The effects of old and recent migration waves in the distribution of HBB*S globin gene haplotypes

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Abstract

Sickle cell hemoglobin is the result of a mutation at the sixth amino acid position of the beta (β) globin chain. The HBB*S gene is in linkage disequilibrium with five main haplotypes in the β-globin-like gene cluster named according to their ethnic and geographic origins: Bantu (CAR), Benin (BEN), Senegal (SEN), Cameroon (CAM) and Arabian-Indian (ARAB). These haplotypes demonstrated that the sickle cell mutation arose independently at least five times in human history. The distribution of βS haplotypes among Brazilian populations showed a predominance of the CAR haplotype. American populations were clustered in two groups defined by CAR or BEN haplotype frequencies. This scenario is compatible with historical records about the slave trade in the Americas. When all world populations where the sickle cell gene occurs were analyzed, three clusters were disclosed based on CAR, BEN or ARAB haplotype predominance. These patterns may change in the next decades due to recent migrations waves. Since these haplotypes show different clinical characteristics, these recent migrations events raise the necessity to develop optimized public health programs for sickle cell disease screening and management.

Keywords: βS globin haplotypes, sickle cell disease, Hemoglobin S, migration.

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Introduction

Sickle cell hemoglobin is the result of a single nucleotide mutation (GAG→GTG) at the sixth amino acid position of the beta (β) globin gene (HBB). Sickle cell anemia (SCA) is caused by HBB*S homozygosity. This gene has a worldwide distribution (Piel et al., 2010). The disease is a severe chronic hemolytic anemia, but its clinical course is highly variable. Although not completely understood, many factors have been suggested to be modulators of this variability, such as coinheritance with Hb C, α and β thalassemias, as well as high fetal hemoglobin (HB F) levels (Higgs et al., 1982; Frenette and Atweh, 2007).

The HBB*S gene is in linkage disequilibrium with five main haplotypes defined by single nucleotide polymorphisms (SNPs) in the β-globin-like gene cluster. These haplotypes are named according to their ethnic and geographic origins: Bantu (CAR, originated in South-Central and East Africa), Benin (BEN, in Midwest Africa), Senegal (SEN, in Atlantic West Africa), Cameroon (CAM, along the west coast of Africa), and Arabian-Indian (ARAB, from the Indian subcontinent and the eastern Arabian peninsula). Based on this haplotype distribution it has been demonstrated that the HBB*S mutation arose at least five times in human history (Pagnier et al., 1984; Kulozik et al., 1986; Lapouméroulie et al., 1992). Moreover these haplotypes have also been investigated in association with clinical features of the disease in order to disclose if some characteristics associated with disease severity such as HB F levels were also associated with a specific haplotype (Steinberg, 2009). It is essential to know about the old and recent dispersions of these haplotypes considering their clinical heterogeneities and their implications to public health programs for sickle cell disease screening and management.

HBB*S haplotypes have been studied in different Brazilian populations (Table 1), as tools to clarify population origins, since the sickle cell mutation is absent among Native Americans and it was introduced into the American continent basically by gene flow from Africa during the slave trade from the 16th to the 19th century (Zago et al., 1995; Salzano and Bortolini, 2002). In this study, we compared the HBB*S haplotypes frequencies in sickle cell disease patients from several world populations, in order to disclose the effects of old and recent wave migrations in the distribution of HBB*S haplotypes.
Material and Methods

A systematic review was performed to find studies that describe sickle cell haplotypes in different world populations. When more than one study from the same population was available, mean haplotype frequencies were calculated. A Wright’s FST (Weir and Hill, 2002) analysis was performed using ARLEQUIN 3.0 (Excoffier et al., 2005) to determine the differentiation among populations based on haplotype frequencies. Principal component analysis (PCA) was performed to summarize the distribution of populations based on the pairwise FST using SPSS v.18 software.

