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REVIEW

Ancestry, diversity, and genetics of health-related traits in African-derived communities (*quilombos*) from Brazil

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Abstract

Brazilian *quilombos* are communities formed by enslaved Africans and their descendants all over the country during slavery and shortly after its abolition. *Quilombos* harbor a great fraction of the largely unknown genetic diversity of the African diaspora in Brazil. Thus, genetic studies in *quilombos* have the potential to provide important insights not only into the African roots of the Brazilian population but also into the genetic bases of complex traits and human adaptation to diverse environments. This review summarizes the main results of genetic studies performed on *quilombos* so far. Here, we analyzed the patterns of African, Amerindian, European, and subcontinental ancestry (within Africa) of *quilombos* from the five different geographic regions of Brazil. In addition, uniparental markers (from the mtDNA and the Y chromosome) studies are analyzed together to reveal demographic processes and sex-biased admixture that occurred during the formation of these unique populations. Lastly, the prevalence of known malaria-adaptive African mutations and other African-specific variants discovered in *quilombos*, as well as the genetic bases of health-related traits, are discussed here, together with their implication for the health of populations of African descent.

Keywords Black Brazilians · Hemoglobinopathies · G6PD · Genetic ancestry · Sex bias · Complex disease

Introduction

Brazil has the highest proportion of Afro-diasporic population in the world, and more than 50% of Brazilians are self-declared Blacks (IBGE, https://www.ibge.gov.br/). Brazil was the last country to declare slavery illegal in 1888 and was the destination of about 40% of the Africans forced to move to America, with estimations that range from 4 to 15 million people (Moura 1993). During the approximately four hundred years that slavery lasted, Africans and their descendants settled over almost the entire Brazilian territory (FCP, http://www.palmares.gov.br/). Due to the inhumanity of the traffic, however, there are no written records of the identity and geographic origins of enslaved Africans (Hall 2005). The only written records of the slave trade in the country were burned by the Brazilian authorities after the abolition to avoid compensation claims by slavers, remaining only rough estimations based on anthropological studies and navy files (Lacombe et al. 1988). Due to this lack of historical records, the ethnicities and/or original populations of the Africans who formed the diverse geographic regions in Brazil as well as specific African-derived populations, like *quilombos*, are mostly unknown (Hall 2005).

Africans and their descendants developed several ways of resistance to exploitation during slavery. Among them, the formation of communities where African traditional ways of living transcended the oppression of slavery was the most

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important (Moura 1993). Popularly known as Black rural communities in Central-Western and Southern Brazil, and as Black territories or *mocambos* in the North and the Northeast, these settlings have more recently acquired the legal name of *quilombos*, as recalled by the National Coordination of Joint of the Rural Black Quilombolas Communities (CONAQ, http://conaq.org.br/). The word *quilombo* derives from Central African Bantu languages, and in Africa, it defines several kinds of human settling (Leite 1999). Over the years in America, however, it has been used with different meanings, being in the last decades revindicated by the Brazilian Black movements as the legal word to identify Afro-derived communities in the context of their fight for land rights and respect for their ancestral traditions (Matos and Eugenio 2019). The legal definition of *quilombo* has changed over the years, given the impossibility to universalize and encompass the diversity of histories and the heterogeneity of their characteristics (Matos and Eugenio 2019). Their common denominator, however, has been their link to African ancestry and the community use of land for subsistence and culture preservation. In most cases, these populations have traditionally subsisted on agriculture or are directly dependent on the land's natural resources (Gomes 2015). The latter make *quilombos*, like other traditional populations in Brazil, crucial for the conservation and sustainable usage of biodiversity (Shiraishi Neto 2007). In addition, these characteristics give *quilombos* their identification as an ethnic group in Brazil (Gomes 2015). Today, there are 5972 Black rural communities throughout Brazil (IBGE). Even so, only 2807 of them have already been legally certified as *quilombos* and have their land right recognized by the official laws (FCP).

Each *quilombo* has a particular history, which has shaped its demographic processes and interaction with the environment and populations around it (Matos and Eugenio 2019). Given that mainly Africans and their descendants participated in their formation, it is expected that African genetic ancestry in *quilombos* should be predominant (Nunes et al. 2020). That fact has important implications for the study of health-related variants in populations of African descent, currently underrepresented in biomedical studies (Peprah et al. 2015; Tawfik et al. 2023). Africa is known to host the highest human genetic and phenotypic diversity in the world, given the origin of modern humans in this continent approximately 200 to 500 thousand years ago and their adaptation to its extremely diverse environments (Pereira et al. 2021). Thus, genetic studies in *quilombos* could help to unveil an important portion of the human genetic variation.

Here we review 57 genetic studies carried out in Brazilian *quilombos* (Fig. 1, Table S1). The data obtained from these studies has great importance in the knowledge of Brazilian, and especially African-Brazilian, history, but also has implications for the health of the entire Brazilian population and other populations of the African diaspora. We expect that this work will serve as a reference and motivation for the continuity of research in the field.

Genetic ancestry and the evolutionary history of *quilombos*

Altogether, we reviewed 15 studies on autosomal genomic ancestry: 14 regarding continental and only one about subcontinental ancestry (Table S2). The studies included 30 communities from all five Brazilian geopolitical regions: North (N, $n=8$), Northeast (NE, $n=8$), West-Central (WC, $n=1$), Southeast (SE, $n=11$), and South (S, $n=2$) (Fig. 1, Table S2). We also reviewed 12 studies on uniparental ancestry (determined through the analysis of the non-recombining region of the Y chromosome and the mitochondrial DNA—mtDNA). The lasts encompass Northern ($n=9$), Northeastern ($n=11$), West-Central ($n=1$), and the Southeastern region ($n=9$) (Fig. 1, Table S3). Only one study (of mtDNA) included a Southern *quilombo* (Bortolini et al. 1997) (Table S3), but since it did not estimate ancestry proportions, it was not included in our discussion.

Slow (protein loci, single-nucleotide polymorphisms—SNPs, and indels), and fast-evolving genetic markers (microsatellites) were used to calculate continental ancestry proportions, with more than one type of marker for the same community in some cases. Due to the heterogeneity of markers, the proportions of the African, Amerindian, and European ancestries obtained differ considerably between communities and between the types of markers used (Fig. 1, Table S2 and S3). However, with a few exceptions, such variations did not change the predominance of each ancestry (Table S2 and S3). The use of different markers along with the use of different sample sets could explain, in part, the divergences between the proportions obtained in the studies. Fast-evolving markers provide information on smaller time scales, so the resulting data is more informative about subcontinental ancestry and recent demographic processes. In contrast, slow-evolving markers furnish information about larger time scales, being more informative about ancestry at the continental level (de Knijff 2000). For the following section of the discussion, we selected the most representative study for each *quilombo*, prioritizing slow over fast-evolving markers, the higher numbers of markers, and the higher sample sizes, when possible (Fig. 1, Table S2 and S3). It should be noted that the most important feature behind the differences in ancestry proportions between *quilombos* is the particularity of each community's demographic processes throughout their development.

