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The African Diaspora: History, Adaptation and Health

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Abstract

The trans-Atlantic slave trade brought millions of Africans to the New World. Advances in genomics are providing novel insights into the history and health of Africans and the diasporan populations. Recent examples reviewed here include the unraveling of substantial hunter-gatherer and "Eurasian" admixtures across sub-Saharan Africa, expanding our understanding of ancestral African genetics; the global ubiquity of mixed ancestry; the revealing of African ancestry in Latin Americans that likely derived from the slave trade; and understanding of the ancestral backgrounds of *APOL1* and *LPL* found to influence kidney disease and lipid levels, respectively, providing specific insights into disease etiology and health disparities.

Introduction

Anatomically modern humans originated in Africa before migrating to populate the rest of the world in the last 100,000 years, hence the expression "we are all Africans beneath our skin" [1,2]. This generally accepted consensus begs the question of why is the global dispersion of some human populations out of Africa referred to as the "African Diaspora" and others are not? Who and from where are these groups that constitute the African Diaspora and how has their history shaped patterns of genomic variation, the distribution of fitness influencing mutations, and health? Here, we review recent data on these questions and explore how these data, especially the accelerated cataloging of global human genetic variation, are informing our understanding of the identities and health of these populations in their current homelands. We illustrate opportunities offered by the African Diaspora to study interactions of old genes with modern environments, thereby lending novel insights into disease etiology, ancestry-based disease gene mapping, and health disparities.

The African Diaspora – History and Definition

The term "African Diaspora" first appeared in the literature in the 1950s and has been broadly defined to include all global communities descended from the historic migrations of peoples from Africa since the 15th century [3,4]. This delineates it from the pre-historic Out-of-Africa migrations that led to the peopling of the world. The African Diaspora has also

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been more narrowly defined to include only the trans-Atlantic slave trade. This narrower definition, which emphasizes the important roles that blackness, slavery, colonialism, racism, and geography played in sustaining the trans-Atlantic slave trade, is the reason why some refer to the "African Diaspora" as the "Black Diaspora" [3,5]. The trans-Atlantic slave trade was the single largest immigration of Africans from the Old World to the New World. The first leg of the triangular trade involved ships from Europe carrying goods (*e.g.*, iron, brandy, weapons, and gunpowder) that were traded for slaves in Africa. The second leg, termed the Middle Passage, involved the shipment of between 12 and 14 million enslaved Africans across the Atlantic Ocean to the Americas. The last leg was the transportation of goods (*e.g.,* sugar, cotton, tobacco, rum, and molasses) from the Americas to Europe.

Most enslaved Africans were brought to European colonies in Latin America, while 3–5% were brought to the United States of America (USA) [6]. These enslaved Africans and their descendants in the USA represent the group "African Americans". As with other diasporan populations and indeed most of the world populations [7], African Americans have multiple ancestries with lineages from Africa, Europe, Asia, and Native America among others. Hence, the term "African American" is not a genetically homogeneous entity as reflected in the fact that self-identified African Americans include individuals ranging from almost no African ancestry to almost no European ancestry [8,9] (Figure 1). In addition, cultural diversity abounds in the descendants of the African Diaspora as exemplified by Brazilians. With over 4 million slaves, Brazil has long been a melting pot of ancestries and cultures, as evidenced by the blending of African and European religions (Candomble, Catholicism), foods (Feijoada), music, and dance (Samba). A recent census indicates that about 50% of the ~200 million Brazilians self-identify as persons of African ancestry or mixed ancestry [10]. These mixtures of ancestries, acquired over hundreds of years, have serious implications for national and global biomedical initiatives such as precision medicine because phenotypic appearances and self and group identification are unlikely to adequately capture the ancestral backgrounds of individuals that make up the African Diaspora.

Population Structure and Genetic Diversity among African Populations

The landscape of population structure and genetic diversity of sub-Saharan Africans (SSA) was recently illuminated by two large international projects: the African Genome Variation Project (AGVP) [11] and the 1000 Genomes Project [12]. The AGVP data, generated from 20 African ethno-linguistic groups, revealed previously unappreciated population structure, including regionally distinct patterns of admixture. Using principal components analysis, unsupervised cluster analysis, and the f_3 test for admixture, evidence for substantial "Eurasian" and hunter-gatherer admixture was observed across SSA [11]. The timing and sources of admixture were regionally distinct, with admixture in West Africans dating to ~9000 years ago and a source similar to present-day Khoe-San populations and with admixture in East Africans dating to ~3000 years ago and a source similar to Mbuti rainforest hunter-gatherer populations [11].

