

# Relationships among genomic ancestry, clinical manifestations, socioeconomic status, and skin color of people with sickle cell disease in the State of Pará, Amazonia, Brazil

Relações entre ancestralidade genômica, manifestações clínicas, status socioeconômico e cor da pele de pessoas com doença falciforme no Estado do Pará, Amazônia, Brasil



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**Abstract** In Brazil about 3500 children are born annually with Sickle Cell Disease (SCD). In the State of Pará, Amazonia, the prevalence is 1%. This article analyzes the Genomic Ancestry (GA) of patients attending the Regional Blood Center in the capital, Belém, in relation to sex, age, clinical manifestations, income, racism, and skin color. Samples were collected from 60 patients (11– 46 years, 34 of them female), and each individual was analyzed for 61 Ancestry Informative Markers (AIM). Semi-structured interviews were conducted to assess socioeconomic status (SES), self-declared color, perception of racism, and symptoms of SCD. From

**Resumo** No Brasil, nascem cerca de 3500 crianças anualmente com Doença Falciforme (DF). No Estado do Pará, Amazônia, a prevalência é de 1%. Neste artigo, analisa-se a relação entre ancestralidade genômica (AG) de pacientes atendidos no Hemocentro Regional da capital, Belém, com sexo, idade, número de sintomas, renda, racismo e cor da pele. As amostras foram coletadas de 60 pacientes (11-46 anos, 34 mulheres) e cada uma foi analisada para 61 Marcadores Informativos de Ancestralidade (AIM). Foram realizadas entrevistas semiestruturadas para avaliar status socioeconômico (SES), cor autodeclarada, percepção de racismo e manifestações clínicas.

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the 55 participants with conclusive DNA samples, 58.2% presented European, 21.8% Amerindian and 20% African DNA. From all the 60 participants, 86.6% self-classified as black or brown, 61.92% were living in poverty and 72% suffered some form of racism due to SCD and/or their skin color. There was an inverse correlation between wage and number of symptoms in all groups. European ancestry and being female was correlated with a greater number of symptoms. In Pará, SCD involves vulnerabilities such as poverty, severe clinical manifestations without treatment, and effects of racism. These results can be useful to develop public policies and to improve quality of life of people with SCD in Brazil and in other countries with heterogeneous populations.

**Keywords:** Health of the black population; clinical symptoms; SES; Amazon; sickle cell disease.

## Introduction

There is a lack of bioanthropological studies about Sickle Cell Disease (SCD), which is a syndrome incorporating the complex relations among the genetic background of the patients, their skin color, and their socio-economic situation in a Western society that values whiteness, social and economic status. Different from hypertension, which is a polygenic complex disease (Gravlee and Dressler, 2005; Gravlee et al., 2005; Non

Dos 55 participantes com amostras conclusivas de ADN, 58,2% tinham ADN majoritariamente europeu, 21,8% ameríndio e 20% africano. Do total dos 60 participantes, 86,6% se autot classificaram como negros ou pardos, 61,92% viviam na pobreza e 72% já sofreram com racismo devido a DF e/ou sua cor de pele. Há correlação inversa entre salário e número de sintomas em todos os grupos. Ascendência europeia e sexo feminino se correlacionaram com maior número de sintomas. No Pará, a DF envolve vulnerabilidades como pobreza, manifestações clínicas sem tratamento e racismo. Os resultados da pesquisa podem ser úteis para gerar políticas públicas e melhorar a qualidade de vida de pessoas com DF no Brasil e em outros países com populações heterogêneas.

**Palavras-chave:** Saúde da população negra; sintomas clínicos; SES; Amazônia; doença falciforme.

et al., 2012), SCD is a Mendelian genetic condition resulting from homozygosity for the missense mutation [Glu6Val, rs 334] in the  $\beta$ -globin gene (HBB), whose phenotypic variation is more limited (Piel et al., 2017). In Brazil, SCD is a condition clouded by racism as many assume the disease is connected to African origins in a derogatory sense, associated with over 300 years of slavery. Therefore, present-day SCD patients suffer a double stigma linked to the disease symptomatology and to racism itself (Silva, 2016).