Regarding autosomal ancestry, as expected, most of the evaluated communities have predominant African ancestry, ranging from 38.2% in Pacoval (Northern Brazil) to

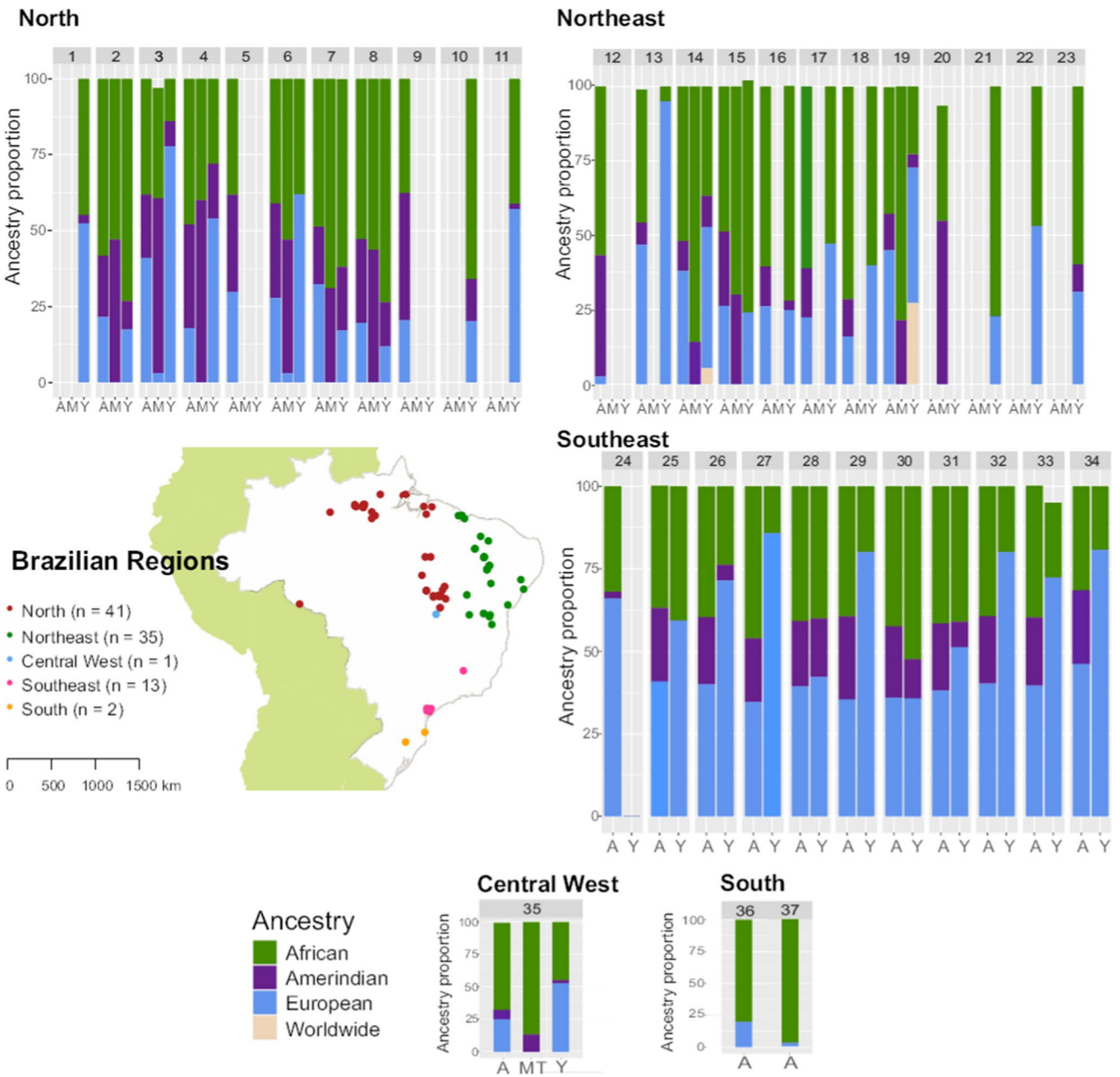

Fig. 1 Autosomal and uniparental ancestry and geographic distribution of Brazilian *quilombos* included in genetic studies so far. A, autosomal; M, mitochondrial; Y, Y-chromosome ancestries. 1—Mazagão Velho; 2—Curiaú; 3—Mazagão; 4—Cametá; 5—Pacoval; 6—Marajó; 7—Pitimandeua; 8—Trombetas; 9—Santo Antonio do Guaporé; 10—Itacoã; 11—Saracura; 12—Santiago do Iguape, 13—Riacho de Sacutiaba and Sacutiaba; 14—Rio das Rãs; 15—Cajueiro; 16—Pontal; 17—Mimbó; 18—Sítio Velho; 19—Mocambo; 20—Tamauari; 21—Barra; 22—São Gonçalo; 23—Gaucinha; 24—Marinhos; 25—Abobral; 26—André Lopes; 27—Galvão; 28—Ivaporunduva; 29—Maria Rosa; 30—Nhunguara; 31—Pedro Cubas; 32—Pilões; 33—São Pedro; 34—Sapatu; 35—Kalunga; 36—Paredão; 37—Sertão do Valongo (Schneider et al. 1987; Bortolini et al. 1995, 1997, 1998, 1999; Arpini-Sampaio et al. 1999; Guerreiro et al. 1999; Ribeiro-Dos-Santos et al. 2002; Cayres Vallinoto et al. 2003; Abe-Sandes et al. 2004; de Souza and Culpi 2005; Barbosa et al. 2006; Silva et al. 2006; Carvalho et al. 2008; Scliar et al. 2009; Ribeiro et al. 2009, 2011; Amorim et al. 2011; Maciel et al. 2011; Palha et al. 2011; Kimura et al. 2013, 2017; Wiezel et al. 2013; Gontijo et al. 2014)