African populations are highly subdivided, with population structure across Africa currently recognized as 11 ancestries that correspond to a combination of geographic and linguistic separation: Khoisan in southern Africa; Central African, predominant in Pygmies; Hadza in

Tanzania; Western African, predominant in Mande-speaking peoples; West-Central African, predominant in both Bantu-speaking and non-Bantu-speaking peoples in the area from Ghana to Cameroon; and ancestries corresponding to speakers of Berber, Cushitic, Eastern Bantu, Omotic, Nilo-Saharan, and Southern Bantu languages [7,11,13]. By comparison, 12 ancestries have been detected in the rest of world, including two that define north-to-south differentiation in Europe and one that encompasses Native American ancestry [7]. Genetic differentiation, measured by F_{ST}, between SSA ancestries can exceed that between pairs of non-African ancestries. For example, F_{ST} is 0.054 between Khoisan and Omotic ancestries, compared to 0.024 between Southern and Northern European ancestries or 0.042 between Arabian and Indian ancestries [7].

Higher levels of genetic diversity are observed among SSA. The number of variant sites per individual of SSA ancestry is ~5 million, compared to ~4.0–4.2 million variants per individual of East Asian, European, or South Asian ancestry [12]. The average rate of nucleotide differences of 1.2 per kilobase between a pair of Khoe-San individuals exceeds that of 1.0 per kilobase between an Asian individual and a European individual [14]. As a function of physical distance, linkage disequilibrium decays faster in SSA populations than in non-African populations [12], such that haplotypes are shorter in SSA. Lower burdens of runs of homozygosity tend to be observed in SSA ancestry populations, as well as in admixed populations [15], leading to lower risk of autosomal recessive diseases.

Genomic Profile of Contemporary Populations of the African Diaspora

In admixed African Americans, continental-level differences between Africans and Europeans can explain up to 8% of phenotypic variance across a range of anthropometric and cardio-metabolic traits [16]. Given the progress in delineating population structure at the sub-continental level described above, a deeper understanding of the fine-scale genetic structure in African Diaspora populations is needed. Western African ancestry is the predominant ancestry in the Mende people from Sierra Leone and Jola, Mandinka, and Wolof peoples from The Gambia [11,12]. West-Central African ancestry is the predominant ancestry in non-Bantu-speaking peoples such as the Ga-Adangbe peoples from Ghana and the Esan, Igbo, and Yoruba peoples from Nigeria [11,12]. Among Bantu-speaking peoples, genetic differentiation following the Bantu expansion gave rise to distinct ancestries in West-Central Africa (found in Bamum and M’fang peoples in Cameroon and Kongo people from the Democratic Republic of the Congo), Eastern Africa (found in Baganda, Barundi, and Banyarwanda peoples from Uganda and Luhya and Kikuyu peoples from Kenya), and Southern Africa (found in Sotho and Zulu peoples from South Africa) [7,8,11]. At the Y DNA level, Western Africans have comparatively more E1b1a1a1f, whereas West-Central Africans have comparatively more E1b1a1a1g [12]. These findings of regional ancestry within continental Africa indicate that some degree of localization of African origin for African Americans and other diasporan Africans is possible.

The genomic profile of contemporary populations of the Americas reflects admixture that occurred among Europeans, Native Americans, and enslaved Africans in the New World. For several reasons, including where slaves disembarked and socio-cultural practices such as ancestry-positive assortative mating, the average percentage of African ancestry in the