Biomedical anthropologists are interested in the study of the origins of health disparities considering a myriad of bio-cultural variables (Leatherman and Jernigan, 2015). Key among these variables are social class and socially construed race, which affect access to health care, adequate food sources and education (Tattersall and DeSalle, 2011; Bengtsson et al., 2020). Additionally, a holistic anthropological view of health and disease demands that researchers question the illness within its own cultural setting, as not all cultures have the same family and social structures for support of the patients (Wiley and Allen, 2017), nor the same view of the human variation in general, and how this impacts specific diseases.

For example, biomedical anthropologists have investigated how the expression of hypertension and other chronic diseases is mediated by social class, genomic ancestry (GA), and the perceptions of racism. Gravlee and Dressler (2005) note that the expression of hypertension in Puerto Rico is mediated not only by individuals' skin color but by their socio-economic standing as well. In the same manner, Non and colleagues (2012) have shown that differences in blood pressure between Euro and Afro-Americans are better explained by education than by GA alone. However, similar studies about SCD are rare (Silva, 2018).

The first purpose of this study is to investigate the congruence between GA and self-declared skin color of SCD

patients in the state of Pará, Brazil, in the Amazon Basin. The objective here is to contribute to the anthropological and the biomedical literature on "race", color, ethnicity, and the lack of objectivity of cross-cultural human classification systems in the health field (Durso et al., 2014; Spector et al., 2016; Yudell et al., 2016).

The second purpose is to analyze if GA, sex, age, socio-economic variables, skin color, and perception of racism affect symptoms of SCD patients. Investigating the GA in these patients is important because the Portuguese brought enslaved people from several parts of Africa and it is possible that their descendants display different symptoms related to their ancestor's origins.

Recently, Alves and colleagues (2020) demonstrated that SCD patients in Brazil have different levels of fetal hemoglobin (HbF) related to the diverse regions where their enslaved ancestors were brought from. Also, SCD has evolved in many populations exposed to malaria, it is not found only in groups of African descent, but also in East India, South China, Mediterranean and Arabian populations, which are historically present in the Brasil (Alves et al., 2020; Piel et al., 2017; Silva, 2015). Additionally, the participants live in one of the poorest regions of the country, which reflects in their living conditions, access to health care, adequate food sources, education, and safe working conditions, all of which are known to affect the disease (Brasil,

2001; 2002). Nevertheless, how the multiple social and biological variables interact is still unknown.

## Materials and methods

### *Population sample*

Small samples of blood from 60 registered patients with SCD were obtained at the main public blood center of the state of Pará (Fundação Hemopa) located in the capital, Belém, between 2016 and 2017, representing approximately 8.5% of people with this syndrome in the state. The sample consisted of people between 11 and 46 years of age, including 34 females and 26 males. DNA was extracted for analyses of GA through Ancestry Information Markers (AIM) of autosomal DNA (Santos et al., 2010; 2016). Patients were also interviewed in relation to their socioeconomic status (SES), color self-assessment, and clinical symptoms (Silva, 2018).

### *Genetic Studies*

The genetic studies were based on Cardoso and Guerreiro (2010), and Cardoso and colleagues (2014). DNA analyses were performed at the Human Genetics and Medical Laboratory (LGHM) of the Biological Sciences Institute (ICB) of the Federal University of Pará (UFPA). GA analyses were performed as described by Santos and colleagues (2010) using 61 AIM. Three multiplex PCR reactions with 16 markers each were performed and the PCR amplification products were analyzed by

electrophoresis using the ABI Prism 3130 sequencer and the software GeneMapper IDv.3.2. The individual ancestry ratios of African Amerindian and European groups were estimated using STRUCTURE software v.2.3.3, assuming three parental populations (African, Amerindian and European) (Santos et al., 2010).