This study also included information about 110 non-consanguineous SCD patients from Rio Grande do Sul, southern region of Brazil, screened using isoelectric focusing (IEF) and/or cation exchange high performance liquid chromatography (HPLC) and confirmed by a PCR-RFLP approach with Ddel enzyme (Wagner et al., 2010). All patients were ascertained by the Neonatal Screening Reference Service or health care centers. The Ethics Committee of the Federal University of Rio Grande do Sul approved the study protocol.

Genomic DNA was isolated from peripheral blood samples using a salting out procedure (Lahiri and Nurnberger Jr, 1991). Haplotype analysis was performed by PCR-RFLP for the following polymorphic sites in the β globin gene cluster: HindIII-GT, HindIII-Aγ, HincII-ψβ, HincII, 3′ψβ, HinfI- S′β as previously described (Sutton et al., 1989). Haplotypes were inferred using the Multiple Locus Haplotype Analysis program (Long, 1999).

Table 1 - Frequency (%) of HBB*S haplotypes in Brazilian populations.

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<tr>
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<th>Haplotypes</th>
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<tr>
<td>Rio Grande do Sul (RS)</td>
<td>220</td>
<td>67.3</td>
</tr>
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</table>

N: number of chromosomes;

Results and Discussion

HBB*S haplotypes identified in several Brazilian populations are shown in Table 1. The CAR haplotype was the most frequent one, followed by the BEN haplotype. These results are in accordance with historical reports on slave traffic to Brazil. It is estimated that during the period between 1701 and 1816, 68% of the imported slaves came from Angola and the remainder from the Benin region. From 1843 to 1871, 90% of slaves came from Congo, Angola and Mozambique (Curtain, 1969). The SEN haplotype has its higher frequency in Brazil in Belem, in the northern region (Cardoso and Guerreiro, 2006). This is in accordance on what was expected based on the slave trade historical data of Atlantic West African populations to northern Brazil (10%), considering the high frequency of this haplotype in Senegal (Currat et al., 2002). The CAM haplotype was always in lower frequencies, with 0.9% in Rio Grande do Sul and 0.9-1.3% in other Brazilian regions, probably due to domestic slave trade and later internal migrations from regions supplied with slaves from Central West Africa, where this haplotype has been found (Oner et al., 1992). These results confirmed the diversity of the African influence in Brazilian regions.

PCA (Figure 1) demonstrated that two components explained 98.9% of the variance observed among Brazilians. The first component showed a group composed by Rio Grande do Sul (RS), Pará (PA), Pernambuco (PE), São Paulo (SP) and Rio Grande do Norte (RN) populations, where the CAR haplotype has a high frequency (from 66 to 81%). The other group was composed by Rio de Janeiro...
(RJ), Bahia (BA) and Ceará (CE) populations, where the CAR and BEN haplotypes have similar frequencies.

The Brazilian populations were then compared to other American populations. The PCA (Figure 2) showed the American populations distributed in different clusters. In this analysis, three groups explained 98.9% of the variance observed. Populations with higher frequencies of CAR are clustered together (Uruguay, Brazil, Panama and Mexico), whereas populations with higher BEN frequencies formed another cluster (USA, Canada, Trinidad, Guadeloupe and Jamaica). The other populations present similar BEN and CAR haplotype frequencies and formed a third cluster comprising Venezuela, Suriname, Colombia and Cuba. This cluster pattern appears to reflect geographical data, since a North, Central and South America separation can be observed, except for Mexico. This distribution could also be explained by historical reports of colonial power in these countries: Spain, France and Great Britain (Curtain, 1969). The British and French bought slaves from Midwestern African regions, where the BEN haplotype was prevalent, while slaves imported by the Spanish and Portuguese colonizers were mainly from Atlantic Central Africa, where CAR haplotype was the most prevalent.