97.33% in Sertão do Valongo (Southern Brazil) (Da Silva et al. 1999; De Oliveira et al. 2001; de Souza and Culpi 2005; Maciel et al. 2011) (Fig. 1, Tables 1 and S2). Variability in ancestry proportions is probably associated with the founder effect (as many *quilombos* are known to have been founded by few individuals) as well as with differences in the level of admixture over the generations. Thus, greater proportions of African ancestry are observed in

Table 1 Autosomal ancestry measures in *quilombos* from the five Brazilian regions. *AFR*, African; *EUR*, European; *AMER*, Amerindian ancestry (Schneider et al. 1987; Bortolini et al. 1995, 1998; Arpini-Sampaio et al. 1999; Guerreiro et al. 1999; Da Silva et al. 1999; Cayres Vallinoto et al. 2003; de Souza and Culpi 2005; Barbosa et al. 2006; Scliar et al. 2009; Amorim et al. 2011; Maciel et al. 2011; Kimura et al. 2013; Gontijo et al. 2014, 2018)

Geographic region	Ancestry average, median, and standard deviation (%)								
	AFR			EUR			AMER		
Central West	67.3	67.3	0	24.9	24.9	0	7.2	7.2	0
North	46.5	44.6	9.5	27.2	27.4	7.4	26.3	26	10.1
Northeast	55.9	56.8	10.3	28.3	32.6	15.2	15.6	13.4	11.4
South	88.8	88.8	12.1	11.2	11.2	12.1	0	0	0
Southeast	42.2	39.8	9	38.5	39.4	3.7	19.3	20.4	6.6

traditionally more isolated communities—such as Sertão do Valongo, Paredão, and Bananal (Maciel et al. 2011).

Only in communities from the North and the Northeast, there are *quilombos* with predominant Amerindian ancestry or the second highest, agreeing with several historical reports which mention that the admixture between Native Americans and *quilombolas* from the Amazon region was quite intense and higher than that observed in other regions (Gomes 2015). This is also consistent with the larger Native American population that inhabits the Brazilian Amazon (Brazilian Socioenvironmental Institute; https://pib.socioambiental.org). It is common for *quilombola* communities and indigenous settlements to be geographically close in Brazil's regions where the Amerindian presence is high, such as the Amazon region. That proximity has favored the gene flow between these groups—despite not always resulting in a harmonious coexistence (Gomes 2015).

The Santo Antônio do Guaporé community, located in Rondônia (N), is the only *quilombo* with predominantly Amerindian ancestry, followed by African and European ancestries (Gontijo et al. 2014). In the Guaporé Valley (*Vale do Guaporé*, located on the Bolivian-Brazilian border), the region where the community is established, several Amerindian groups have traditionally been settled, which favored the relationship with the Afro-Brazilians when they founded *quilombos* in this area in the late nineteenth century (Teixeira and Xavier 2018).

The Amerindian presence in the *quilombos* was frequently associated with voluntary entry, given that the *quilombos* may have provided refuge to Amerindians and other social classes marginalized in the colonial society, including prostitutes and military service deserters (Moura 1992; Gomes 2015). However, it is important to emphasize that there are several reports of abduction of Amerindian women by *quilombolas*, highlighting that the female Amerindian presence in *quilombos* could also have been forced (Gomes 2015). Since both populations were widely enslaved, some authors suggest that the first resistance communities of enslaved people were formed by Africans, their descendants, and Amerindians (Gomes 2015). Accordingly, although Santo Antônio do Guaporé was the only community in which Amerindian ancestry exceeded the others, considerable proportions of this ancestry (> 20%) are also identified in other *quilombos* such as Santiago do Iguape (Bahia, NE), Pacoval, and Cametá (Pará, N), and the communities of the Ribeira River Valley (*Vale do Ribeira*, São Paulo, SE) (Bortolini et al. 1995; Maciel et al. 2011; Gontijo et al. 2014).

According to Brazilian demographic history, high proportions of European ancestry would be expected in Southern communities due to the larger contingent of European migrants received in that region during the nineteenth and twentieth centuries (IBGE, 2007). In the Southern *quilombos* studied so far (Sertão do Valongo and Paredão), nevertheless, the proportions of European ancestry described do not exceed 20% (Bortolini et al. 1995, 1999; de Souza and Culpi 2005) (Fig. 1, Table S2). Notably, the proportion reported for Sertão do Valongo (2.67%) was the second smallest yet reported in Brazilian *quilombos*, except for the Santiago do Iguape community (NE, 2.5%) (de Souza and Culpi 2005; Gontijo et al. 2014). It should be noted that the low contribution of European ancestry in both communities mentioned contrasts sharply with that reported for other Brazilian *quilombos*, in which the estimates for such ancestry exceed at least 10%. This particularity possibly comes from the semi-isolation of the communities, resulting from their remote location and the historically recorded segregation generated by European-derived neighboring populations (de Souza and Culpi 2005; Gontijo et al. 2014).

Predominant European ancestry, followed by African and Amerindian, was found in communities from the North, Northeast, and Southeast of Brazil (Fig. 1, Table S2). In addition to these, most of the evaluated communities have significant estimates of European ancestry (> 20%)—especially those located in the Ribeira River Valley (SE), in which the estimates exceed 30% (Table S2). The European contribution to *quilombos*, possibly stems from founders of the communities already having European ancestry but also

from the more recent migration of people with this ancestry (Amorim et al. 2011; Kimura et al. 2013).

The data reviewed here demonstrated that, differently from the gradient of ancestry proportions that has already been shown for the Brazilian urban populations (with the highest European ancestry at Southern longitudes and higher Amerindian and African ancestry in the North and the Northeast, respectively), it is not possible to identify a pattern associating the geographic location of *quilombos* to their ancestry proportions (Fig. 1 and Tables 1, S2) (Pena et al. 2011; de Souza et al. 2019). Interestingly, however, we observed that, on average, *quilombos* from all five Brazilian geographic regions had predominant African ancestry and the highest Amerindian contribution is observed in the North of Brazil (Table 1).