### *Interviews/Questionnaires*

The research used ethnographic methodology, with interviews and conversations during the collection of information. SES was determined based on income, level of education, occupation/employment, place of residence (urban or rural), and health services access. Self-declared color was asked following the Brazilian Census standard, classifying individuals as “white”, “black”, “brown”, “yellow” and “indigenous” (Brasil, 2010), in addition to inquiring about situations of racism or institutional racism suffered in everyday life (in health services, at school, in the church, family and other places). Data on the number and severity of clinical symptoms were based on recall of the clinical manifestations of the past twelve months following the Manual of Acute Symptoms for SCD (Brasil, 2009), with questions about pain, fever, infections, vase occlusive crises, chest syndrome, abdominal pain, vascular cerebral accident, and other reported symptoms. The narrative deduction technique was used with the intention of obtaining data about the topics

covered in the questionnaire. The deduction of narratives is based on the highest number of repetitions of the group's answers to a specific question, which are organized together as a standard answer in qualitative health research (Minayo, 2010; Ramos et al., 2016; Silva, 2018).

### ***Color Classification***

In this research, the classification of "color" derives from the Brazilian Demographic Census — carried out by IBGE —, which divides the population into black, brown, indigenous, white and yellow groups. In the national censuses, the categories brown and black are usually joined together as black (Brasil, 2010). These are commonly used categories through the country, including in Pará. Participants were asked to self-classify into one of the groups so that they, not the researchers, chose their own color categorization. It is important to note that in our sample, individuals self-classified as "yellow" are not related to the Asian and/or indigenous group of IBGE, as we will show in the results (Silva, 2018; Silva et al., 2018).

### **Symptoms of SCD**

The symptoms analyzed followed the Brazilian standard of the Manual of Basic Conducts for the Treatment of Sickle Cell Disease (Brasil, 2013a) and the Manual of Acute Events in Sickle Cell Disease of the Brazilian Health Ministry (Brasil, 2009). The Brazilian scale of

acute SCD events depends on each individual's assessment and does not use numbers. However, the most reported symptoms in the Manual among people of any age, of both sexes, throughout life are: pain crises, infections, acute splenic sequestration crisis, stroke, aplastic crisis, in addition to jaundice, fever, ulcers and others, which vary in percentage and frequency depending on the phylogeographic condition of each person or group studied (Brasil, 2009). The clinical severity of SCD as reported by the patients was investigated to verify potential associations of disease symptoms with GA and socio-economic variables.

### **Statistical Methods**

The software STRAT version 1.01 was used in the analysis of association between cases and controls assuming 10000 simulations. STRAT uses the STRUCTURE software output to test for association in the presence of stratification in the population based on the information of the ancestry of each individual. The DNA classification of the group of people with SCD in "Africans", "Amerindians" and "Europeans" was defined according to the highest percentage of genomic continental ancestry for each individual. The sum of each ancestral group in question equals the final value of the percentages (Santos et al., 2010).

For the statistical analysis about clinical symptoms, sex, age, race-color, income, racism and SES versus DNA the SAS

Software 9.4 (Statistical Analysis System) was used. The normality of quantitative variables was tested with the Durbin-Watson statistics before carrying out parametric tests. All variables were found to be normal and no assumptions were violated (SAS Institute Inc., 1992; Madrigal, 2012).

### **Ethics in Research Committee and Informed Consent Forms**

The original project followed all national research protocols according with SISNEP — the National System of Ethics in Research (CAAE: 56133516.3.0000.0018) and Resolutions 196 and 466 of the National Health Council. After approval by the Ethics in Research Committee and before taking the blood sample, each participant signed an Informed Consent Form, authorizing the use of their clinical data, interviews, ancestry results, and the use of images, when applicable. In all, 120 interviews were conducted in two stages: in the first part, questions about the SES data and clinical symptoms were asked, and, in the second part, the ancestry report was delivered and discussed with each person (Silva, 2018).

### **Results**

The study team met individually with each adult and subadult participants, and their parents, first to present the research and later to discuss the results at the end of the project (Silva, 2018).