Americas varies widely. Recent estimates range from 87% in African Caribbeans from Barbados, 75% in African Americans in Southwest USA, 19% in Puerto Ricans, 12% in Colombians in Medellín, 7% in people with Mexican ancestry in Los Angeles, and 4% in both Peruvians in Lima and Argentinians sampled from across Argentina [12,17] (Figure 1). African ancestry in the Caribbean appears consistent with two waves, the first from Western Africa followed by the second from West-Central Africa [18]. In Spanish-speaking South America, African ancestry averages 5% [19]. In Brazil, African ancestry varies from 51% in Salvador in the Northeast to 15% in Bambuí in the Southeast and 16% in Pelotas in the South [20]. Western African and West-Central African ancestries are more prevalent in Northeastern Brazil due to a larger proportion of disembarkation from Western and West-Central Africa in Salvador whereas Eastern African ancestry is more prevalent in the Southeast and South due to a larger proportion of disembarkation from Mozambique in Rio de Janeiro [20]. Population structure in the Americas displays further complexity by the widely varied average percentage of Native American ancestry in these populations, with about 1% in African Caribbeans from Barbados, 4% in African Americans in Southwest USA, 15% in Puerto Ricans, 28% in Colombians in Medellín, 49% in people with Mexican ancestry in Los Angeles, and 78% in Peruvians in Lima [12] (Figure 1).

Genetic Signals of Natural Selection and Implications for Health and Disease

Genetic adaptations that took place across Africa, particularly against fatal pathogens and ecological forces, have resulted in elevated frequencies of alleles conferring survival advantages detectable in present-day African ancestry individuals on the continent and in the Diaspora (Table 1) [21–26]. Unfortunately, some of these alleles are maladaptive in modern-day environments. The discordance between ancestral genetic background and modern-day environmental exposures became pronounced in the African Diaspora, contributing to the disproportionately high burden of some chronic diseases and health disparities in these groups.

A recent striking example of the evolutionary importance of genetic variants in populations of the African Diaspora, with implications for health disparities, is the link between kidney disease, African sleeping sickness, and two missense haplotypes called G1 (consisting of S342G and I384M) and G2 (delN388/Y389) in the gene Apolipoprotein L1 (*APOL1*) [27,28]. The initial studies that linked this genomic region to kidney diseases took advantage of the demographic history of African Americans by conducting admixture mapping [29,30]. The two renal disease risk haplotypes are present at relatively high frequency in individuals of recent African ancestry (especially from West-Central Africa where the trypanosome parasite is endemic) but are absent in Europeans and Asians. These observations, and the known trypanolytic activity of the variants against *Trypanosoma brucei rhodesiense*, have led to the hypothesis that these variants evolved in SSA and have risen to high frequency because they confer protection against a deadly form of African sleeping sickness [27]. Interestingly, these African-specific renal risk variants are also seen in the Americas as a result of admixture since the trans-Atlantic slave trade [28,31] (Figure 2). G1 and G2 haplotypes recapitulate the molecular characteristics of *APOL1* in Old World monkeys, and

innate immune activity afforded by APOL1 may extend beyond trypanosomes [32]. S342G has the highest frequency in West-Central Africa, whereas G2 is more evenly distributed and at lower frequency throughout SSA (Figure 2). S342G was the most differentiated locus (P=5.11×10^{-7}) in a genome-wide comparison of the Western African Yoruba and the Eastern African Luhya ethnic groups, suggesting the role of positive selection in the evolution of the locus [32]. Clinically, kidney transplant failure is higher in recipients of donor kidneys from African ancestry individuals carrying *APOL1* renal risk variants [33]. *APOL1* high-risk genotypes (i.e., two risk alleles) explain an estimated 7–37% variance and 52–68% population attributable risk for different forms of end-stage kidney disease [34]. The *APOL1* variants have also been implicated in cardiovascular diseases (CVD) [35]. Individuals of African ancestry with the risk genotype display less protection against kidney disease from HDL compared to Europeans and Asians [36].

Ecological adaptations to tropical climate have also shaped the genetic structure of Africans. Local temperature-induced adaptive genetic changes may be one mechanism involved in hypertension and differences in salt sensitivity in humans [37]. Heat-adapted people, particularly members of the African Diaspora, have greater risk of hypertension due to exposures of the modern world (*e.g.*, increased salt intake) interacting with ancestral susceptibility [37]. Consistent with this hypothesis, signals of selection have been detected in *ATP1A1, AQP2*, and *CSK* genes previously implicated in hypertension and osmoregulation [11]. The ancestral allele of the *CSK* locus displaying high differentiation among African populations is strongly correlated with hypertension risk and its frequency is inversely correlated with latitude [11]. These findings support the hypothesis that adaptation to climate produced a latitudinal cline in hypertension susceptibility. If validated with more mechanistic studies, these observations could provide significant insight into the pathogenesis of hypertension. However, the ubiquity of exposure to environmental risk factors for hypertension at the global level is likely to make validating this hypothesis difficult; some of the highest rates of hypertension have been observed in non-African Diaspora populations [38].