Table 2 and the PCA of world populations (Figure 3) showed the distribution expected according to the haplotypes’ distribution and origin. Three different components could be observed with ARAB, CAR or BEN haplotype predominance. The first group was composed by Kuwait, Bahrain, Iran, India, United Arab Emirates and Senegal. All of them have a predominance of the Arabian-Indian (ARAB) haplotype, except Senegal. The second group was composed by Madagascar, Mexico, Angola, Tanzania, Kenya, Congo, Uganda, Brazil, Uruguay and Panama. All of them have a predominance of the Bantu (CAR) haplotype. The third group was composed by USA, Jordan, Tunisia, Guadeloupe, Canada, Jamaica, Suriname, Greece, Cameroon, Oman, Palestine, Algeria, Venezuela, Egypt, Syria, Cuba, Saudi Arabia, Turkey, Nigeria, Colombia, Sudan, Portugal and Italy. These populations have a predominance of the Benin (BEN) haplotype. The trade slave to the Americas and migration routes to the Mediterranean areas and the Middle East from West Africa determines the BEN haplotype predominance in these regions. Finally, the ARAB haplotype predominated in areas where it was originally derived.

This clear pattern of origin and dispersal of HBB*S haplotypes can suffer radical changes in the next decades due to global migrations. At present, the mobility of humans has reached unimaginable levels. This mobility can affect the epidemiology of several diseases, with an increase in the risk of a local disease spreading globally and the introduction of deleterious alleles into populations.
which they were previously absent. Information about the number of international migrants in the last decades showed a noticeable difference between migrants with and without HB S. Whereas the number of migrants without HB S increased from 92.6 million in 1960 to 165.2 million in 2000, the number of migrants with this hemoglobin increased faster (from 1.6 million in 1960 to 3.6 million in 2000) (Piel et al., 2014). The estimated number of migrants from African countries, India and Middle East with HB S moving to North America, Western Europe and Australia increased (Piel et al., 2014). An increase in the Arab-Indian haplotype frequency in several countries in the next decades could potentially be expected due migration processes that are occurring from the Middle East to Europe (Figure 4).

A similar process can also be observed in Brazil, where the number of migrants from Bolivia, Haiti and Senegal increased in the last years. The dispersal of these migrants is still uneven, but Bolivians tend to remain in São Paulo state while Senegalese individuals tend to move to Rio Grande do Sul (Figure 4). Therefore, an increase in the contribution of the Senegal haplotype is expected in southern Brazil, reflecting this new migration process. No studies about HBB*S haplotypes in Haiti population are available. This country does not have any national newborn screening program to measure the prevalence of SCD. Nevertheless, a study with infants born in Port-au-Prince showed that the prevalence of SCD in Haitian newborns appears to be more than twice higher than that found among African Americans in the United States (Rotz et al., 2013). This study showed a prevalence of the SCD genotypes Hb SS and HbSC of 1:173 newborns. The authors discuss the importance to consider these results carefully, since many children are born outside hospitals in Haiti, and therefore this prevalence may probably be an underestimate (Rotz et al., 2013). Since Haiti was colonized by French the most probable frequent haplotype would be BEN, as observed in Guadeloupe (Kéclard et al., 1997). Considering this information, independent from the HBB*S haplotype that predominates in these migrants, an increase in HB S prevalence in Brazil is expected in the next years. It is important to consider that the effect of migration cannot be assessed only by the number of migrants, but also by their behavior and habits. In this context, it is essential to consider that a higher intermarriage rate is likely among migrants from the same group, leading to an increase in sickle cell disease.

Figure 2 - PCA based on $F_{ST}$ distances calculated using haplotype frequencies showing clustering patterns for different American populations according to HBB*S haplotypes.
Table 2 - Frequency (%) of HBB*S haplotypes in different world populations.