The GA data were compared with the information on self-declared color. The identification of congruence between self-declared color and DNA of the patients as African, Amerindian and European was made according to the highest percentage present in the GA test of each individual. The results showed that 58.2% of the 55 participants with conclusive DNA samples had mostly European ancestry, 21.8% showed mostly Amerindian ancestry, and 20% mostly African ancestry (Table 1). Regarding self-declared color of the total sample (60), the participants classified themselves as black/brown (86.66%), white (6.67%) and yellow (6.67%) (Table 2).

People in the group with mostly European DNA (32 individuals) described themselves as brown (65.63%), black (12.5%), white (12.5%), and yellow (9.37%). The results of this group indicated only 12.5% congruence between GA and self-declared color (4 individuals). The group with mostly Amerindian DNA (12 individuals) identified themselves as brown (75%) and black (25%), but none of them self-declared as indigenous. Only for the group with mainly African DNA (11 individuals) was there higher congruence between GA and color, as 64% self-declared as brown and 27% reported being black, with only 9% reporting being yellow. Hence, the similarity between the GA result and the self-declaration of color for these individuals was 91% (Table 1). Even though it is essential to recognize the genetic and ethnic diversity of the Brazil-

ian population to improve the diagnosis and treatment of many chronic diseases, research on GA and self-reported color of people with SCD is still rare in Brazil (Silva, 2018; Silva et al., 2018).

According to the sample, in Pará, 82% of SCD patients live in small cities with poor basic sanitation and with great difficulty in accessing public health services. The most common symptoms reported were jaundice (85%), occlusive vessel crisis (78%), fever (60%), infections (52%), abdominal pain (20%), and stroke (10%). All individuals self-classified as yellow reported suffering abdominal pain (64% among women and 36% among men). Additionally, the whole group indicated a 52% occurrence of infections, such as pneumonia (43%), bronchitis (3%), throat infection (2%), lungs infection (2%) and blood infection (2%), occurring during the previous year. The 52 self-identified Black individuals (black and brown combined) had a significantly higher frequency of infections than whites or yellows (57.69%, 25% and 0%, respectively,  $p < 0.03$ ) (Table

2), with pneumonia as the main cause reported, and 71% of cases occurring in the last 12 months. Self-identified white individuals, in particular females, have a higher probability of experiencing strokes. However, the small subsample does not allow for statistical inferences.

When estimating the average number and severity of clinical manifestations among women with SCD considering 5 years age ranges — namely between 11 and 16 years, 17 and 21 years, 24 and 28 years, 29 to 45 years — it was observed that they had the highest quantity and severity of symptoms in adulthood in relation to men, with, respectively, 13.37 (quantity) and 11.62 (severity) of clinical symptoms reported. The intervals are imperfect due to the absence of some ages in the sample. Multiple regression analysis in the different phases of life demonstrated that men presented significantly lower amount and severity of symptoms, especially during the adolescence phase, with an average of 5.08 severe symptoms compared to 11.14 severe female symp-

**Table 1.** Self-declared color and DNA ancestry in a sample of people with SCD in the State of Pará ( $n = 55$ )\*.

<b>Genetic Ancestry of Autosomal DNA</b>	<b>European DNA (58.2%) n=32 individuals</b>	<b>American DNA (21.8%) n=12 individuals</b>	<b>African DNA (20.0%) n=11 individuals</b>
<b>Self-Declared Color</b>	Brown: 21 (65.63%)	Brown: 9 (75%)	Brown: 7 (64%)
	Black: 4 (12.50%)	Black: 3 (25%)	Black: 3 (27%)
	Yellow: 3 (9.37%)	-	Yellow: 1 (9%)
	White: 4 (12.50%)	-	-

\* 60 people were interviewed in total; however, 5 DNA samples were inconclusive.

Source: Field Research at the HEMOPA Foundation 2016–2017.

**Table 2.** Self-declared color and frequency of infections among people with SCD in the State of Pará, Amazonia, Brazil.