Complementing autosomal ancestry studies, the analysis of uniparental ancestry patterns provides a fine-scale picture of demographic processes in human populations (Underhill and Kivisild 2007). Despite the fact that both mtDNA and the Y chromosome were not studied simultaneously for all the populations, we could observe some recurring patterns. In the first place, the European gene flow was exclusively male-mediated in 89.5% of the *quilombos*, being the predominant paternal ancestry in more than half of the *quilombos* assessed, representing all the regions studied (Fig. 1 and Table S2). Indeed, European ancestry was observed in Y chromosomes from all the *quilombos* studied, whereas its introduction by the maternal line was only observed in a few communities from the Northern region (less than 30% of the populations). Even though the African paternal contribution was observed in all *quilombos*, different from the expectations, it was the highest only in less than 40% of them. Even more striking, the African paternal contribution was less than 10% in some Northeastern communities. In sharp contrast, the African maternal contribution was detected in all *quilombos*, being African the predominant maternal ancestry in more than 70% of them. In the only communities where African maternal ancestry was lower than 40% (Mazagão and Tamauari, in the Amazon region), the reciprocal contribution was almost exclusively from Amerindian women (Fig. 1, Table S3).

That evident sex-biased admixture pattern observed in the *quilombos* studied so far agrees with that already reported for other admixed populations from Brazil and populations throughout America, as well as from other European colonized countries in the world (Trovoada et al. 2007; Ongaro et al. 2019; Korunes et al. 2020; Martínez et al. 2020). This sex-biased gene flow can be related to the extensive historical records of sexual exploitation of enslaved African and Amerindian women by European men, common during the colonial period (Walsh 1830; Nascimento 2016; Aidoo 2018). The continued abuse of enslaved women by their slavers frequently resulted in children not only unrecognized by their male progenitors but also enslaved (Aidoo 2018). In contrast, despite the fact that the majority of Africans brought to America were male, their relatively short life expectancy due to maltreatment and compulsory work (10 years, on average) can potentially be reflected in the relatively low paternal African contribution (Carvalho et al. 2008; Myscofski 2013).

Regarding the Amerindian ancestry, the paternal contribution was less expressive, being detected in 60% of the populations. None of the communities showed more than 21% of Amerindian paternal ancestry. In comparison, the Amerindian maternal contribution was observed in all populations in higher proportions (10–60%), being predominant in some populations of the Amazon region (Tamauari, Mazagão, and Cametá) (Fig. 1, Table S3).

Quilombos were not always isolated

The persecution and recurrent destruction of *quilombos* by colonial slavers led several communities to settle in remote locations (de Andrade 1995). As expected from their relatively higher isolation in comparison to urban Brazilian populations, the levels of inbreeding of *quilombos* are also higher (Lemes et al. 2014). However, and as expected, they varied greatly according to the *quilombo* studied, reflecting the diverse demographic processes involved in their formation (Lemes et al. 2014; Cruz et al. 2020). High levels of inbreeding have been seen in the more isolated *quilombos* such as Sertão do Valongo and Tucum (from Southern and Northeastern Brazil, respectively). In particular, Sertão do Valongo was founded in the 1880s by four couples including seven freed enslaved Africans and a white man (de Souza and Culpi 2005). Since then, the community has experienced population growth with low exogamy, which explains the high levels of inbreeding and high African ancestry observed in that community (de Souza and Culpi 2005). On the other hand, a significant amount of gene flow and shared ancestry has been detected in the *quilombos* of the Ribeira River Valley (Southeastern Brazil), suggesting a high level of interaction among nearby *quilombos* (Lemes et al. 2014). The interaction between different African-derived communities, as well as with the urban and Native populations around them, has been extensively recorded as the means of articulation and subsistence of *quilombos* (de Andrade 1995; Gomes 2015). Bearing in mind that the definition of *quilombo* in Brazil is critical for preserving their land rights and affirmative actions benefits, it is crucial to consider that not only one historical trajectory or demographic process can be attributed to *quilombos* in general (Guimarães Paiva et al. 2020).

Insights on the within-Africa roots of African-Brazilians

From the limited extant historical records on the origin of enslaved Africans (mainly transatlantic slave trade voyage documents), it is known that, roughly speaking, two African coasts were the main points of departure of the people brought to Brazil (Hall 2005; Pinheiro et al. 2015). From West Africa (mainly from what is today Ghana, Nigeria, Benin, and Togo but also from the Greater Senegambia region – the region between Senegal and Sierra Leona rivers) they came speakers of Niger-Congo non-Bantu languages, such as Yoruba, Fon, Monde, etc. From the Portuguese colonies of Angola, Congo, and Mozambique, in West-Central and Southeastern Africa, respectively, were brought people who spoke Bantu languages (like Kikongo, Kimbundu, and Mbundu) (Hall 2005). There is no information, however, about the specific ethnicities of these people nor if they came from regions on the continent more distant from the coasts (Hall 2005). Despite uniparental markers showing biogeographic specificity, and being useful to estimate the relative contribution from specific regions within the African continent, no study has inferred subcontinental African contributions to the formation of *quilombos* (Table S3). However, a few studies have discussed the possible origin of the uniparental haplotypes detected. For example, Y chromosomes belonging to haplogroup (Hg) E1b1a, with haplotypes typical from West-Central Africa, were detected in *quilombos* from Southeastern Brazil (Kimura et al. 2017).

In most *quilombos*, the mitochondrial haplogroups (Hgs) detected belong to the African clades L1, L2, and L3, which have a broad distribution over sub-Saharan Africa (Table S3). Similarly, all African Y Hgs were shown to belong to clade E, which is also the most common Hg in sub-Saharan Africa (Table S3). No study detected the Y Hgs typical from West-Central African hunter-gatherer populations nor Southern or Eastern African populations, such as the lineages derivatives from clades A or B (Table S3) (Knight et al. 2003). Also, no Southern African Khoisan mitochondrial Hg (such as L0d and L0k) was detected in the *quilombos* assessed so far (Table S3) (Salas et al. 2002; Knight et al. 2003). Nevertheless, both mtDNA Hg L0d and Y chromosome clade B derivatives have been detected in low frequencies in urban admixed Southern Brazilian populations (Hünemeier et al. 2007). As the studies reviewed here have sampled an average of 30 individuals per study per *quilombo*, there is a possibility that some of the less frequent lineages could have remained undetected or lost by genetic drift. Thus, despite these results being consistent with the absence of an expressive involvement of West-Central African hunter-gatherer populations or Southern and Eastern African populations in the trans-Atlantic traffic of human beings, a more in-depth investigation of subcontinental ancestry in *quilombos* and a broader sampling could be helpful to fill the historical gaps (Salas et al. 2004; Hall 2005).

