% of HbS alleles. While in Recife HbC frequency it is as low as 9% and Benin HbS haplotype frequency is only 20%, despite it being geographically closer to west Africa,

Conclusions

The frequencies of HbS and HbC vary quite a bit in different parts of Brazil. We found there to be only two primary HbS haplotypes (Bantu and Benin) in Brazil and one HbC haplotype.

While the majority of Brazilian people of African descent ancestors' were brought from West Central Africa, the genetic and slave trade data support that there was much higher rates of slave trade from Ghana/Bight of Biafra to Bahia/Minas Gerias than the rest of the country. This likely accounts for the higher rates of HbC and Benin HbS haplotypes in Minas Gerias as compared to the rest of the country.

This data show that distant population movements can still have an impact upon the current frequencies and distributions for disease allele.



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