Self-Declared Color	Infections		
	No	Yes	Total
<b>Black*</b>	22	30	52
	36.66% (42.31%) <sup>a</sup>	50.00% (57.69%) <sup>a</sup>	86.66%
<b>White</b>	3	1	4
	5.00% (75.00%) <sup>a</sup>	1.67% (25.00%) <sup>a</sup>	6.67%
<b>Yellow</b>	4	0	4
	6.67% (100%) <sup>a</sup>	0.00% (0.00%) <sup>a</sup>	6.67%
<b>Total</b>	29	31	60
	48.33%	51.67%	100.00%

\* Self-classified black and brown pooled together.

<sup>a</sup> The percentages between brackets correspond to the total number of the respective self-identified color.

Source: Field Research at the HEMOPA Foundation 2016–2017.

**Table 3.** Regression analysis of sex, age, and genetic ancestry on the study population with SCD in the state of Pará.

Sex	-2.87364	1.01809	110.50457	7.97	0.0067	
<b>Model</b>		3	196.448	65.482	5.14	0.0035
<b>Error</b>		51	649.187	12.729		
<b>Corrected Total</b>		54	845.636			
<b>Root MSE</b>		3.56780	R-Square	0.2323		
<b>Dependent Mean</b>		9.45455	Adj R-Sq	0.1872		
Parameter Estimates						
Variable	DF	Parameter Estimate	Standard Error	t value	Pr >  t	
<b>Intercept</b>	1	11.4265	0.738	15.48	<.0001	
<b>Sexage</b>	1	1.39	0.70	2.00	0.0512	
<b>Ancestry</b>	1	-1.232	0.614	-2.01	0.0501	
<b>Sex</b>	1	-6.11793	1.887	-3.24	0.0021	

Source: Field Research at the HEMOPA Foundation 2016–2017.

toms ( $p < 0.05$ ). This finding is relevant when considering the sex by age of individuals with SCD in clinical interventions.

The regression analysis predicts a decrease of 6 symptoms from females to males, and this is a significant decrease ( $p = 0.00$ ). In addition, there is a clear, albeit not statistically significant, sex by age interaction, suggesting that the disease does not affect males and females in the same manner throughout their lifespan (Table 3).

The results also show that GA is directly associated with the severity of symptoms ( $p = 0.05$ ). The slope estimate is  $-1.23$ , which means that the number of symptoms decreases as GA changes from African to Native American to European Ancestry, with the highest number of symptoms among Europeans (10.09) and the lowest among Africans (7.18),

although this difference did not reach statistical significance.

In the analysis of the socioeconomic aspects, irrespective of GA, age or sex, the higher the income the lower the number of symptoms presented by individuals (Table 4). It was observed that 55% of the Black group received on average one Brazilian Minimum Wage per month (MW = \$280.00 USD), including social benefits such as retirement or disability pensions; 37% presented income of up to 2 MW per month, and the remaining 8% received 3 MW or more per month. The statistical association is highly significant ( $X^2 = 26.35$ ,  $df = 8$ ,  $p = 0.00$ ).

Besides differing in number and severity of symptoms, women also received, on average, 50% lower wages per month than men. The sex difference in the symptoms may be associated

**Table 4.** Relation of DNA ancestry, income and frequency of the symptoms in a sample of people with SCD in the State of Pará.

Majority Ancestry DNA of SCD People in the State of Pará	Monthly Income (Minimum Wage — MW)*					Total
	0	1	2	3	4	
	Frequency of the SCD Symptoms (%)**					
<b>European</b>	38.27%	6.73%	7.12%	7.88%	2.12%	62.12%
<b>Amerindian</b>	11.54%	4.04%	2.88%	2.12%	0.00%	20.58%
<b>African</b>	12.12%	3.27%	1.92%	0.00%	0.00%	17.31%
<b>Total</b>	61.92%	14.04%	11.92%	10.00%	2.12%	100.00%

\* Minimum Monthly Wage = R\$ 888.00/250 U\$. Values for monthly income: 0 = up to 1 MW and/or sickness aid; 1 = between 1 and 2 MW; 2 = between 2 and 3 MW; 3 = between 3 and 4 MW; 4 = greater than 4 MW.