We identified only one study that estimated the subcontinental African contributions in *quilombos* from Northern and Northeastern Brazil. Those contributions were inferred based on the frequency of the beta-globin S (HbS) haplotypes (Pante-De-Sousa et al. 1999; Silva et al. 2010). Five haplotypes of the beta-globin gene, in chromosome 11, have been described and are identified based on the geographic locations where they occur more frequently. These are the Arab-Indian, Benin, Cameroon, Bantu (also called the Central African Republic (CAR) haplotype), and Senegal haplotypes (Cruz et al. 2019). The *quilombos* Santiago do Iguapé (Northeast), Curiau, Pacoval, and Trombetas (North) were studied for these loci. In Santiago de Iguapé, 52.9% of the haplotypes were from Benin, whereas 32.5% were Bantu, with an absence of the Senegal haplotype (Silva et al. 2010). In the *quilombos* from the Amazonian region (Curiau, Pacoval, and Trombetas), the Bantu haplotype was more frequent, followed by the Senegal and Benin haplotypes (60, 30, and 10%, respectively) (Pante-De-Sousa et al. 1999). The frequencies from Santiago do Iguapé, however, were computed together with other admixed populations from the state of Bahia. Hence, they are not informative about the subcontinental ancestry of the *quilombo* itself. The prevalence of the Bantu haplotype in the Amazonian *quilombos* agrees with that observed in other admixed Brazilian populations. In contrast, the Senegal haplotype, which proved to be relatively common in the assessed *quilombos*, has been proportionally less observed in other admixed populations from Brazil (Silva et al. 2010). Caution must be taken because, as the Senegal HbS haplotype has been associated with a more benign clinical course, hence less hospitalization rate, it could be underrepresented in studies including only sickle cell patients from health centers (Silva et al. 2010). Besides, another two elements should be considered when the contribution of Africans from Senegambia is concerned. In the first place, this contribution is expected in the Northern region, due to the known migration of enslaved Africans from French and Dutch Guyana to that region (Ribeiro-Dos-Santos et al. 2002). And, secondarily, there is a known underestimation of the numbers of Africans brought from the Greater Senegambia region (the region between the Senegal and Sierra Leona rivers) to America in historical records (Hall 2005). Thus, for the Amazonian *quilombos*, these results both corroborate the West-Central and Western origin of the Africans brought to the region between the sixteenth and the nineteenth centuries and highlight the significant contribution from Senegambia (Pante-De-Sousa et al. 1999).

African adaptations in the Brazilian environment

Genomic studies have shown that the main drivers of recent human evolution are those related to skin pigmentation, metabolism, and infectious disease resistance (Grossman et al. 2013). Among them, the exposure to *Plasmodium* species (including *P. falciparum*, *P. ovale*, *P. malariae*, and *P. vivax*), transmitted by female *Anopheles* mosquitoes, and resulting in the parasitic disease malaria in susceptible individuals, is considered one of the strongest selective pressures and has been linked to a plethora of adaptations (Pereira et al. 2021). The growth of the mosquito population, and thus the spreading of malaria, is associated with the introduction of agriculture in African populations (Relethford 2012). In Africa, malaria spreads in the equatorial belt (the Sub-Saharan region) and diminishes its incidence southward after the Kalahari Desert. Several variants that confer resistance to infection originated in that region and have reached high frequencies due to selection (Pereira et al. 2021). Common African variants associated with malaria resistance include those in the genes *HBB*, *G6PD*, and *DARC* (Pereira et al. 2021). Some of these variants have been studied in *quilombos*, among them, those that cause hemoglobinopathies (hemoglobin S and C, and α- and β-thalassemia) and glucose-6-phosphate dehydrogenase (G6PD) deficiency (Table S4) (Gomez et al. 2013).

Hemoglobinopathies are hemoglobin hereditary disorders that can affect the structure of hemoglobin itself, or alter its production, as occurs in thalassemias (Gomez et al. 2013; Nussbaum et al. 2016).

Hemoglobin S (HbS) mutation is the result of a nucleotide change in the sixth codon of the β-globin gene (rs334(T)), replacing an adenine with thymine (GAG → GTG), causing the substitution of a single amino acid, with valine replacing glutamic acid ($\beta^{6\ Glu \rightarrow Val}$). That changes the round-shaped hemoglobin to a crescent or "sickle" shape, which can block blood flow to the rest of the body. Hemoglobin C (HbC) mutation also changes the sixth amino acid of the β-globin gene (rs33930165(A)), replacing it with a lysine ($\beta^{6\ Glu \rightarrow Lys}$) (Nussbaum et al. 2016).

These variants confer resistance to malaria in the heterozygous state whereas, in homozygosity, constitute severe genetic disorders, being only maintained in the population by balancing selection (Gomez et al. 2013). The presence of two hemoglobin S alleles causes sickle cell anemia, being the most common type of sickle cell disease (SCD). The association between HbS with any other hemoglobin variant (HbC, HbD, HbE, or β-thalassemia), also causes sickle cell disease, having an autosomal recessive pattern of inheritance. Approximately two-thirds of the SCD-affected newborns occur in Africa (Piel et al. 2013a).

Today, there is evidence for a single African origin of the HbS variant, at least 7000 years ago in the Sahara or in the rainforests of Central Africa (vicinity of present-day Cameroon) (Shriner and Rotimi 2018; Esoh and Wonkam 2021). However, HbS occurs throughout Sub-Saharan Africa surrounded by at least four different haplotype backgrounds with well-defined geographic distributions (discussed in the previous section) (Ngo Bitoungui et al. 2015). HbC, on the other hand, is assumed to have emerged only once in Western Africa, reaching its highest frequency around Burkina Faso and the Bight of Benin (Piel et al. 2013a).

The introduction of the *Plasmodium* sp. (and, in this way, malaria) in Brazil is thought to have occurred through the navies of the Transatlantic Slave Trade, during colonial times. Since then, the Brazilian Amazon has become malaria-endemic, whereas other Brazilian regions, such as the West-Central, Southeastern, and Southern regions, maintain a residual transmission (Prefeitura de São Paulo 2018) . For this reason, the knowledge of the prevalence of malaria resistance variants in populations of African descent is of public health concern in Brazil. Here, we reviewed 17 studies encompassing 60 *quilombos* from the five Brazilian regions (Table S4).

The distribution of the HbS and HbC alleles in *quilombos* is heterogeneous, and their frequency varies widely, even within the same region (Fig. 2 and Table S4). The allele frequencies for hemoglobin S (HbS) ranged from 0 to 13% in the *quilombos* assessed, with the highest number found in the *quilombo* Riacho de Sacutiaba (Northeast). This variation is in agreement with the one observed in African populations (Piel et al. 2013b). The allele for hemoglobin C (HbC) was present in 18 out of 51 populations analyzed and its frequency ranged from 0.20% (Queimada Nova, Amarante, and Paulistana, NE) to 12.5% (Lajeado, N). Only 3 *quilombos* (from the Northern region) did not present the S and C hemoglobin mutations.