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<td>Schilirò et al., 1992</td>
</tr>
<tr>
<td></td>
<td>Portugal</td>
<td>33</td>
<td>42.4</td>
<td>36.4</td>
<td>21.2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Lavinha et al., 1992</td>
</tr>
<tr>
<td></td>
<td>Turkey</td>
<td>214</td>
<td>-</td>
<td>96.3</td>
<td>-</td>
<td>-</td>
<td>0.5</td>
<td>3.3</td>
<td>Oner et al., 1992</td>
</tr>
</tbody>
</table>

N: number of chromosomes; *mean frequency for Brazilian populations showed in Table 1; **mean frequency for Arends et al., 2000; Moreno et al., 2002.
prevalence. Some religious or cultural beliefs could be also a factor complicating an effective genetic counseling. The public health system agents should be prepared to address these problems in the best way possible.

Several chromosomes were identified as atypical (chromosomes with less common haplotypes) in all populations. Some of these atypical haplotypes were previously studied and diverse genetic mechanisms were inferred as

Figure 3 - PCA based on $F_{ST}$ distances calculated using haplotype frequencies showing clustering patterns for different world populations according to HBB*S haplotypes.

Figure 4 - World map showing the main migrations concerning HBB*S dispersion. The full lines represent the old migrations, while the dotted lines represent recent migrations.
involved in their origin, such as recombination, point substitu-
tions, or nonreciprocal sequence transfer (conversion) in the pre-existing common haplotypes instead of recurrent de novo HBB*S mutations (Zago et al., 2000). Subsequ-
ently, it was demonstrated that these events can be ob-
served in typical HBB*S haplotypes in a way similar to those that generate atypical haplotypes (Zago et al., 2001).

An extended haplotype within the HBB gene cluster is composed by three elements: a four repeats sequences con-
figuration (AT)xN12(AT)y motif within the 5’ HS2 region of
β- LCR site, (TG)n (CG)n motif within IVSII region of
fetal globin gene (αγ and βγ), and (AT)xTy motif within 5’
region of β-globin gene region. Molecular investigations of
this extended haplotype confirmed that the atypical hapl-
types are obtained through recombination among the clas-
sical SNPs in the β-globin-like gene cluster and these sites
in the extended haplotype region (Moumni et al., 2014).

In addition to population origin effects, these waves of
migration can have important effects on public health. It
was well established that there is a substantial phenotypic
heterogeneity among patients with sickle cell anemia. In
general, carriers of the CAR haplotype have the most se-
vere clinical course, while carriers of the Senegalese or Arab-
Indian haplotypes have the best clinical course. Carriers of
the BEN haplotype are intermediate in this respect. As
HBB*S presence alone cannot explain this heterogeneity
among patients, environmental influences and variations in
others genes are likely to modulate the sickle cell anemia
phenotype. The main pathophysiological factor determi-

ning disease severity is the HbF concentration, leading to a
reduced severity in patients with higher concentrations
of this hemoglobin. In addition to HbF concentration, α-
thalassemia can also affect the disease phenotype because
both decrease HbS polymerization. Several genetic and
epigenetic factors modulate HbF levels, such as the locus
control region (LCR), the HbF-related quantitative trait lo-
cus (QTL) and secretion-associated and RAS-related gene
(SARAI). In addition, several SNPs in candidate genes have
been associated with subphenotypes of sickle cell anemia.
For example, nonhemorrhagic stroke has been associated
with variation in VCAM1, TNFA, ADRB2, IL4R, LDLR,
HLA, ANXA2, SELP and TGF-β/BMP genes (a complete
review about this topic could be found in Steinberg, 2009).

Considering the possible increase in HbS frequency
in Brazil due the recent wave migrations, it should be im-
portant to consider a more appropriate public health policy,
including screening, adequate care and counseling, not
only to Brazilians but also to migrants. Sometimes it could
be difficult for migrants to have full access to public health
dervices due to linguistic, cultural, religious, and social bar-
riers but the government’s role is to provide the best oppor-
tunities to everyone.

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Migrations and $\beta^6$ haplotypes


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