\*\* The salary scale from 0 to 4 is related to the frequency of symptoms. As the wage level increases, the number of symptoms decreases in all ancestry groups.

Source: Field Research at the HEMOPA Foundation 2016–2017.

with hormonal variations, menses, pregnancies, but the fact that women, especially Black women, receive lower wages also increases their biosocial vulnerability and may influence their clinical manifestations as well.

Noteworthy is that for the group with predominance of African DNA, the number of symptoms in the wage range between 3 and 4 is equal to 0 because nobody in the sample reaches this wage range, which is equivalent to say that among these individuals, the SES is lower. Equally relevant is the fact that people whose GA is mainly European, though fewer, still occupy positions of higher SES levels in Pará, as they are the only ones to have incomes in level 4. Nevertheless, even reaching only wage range 2, people with higher African DNA have fewer symptoms than those with other GA.

Overall, 72% of the participants indicated having suffered some form of institutional and/or social racism throughout their lives and/or treatment as a consequence of SCD and/or their skin color, including discrimination in the health services, in their own home/family, school, and/or at work.

In the studied group, there is a deficit of schooling by age in 48% of men and 21% of women, with only 31% being of adequate age per grade in both sexes. The school deficit is responsible for low family income for 55% of the people surveyed. The main reported causes of school dropout and age-deficit are the

occurrence of pain crises, constant hospitalizations, demotivation to study due to chronic pain and other symptoms, prejudice, social isolation, bullying, absence of family support, and racism.

## Discussion

In a previous study, Silva (2018: 06) reported that SCD is the genetic disease that most affects people around the world, mainly "in the African continent, with high and medium prevalence in communities in East and Equatorial Africa, reaching regions of the Arab-Indian Continent". Further on, the author indicates that the estimate of SCD in Brazil is around 3500 children per year born symptomatic (Hb SS). Cases of children born with the Sickle Cell Trait (Hb AS), in general asymptomatic, are around 200000 per year (Silva, 2018).

It is important to highlight that, in the Amazon, SCD patients have genotypes associated with the history of the human occupation of the territory, with a very large flow of African people who came on colonial ships from the 17<sup>th</sup> century onwards, demonstrating the early arrival and dissemination of the mutant S gene in the state of Pará, and among the other states of the North Region (Silva, 2018).

Haplotypes of contemporary Amazonian populations were previously characterized by Cardoso and Guerreiro (2010) in SCD (SCA in Portuguese) patients with four main gene frequencies identified as

follows: "The four African haplotypes (Bantu, Benin, Senegal, and Cameroon) were identified among the 130 SCA patients. Sixty percent of the  $\beta$ S chromosomes analyzed were of the Bantu type, 27% Benin, 12% Senegal and 1% were of the Cameroon type" (Cardoso and Guerreiro, 2010: 2).

Regarding the severity of SCD symptoms, Cardoso and colleagues (2014) analyzed the high prevalence of Fetal Hemoglobin (Hb F) among individuals in the state of Pará, and mentioned that the condition may provide some protection to the group in relation to the severity of clinical symptoms that "were primarily influenced by alleles of BCL11A (rs4671393) and HMIP (rs4895441) loci, and to a lesser extent by rs748214 G $\gamma$ -globin (HBG2) promoter gene" (Cardoso et al., 2014: 178).

Concerning to the Single Nucleotide Repeats (SNP's) found in their sample, the authors point out that "the SNPs rs4671393 and rs4895441 explained 10% and 9.2%, respectively, of the variation in Hb F levels, while 4.1% of trait variation was explained by rs748214" (Cardoso et al., 2014: 178). Finally, Cardoso and colleagues (2014) refer that it is still necessary to show that "these results can be considered as consistent with the estimates of ancestry proportions of the sample: 39.6% European, 29.6% African, and 30.8% Native American" (Cardoso et al., 2014: 178). Their GA estimates are not very far from the ones obtained in this study (58.2% European, 21.8% African, and 20% Amerindian).