Due to the African origin of these variants, it should be reasonable to expect that their frequency increases with African ancestry. In the *quilombos* assessed for the HbC and HbS variants frequencies, the average of African ancestry was 51.6 ± 16.2 (Table S2 and S4). However, the frequency of HbC and HbS variants did not show a significant correlation with the percentage of African ancestry (Pearson's correlation p-value > 0.05, Figure S1 a, b, and c). This lack of correlation could be explained not only by the founder effect in the formation of *quilombos*, but also by the variable frequency of these variants in the African populations that contributed to the Brazilian gene pool (Piel et al. 2013b; Ngo Bitoungui et al. 2015). Furthermore, we observed that the frequency of the HbC variant showed significant variation among *quilombos* from different geographic regions, with a higher frequency of HbC in the North and Northeast when compared to the Southeastern region (Fisher's exact test p-value < 0.05 and Table S4). This result agrees with the historical records showing that the greatest contribution

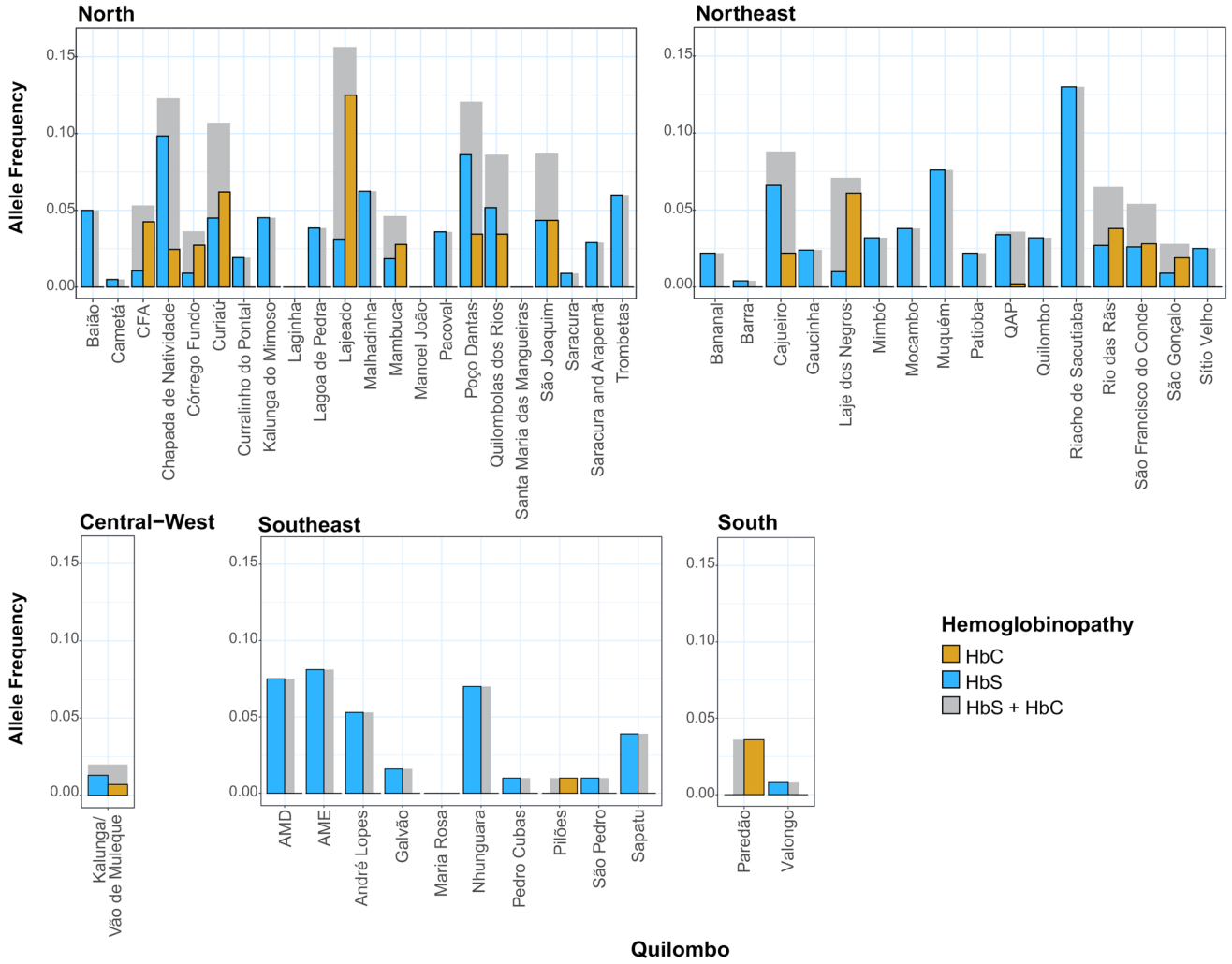

Fig. 2 HbS and HbC allele frequencies and distribution in Brazilian *quilombos*. CFA, Carrapato, Formiga and Ambrósio; CN, Chapada de Natividade; CP, Curralinho do Pontal; KM, Kalunga do Mimoso; QR, Quilombolas dos Rios; SMM, Santa Maria das Mangueiras; SA, Saracura and Arapemã; QAP, Queimada Nova, Amarante, and Paulistana; RS, Riacho de Sacutiaba; SFC, São Francisco do Conde; AMD, Abobral Margem Direita; AME, Abobral Margem Esquerda (Schneider et al. 1987; Bortolini et al. 1992, 1998; Arpini-Sampaio et al. 1999; Guerreiro et al. 1999; Oliveira et al. 2002; De Mello Auricchio et al. 2007; Cardoso et al. 2012; de Souza et al. 2013; De Assis et al. 2015; Dantas et al. 2016; Santiago et al. 2017; Teles et al. 2017)

from Western Africans, where this variant predominates, was for the North and Northeast regions of Brazil (Piel et al. 2013b).

On the other hand, α- and β-thalassemias have been studied only in the *quilombo* of Saracura (N) where it was reported a frequency of 9.5% for the 3.7-kb deletion for α-thalassemia ($-\alpha^{3.7}$) and 1.3% of the Mediterranean deletion. β-thalassemias were detected at 8,9%, in a spectrum of seven different mutations, being only 2.1% African, and the remaining forms of Mediterranean origin (Cardoso et al. 2012). The frequency of $-\alpha^{3.7}$ is higher than the 3.3% frequency found in the urban area of Santarém, PA (Cardoso et al. 2012), where the *quilombo* is located; however, it is similar to that observed in African-Brazilians from other urban Brazilian regions (Adorno et al. 2008; Wagner et al. 2010). It is remarkable, however, that the highest proportion of thalassemias detected in this *quilombo* were most possibly introduced by European gene flow (Cardoso et al. 2012).