In relation to the perception of racism, a surprising result of this study is that the participants experienced racism from the people who were supposed to give them most support: health care workers and their own families. Also, in a society that values "whiteness" and European ancestry, and which sees SCD as associated with "blackness" and African ancestry, 78.3% of the participants whose GA was mainly European, self-classified as black (65.63%) or brown (12.5%), showing that even they are internalizing the racist narrative of the society which equates SCD exclusively with African ancestry.

It should be noted that the term "yellow" does not translate directly to a GA category in this study. The four individuals who chose to self-classify as "yellow" did not see themselves as having Asian or Indigenous ancestry. Rather it seems that they were referring to the poor state of their health as reflected in their skin color. Therefore at least in this region of Brazil, the folk taxonomy according to skin color includes both taxonomic and health-derived directives. As such, this is a good example of why color taxonomies of humans are nothing more than "folk taxonomies" (Ramos et al., 2016). In addition to the particularity of the self-declared color as a new identity, discrimination due to the color of the skin considered yellow is another reality, as these individuals may not be accepted for a job, or be excluded from school or friendship, because their skin shade is confused with them suffering hepatitis or cancer.

Cases of racism due to dark skin color are frequent in Brazil (Geledés, 2013). Among individuals with SCD who reported having suffered some sort of racism because of the skin color, situations occurred associated to differences in treatment in health services, as they reported not receiving due attention in clinical care and/or with urgency and emergency services, being taxed as addicted to opioids or “sly”; for the workers not believing in the intensity of a crisis of pain or when care givers avoid to touch them directly during routine exams. In addition, it is common for them to hear that it is better to avoid generating children so that they are not born sick (Silva and Silva, 2013; Silva, 2016). In the last demographic census, in 2010, 54% of the Brazilian population self-declared as “black or brown”, but racial discrimination increased, even in public health services (Brasil, 2010; Geledés, 2013).

As shown previously, poverty exacerbates the symptoms of SCD irrespective of other variables. However, the poorer participants are also female and darker-skinned, compounding socioeconomic to biological factors. Obviously, the fact that women have lower wages than men also increases their vulnerability (Cordeiro and Ferreira, 2009; Nomura et al., 2010; Elenga et al., 2016; Renoux et al., 2016). Therefore, this study provides additional contribution to show the impacts of sex, color/ethnicity and SES on health care disparities (Koganebuchi and Kimura, 2019; Martinez et al., 2020).

This research also helps subsidize the discussion of how GA relates to health outcomes in SCD patients by incorporating a bioanthropological perspective in the study of health and disease. Among our participants, the worst clinical outcomes were found among those with greater European GA and less symptoms were found in participants with greater African GA. It is possible, for example, that the groups have diverse ancestry markers associated with different levels of fetal hemoglobin (HbF) (Cardoso et al., 2014) or other genetic variations. This hypothesis will be tested in the future. Regardless, these findings are somehow ironic given the prevalent racist cultural attitudes towards “whiteness” and “blackness” in Brazil (Brasil, 2013b; Canavese et al., 2018).

The findings also support the analysis of GA in relation to SCD for the understanding of genetic factors associated with the prevalence and severity of clinical symptoms in both sexes and at different ages, which would facilitate the health monitoring of patients and provide them with better quality of care. Unfortunately, access to GA tests, especially in the Amazon, is still rare (Cardoso and Guerreiro, 2010; Cardoso et al., 2012; Ramos et al., 2016).

Nevertheless, with adequate investment, GA testing can be used by governments as a tool to understand genetic diversity of the population as well as to analyze the different health implications in highly admixed countries (Cardoso e Guerreiro, 2010; Santos et al., 2010). In Bra-

zil, this would mean investment in the promotion of more effective public policies as recommended by the National Policy of Integral Health for the Black Population, and the Brazilian Unified Health System (SUS) legislation (Brasil, 1990; 2013b).