Besides hemoglobinopathies, another two red blood cell traits have been studied (despite that less comprehensively), in *quilombos* from the Brazilian Amazon. In the first place, the deficiency of the G6PD enzyme (G6PDd) and, secondarily, the Duffy antigen (Fy).

G6PDd is an X chromosome-linked enzymopathy determined by missense single nucleotide variants (SNVs) in the *G6PD* gene (Howes et al. 2013). Two known G6PD variants of African origin have clinical importance: *G6PD*A* (determined by the SNP rs1050829, a c.376 T > C mutation), and

*G6PD*A-* (determined by rs1050829 and a second mutation: rs1050828 (c.202C > T), rs137852328 (c.680G > T), or rs76723693 (c.968 T > C)). Besides being associated with protection against malaria infection, G6PDd is of great public health importance in malaria-endemic regions, such as the Brazilian Amazon, for causing hemolytic crises induced by antimalarial drugs—such as primaquine—in G6PD deficient individuals. Besides that, other anti-malarial drugs, such as chloroquine and hydroxychloroquine, have been widely promoted by Brazilian official authorities and health professionals for treatment and prevention of coronavirus disease (COVID-19) (even with existent studies reporting on the ineffectiveness and adverse events of these drugs) further compromising the health of G6PDd individuals (Brito-Sousa et al. 2019; Kuipers et al. 2020; Melo et al. 2021; Singh et al. 2021; da Rocha et al. 2021). As screening G6PD activity is not mandatory before treatment with aminoquinolines in Brazil, monitoring the prevalence of G6PDd is crucial, especially in vulnerable populations with a higher predisposition to G6PDd, such as African-Brazilians. Notwithstanding its relevance, only one study has evaluated G6PDd prevalence in Brazilian *quilombos* so far. Oliveira et al., (2018) evaluated *G6PD*A-* and *G6PD*A* variants in nine *quilombos* from the Amazon region (the *quilombos* Arancuan, Tapagem, Abuí, and Cachoeira Porteira, along the Trombetas River, and Serrinha, Jauari, Araçá de Fora, Jarauacá and Boa Vista do Cuminá, along the Erepecuru and Cuminá Rivers). The allele frequencies reported for *G6PD*A-* and *G6PD*A* were 6.1% and 10.4%, respectively, substantially lower than those found in Sub-Saharan African populations (15–20%) (Oliveira et al. 2018). In these populations, 1.9% of males and 1.5 of females were G6PD deficient (hemizygous and homozygous, respectively).

The *DARC* gene encodes a membrane-bound chemokine receptor necessary for the infection of red blood cells by *P. vivax* and *P. knowlesi*. It has two codominant alleles, *FY*A* and *FY*B*, determining three serological phenotypes: Fy(a − b +), Fy(a + b −), and Fy(a + b +). A fourth phenotype, the Duffy-negative blood group (Fy(a − b −)), is determined by the disruption of its erythroid expression by a substitution in the gene´s promoter ($FY*B^{ES}$) (Howes et al. 2011). As it generates resistance against infection, the Duffy-negative blood group is fixed or near fixation in most Sub-Saharan African populations and other malaria-endemic regions, being rare outside these regions (Howes et al. 2011). In the *quilombos* around the Trombetas, Erepecuru, and Cuminá rivers, 20.4% of the individuals were Duffy negative, whereas 41.3% were heterozygous for the $FY*B^{ES}$ allele (Oliveira et al. 2018). The $FY*B^{ES}$ allele was the most frequent in these communities (41%) (Oliveira et al. 2018). On the other hand, the *quilombos* of Curiaú and Mazagão Velho (Amapá, N), and Pitimandeua (Pará, N) were studied in a different work, demonstrating also that the $FY*B^{ES}$ allele was the most prevalent (Perna et al. 2007). The frequencies of the Duffy-negative blood group in these communities were 32.3%, 50%, and 58% in Mazagão Velho, Pitimandeua, and Curiaú, respectively (Perna et al. 2007). The lowest frequency of the Duffy-negative blood group in Mazagão Velho is consistent with the history of this *quilombo* and its foundation by descendants of enslaved North Africans from Morocco, a region where Duffy-negative group frequency is lower than in Sub-Saharan African populations (> 50%) (Fernández-Santander et al. 1999).

Despite that Hemoglobinopathies have been the most studied traits in *quilombos* it is important to highlight that 83% of the communities studied for these traits were from the North and Northeast regions. Also, the prevalence of G6PDd and the different Duffy antigens in *quilombos* from regions outside of the Amazonian regions remain to be elucidated.

African-specific variants occur in *quilombos*

Despite that African-derived populations are expected to harbor higher genetic diversity, studies of genetic variability not linked to known African adaptations in Brazilian *quilombos* are scarce. During this research, we have found only two studies that discovered new variants in *quilombos*. One of them evaluated the haplotypic profile of *HLA-A*, *HLA-B*, *HLA-C*, and *HLA-DRB1* in a sample of 144 individuals from *quilombos* of the Ribeira Valley, in the Brazilian Southeast. The researchers detected a new null *HLA-C* allele shared by three individuals. The new variant was found to occur in a haplotype common in populations of African descent and was not detected in African-Brazilians from nearby urban centers (Nunes et al. 2016). On the other side, a rare and possibly African allele from the FRAXAC1 locus has been detected in *quilombos* from the Brazilian Northeast (Mingroni-Netto et al. 2002). Locus FRAXAC1 flanks the fragile X mental-retardation-1 gene (FMR-1) and its alleles have been correlated with the copy number variation that causes X fragile syndrome (Mingroni-Netto et al. 2002).