Brazil has one of the largest public health systems in the world, which is free and universal (Brasil, 1990). Over 75% of the population depends exclusively on SUS for all their health care needs, being this the main access to services for people with SCD, who need constant care and hospitalizations throughout life (Bahia, 2018).

There is a high prevalence of Sickle Cell Trait (SCT) in the Brazilian population (Brasil, 2001; 2002; Naoum and Naoum, 2004). The present data on self-declared color and income of patients with SCD corroborate the literature, in that 65% of the poor and 70% of the extremely poor in the country are Black individuals (Silva et al., 2018). In the Amazon, it is common for individuals to have to leave from rural areas far from the capital, by boat or interstate bus, to obtain hematological care. These trips may take many hours to several days. In Pará, specialized care for SCD is centralized in the capital, and there is a shortage of hematologists, making diagnosis and emergency care difficult in situations of sickle cell crisis (Silva, 2018). The socioeconomic and environmental conditions generate further restrictions and insufficient access to clinical care, which contributes to the

grave situation faced by SCD patients (Naoum, 2011; Brasil, 2010; Amaral et al., 2015; Silva, 2016; Silva et al., 2018).

The fact that male and female SCD patients display different symptoms is in agreement with currently available literature (Ceglie et al., 2019). Investigating the effects of sex and age on the expression of the disease is important because the manifestations may change with the passing of the years, and because the sexes may experience different numbers or severity of symptoms. Moreover, in different cultures, males and females are exposed to different risk factors along their lives because they occupy different positions in the socio-economic structure of the community and labor force. The impacts of the combined sex-age effects on SCD patients need to be further investigated.

One limitation of this study is that, in addition to the research of the GA, it would be necessary to investigate Hb F and other polymorphisms (SNPs<sup>1</sup>) of these patients for a fuller understanding of the clinical manifestations. Another limitation is the low number of participants. Even though experience shows

<sup>1</sup> According to the US National Library of Medicine, Single Nucleotide Polymorphisms (SNPs) are the most common type of genetic variation. Most commonly, these variations are found in the DNA between genes. They can act as biological markers, helping locate genes that are associated with disease or, when occurring within a gene or in a regulatory region near the gene, they may play a direct role in disease by affecting the gene's function. Available at: <https://ghr.nlm.nih.gov/primer/genomicresearch/snp>.

that the sample is likely representative of the reality of Pará, additional research is needed to evaluate how applicable these results are to the entire SCD-affecting Brazilian population.

## Conclusion

With this paper, we aim to contribute to the literature on the interrelations of socio-cultural and biological components of health and disease in relation to SCD. In this research, the focus was a Mendelian disease which is considered to display low phenotypic variability and more limited environmental input than polygenic diseases. However, the results clearly show that sex, age, GA, and socio-economic status have important association with symptoms and quality of life.

The study shows that SCD patients in the state of Pará, Amazonia, have diverse clinical manifestations and socioeconomic vulnerabilities in relation to their GA and self-declared color, demonstrating that biological and social determinants of health should be taken into consideration when managing the disease, which presents more symptoms among people with European ancestry and greater severity of clinical manifestations among low-income individuals and women. Also, associations of severity of SCD symptoms with sex, age and income are influenced by structural racism and the social inequalities within the Brazilian population.

In Pará, late diagnosis of SCD is common, maintaining treatment is expensive,

and access to public and private health services is limited. The effects of GA, sex, age, and SES, along with racism, fragility of the health system, and limited information available to health professionals and patients with SCD sum up to complicate diagnostic and care. It is suggested that in countries with high genetic admixture, the health care of SCD patients should consider GA characteristics in the groups surveyed. In addition, GA information combined with sociocultural data can be useful for continuing public health education in relation to racism, for helping combat disinformation about SCD origin and manifestations, and for improving the quality of care of people with the disease.

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