The genetics of health-related traits in *quilombos* and the implications for the health of populations of African descent

Black Brazilians have lower socio-economical and health indices when compared to White Brazilians (IBGE). This higher vulnerability worsens the outcome of both infectious-parasitic as well as chronic non-transmissible diseases. The prevalence of chronic non-transmissible diseases has increased due in part to the epidemiologic transition taking place in Brazil, which has led to increased consumption of industrialized food and an increase in population densities (Silva et al. 2016; Nunes et al. 2020). In particular,

the restrictions on hunting, fishing, and the reduction of their lands by predatory entrepreneurship have been forcing changes in the lifestyle of the *quilombolas*, who were traditionally involved in subsistence agriculture (Shiraishi Neto 2007; Nunes et al. 2016; Silva et al. 2016). It is worth noting that a higher level of urbanization, linked to a shift to a capitalist economy, is related to more sedentary lifestyles, higher stress, and a decrease in dietary quality, associated with increased chronic disease risk (Wells 2012; Ghimire et al. 2022; Kidokoro et al. 2022). Brazilian *quilombos* are not exempt from this pattern, with more urbanized *quilombos* showing higher chronic disease-related risk factors than their urban counterparts (Paiva et al. 2022).

Despite that some public policies have been promoted to reduce the mentioned health disparities, they have not been efficiently established yet (Voss kominek and Vanali 2018). In part, that responds to the structural racism present in Brazil, which makes the living conditions and access to health services difficult for the Black population (Voss kominek and Vanali 2018), but also there is a scarcity of studies aimed to improve the knowledge of the ancestry specific parameters and genetic bases of diseases, that are crucial for the proper health care of this population. Black Brazilians present a higher prevalence of diabetes, hypertension, and related conditions (such as obesity and cardiovascular disease) than Whites (Ministério da Saúde 2001).

Some *quilombos* are semi-isolated and, for that reason, represent optimal populations for the study of the genetics of complex traits. They present relatively higher inbreeding and founder effect, which can empower genetic association studies by drifting up the frequency of rare variants (Zeggini 2014).

So far, a few studies have assessed the genetics of multifactorial diseases in *quilombo*s (Table S6). Angeli et al., (2011) studied the association between multiple candidate loci and obesity in the *quilombos* from the Ribeira Valley (SE). They detected a significant interaction between *LEPR* (Arg16Gly) and *ADRB2* polymorphisms (Gln223Arg), suggesting a role of the interplay between the Leptin-signaling and the catecholaminergic pathways for the susceptibility to obesity-related traits (Angeli et al. 2011).

Regarding hypertension, Kimura and collaborators detected a putative multilocus effect of the *GNB3* variants, rs5441, and rs5443, on diastolic blood pressure levels (DBP) in a family-based study in the *quilombos* from the Ribeira Valley (SE). The same authors also showed an interaction between *NOS3-GRK4* variants rs1799983 and rs1801058, respectively, in an unrelated case–control study in the same populations, concerning DBP (Kimura et al. 2012). On the other hand, Neto et al., (2021) also detected an association between the *NOS3* SNP rs1799983 and the *IGFBP3* SNP rs11977526 with arterial hypertension in a sample constituted only by women from *quilombos* of Alagoas (NE) (Neto et al. 2021). The authors also highlight the need to test for multilocus effects in the study of complex traits, as the individual polymorphisms did not show significant associations (Yeh et al. 2008; Angeli et al. 2011; Kimura et al. 2012).

On the other hand, infectious diseases like acquired immunodeficiency syndrome (AIDS) are more prevalent and mortal for Black Brazilians (Brazilian Ministry of Health 2017). Although social factors are pointed out as the major determining factor of susceptibility, genetic factors have also been studied. A 32 bp deletion in the *CCR5* gene, which codes for the β-chemokine receptor 5, results in a truncated protein associated with resistance to HIV-1 infection (Samson et al. 1996). The mutated allele (*CCR5D32*) is considered an indicator of European ancestry, as it is more frequent in that continent, being virtually absent in Asian, African, and Amerindian populations. The presence of the *CCR5D32* allele has been studied in the *quilombos* Mocambo, Rio das Rãs, and São Gonçalo (NE). It was detected exclusively in the heterozygous state, both in native and immigrant inhabitants of those communities. Its presence has been interpreted as introduced by European gene flow, possibly due to recent admixture but also to the founder effect (Carvalho et al. 2004). The last is potentially the case of the *quilombo* Mocambo, which showed the highest frequency of the *CCR5D32* allele (5.6%) (Carvalho et al. 2004).

Final considerations and perspectives

A total of 57 articles addressing genetics in Brazilian *quilombos* were analyzed to describe the ancestry and genetics of health-related phenotypes in these populations. Only approximately 93 out of 5972 extant African-derived communities have been included in genetic studies so far (Table S5). We also observed a strong bias in the regional distribution of the *quilombos* studied throughout Brazil, with the great majority of them concentrated in populations from the Northern and Northeastern regions (> 80%), and underrepresentation of Southern, Southeastern, and Central Western *quilombos*.

The variability in the African, Amerindian, and European admixture proportions observed in Brazilian *quilombos* emphasizes the well-known singularity of their history and the great influence of the surrounding populations in their formation, stressed by the effect of genetic drift on these historically small populations. Some examples of these particular histories are the strong effect of the segregation caused by Euro-descendant populations to Sertão do Valongo or the high Amerindian genetic contribution (predominantly maternal) to Amazonian *quilombos*. The uniqueness of each *quilombo* certainly contributed to the absence of a pattern of ancestry referring to the geographic region in which the community is located, in contrast with Brazilian urban populations. The uniparental ancestry patterns, on the other hand,

in general, reflects sex-biased gene flow and are consistent with the historically recorded sexual exploitation of African and Amerindian women by European men. It is remarkable the scarcity of subcontinental ancestry studies—only one was developed until the publication of this work. Even so, the study of different molecular markers allowed the demonstration of the heterogeneous within-Africa roots of *quilombolas*, with high contribution from Central-Western African Bantus (from Angola and Kongo), and Western Africans (from Senegambia and the Bight of Benin) but also from more remote regions such as Morocco, in Northern Africa. Altogether, the higher prevalence of HbC and the HbS Senegal and Benin haplotypes in Northern and Northeastern *quilombos* agrees with historical estimations of a higher number of Western Africans brought to these regions through the transatlantic slave trade.

The study of malaria adaptive variants is of public health concern in Brazil, a country where *Plasmodium vivax* is prevalent and where the use of anti-malarial drugs can cause hemolytic crises in G6PDd individuals. This review reflects a paucity of studies of red blood cell traits and malaria adaptive variants in *quilombos* from the Central-Western, Southeastern, and Southern regions of Brazil and reinforces the need to assess their prevalence.

Despite the scarcity of studies detected here, we reinforce the potential of the study of *quilombos* for the detection of African-specific variants and for a better understanding of the genetic basis of complex diseases such as diabetes, hypertension, and obesity that affect, to a greater extent, populations of African descent.

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