Climatic adaptations in low latitude and high ultraviolet radiation (UVR) regions of the tropics are thought to have maintained dark skin pigmentation to protect against UVR-induced DNA damage and folate photolysis [39]. After modern humans migrated out of Africa, the challenges of producing vitamin D in the skin from the low UVR outside of the tropics were met by natural selection acting on mutations producing skin depigmentation more than 30,000 years ago [40]. Dark skin pigmentation is maladaptive in low UVR environments, potentially contributing to health disparities in diseases associated with vitamin D deficiency including several forms of cancer and cardiometabolic diseases [41]. Future mechanistic studies are needed to disentangle the effects of the ancestral alleles of genes selected for skin pigmentation from those of dietary and lifestyle changes leading to vitamin D deficiency and related co-morbidities.

Novel insights into disease etiology have also been gained by comparing diasporan populations to their ancestral populations in SSA and by characterizing local admixture at disease risk loci. A recent study found that the association between the *LPL* SNP rs328 and lipid levels was stronger and the levels of HDL cholesterol were higher among African

Americans with predominantly European ancestry than among those with African ancestry at this locus [42]. Lipid levels and their association with the *LPL* variant in African Americans with two African ancestry alleles at this locus were similar to those of West Africans despite widely different lifestyles and diets [42]. Another example of disease-associated alleles introduced to the Americas during the trans-Atlantic slave trade is the *LEPRE1* c.1080+1G>T allele that causes type VIII osteogenesis imperfecta, so far found only in African Americans and West Africans [43]. This *LEPRE1* mutation arose in West Africa more than 650 years ago and was transported to the Americas during the trans-Atlantic slave trade. Approximately 0.4% of African Americans and 1.5% of Nigerians and Ghanaians are heterozygous carriers [43].

Call for Large-Scale Deep Sequencing across the African Continent and the Diaspora

Earlier genotyping arrays were less efficient for interrogating the genomes of African ancestry populations [44] due to the fact that greater genetic variation is seen in present-day Africa populations than in populations outside of the continent, resulting in an increased number of haplotypes, lower levels of linkage disequilibrium (LD), more divergent patterns of LD, and more complex patterns of population substructure [11–13]. For example, our recent whole-genome sequencing effort in 320 SSA identified about 30 million variants [11], of which up to a quarter were unobserved in other populations from the 1000 Genomes sequencing project [12], indicating a need for large-scale deep sequencing of diverse populations across SSA and a need for a better genotyping array. Although some efforts have been made to address these concerns, including the recent development of the Infinium Multi-Ethnic Genotyping Array (MEGA) and the Affymetrix® Axiom® Genome-Wide Pan-African (PanAFR) Array, there remains a need for the development of a pan-African genotyping array that captures a larger proportion of common genetic variation across diverse African populations [11]. To achieve this goal, the H3Africa consortium has joined with the Wellcome Trust Sanger Institute, Illumina, and others to develop a genotyping array by interrogating whole-genome sequences from over 4,000 Africans sampled across the continent. There is also a need for improvements in algorithms for ancestry inference from whole-genome sequence data. Methodological issues include accounting for uncertain genotypes [45,46], linkage disequilibrium and phase [47], low-coverage sequence reads [48], and inadequate or missing source populations.

Conclusions

The history of the African Diaspora as defined in this opinion piece is complex, dynamic and continuous. With Africa at its root, members of the Diaspora developed multifaceted religious, cultural, and socio-political characteristics to adapt and survive in their new environments. As demonstrated above, genomics is beginning to facilitate better understanding of these multilayered stories and their implications for human history and health. However, more comprehensive sampling and genetic characterization of the populations of the African Diaspora and their ancestral homelands is urgently needed if these groups are to benefit from genomic medicine.

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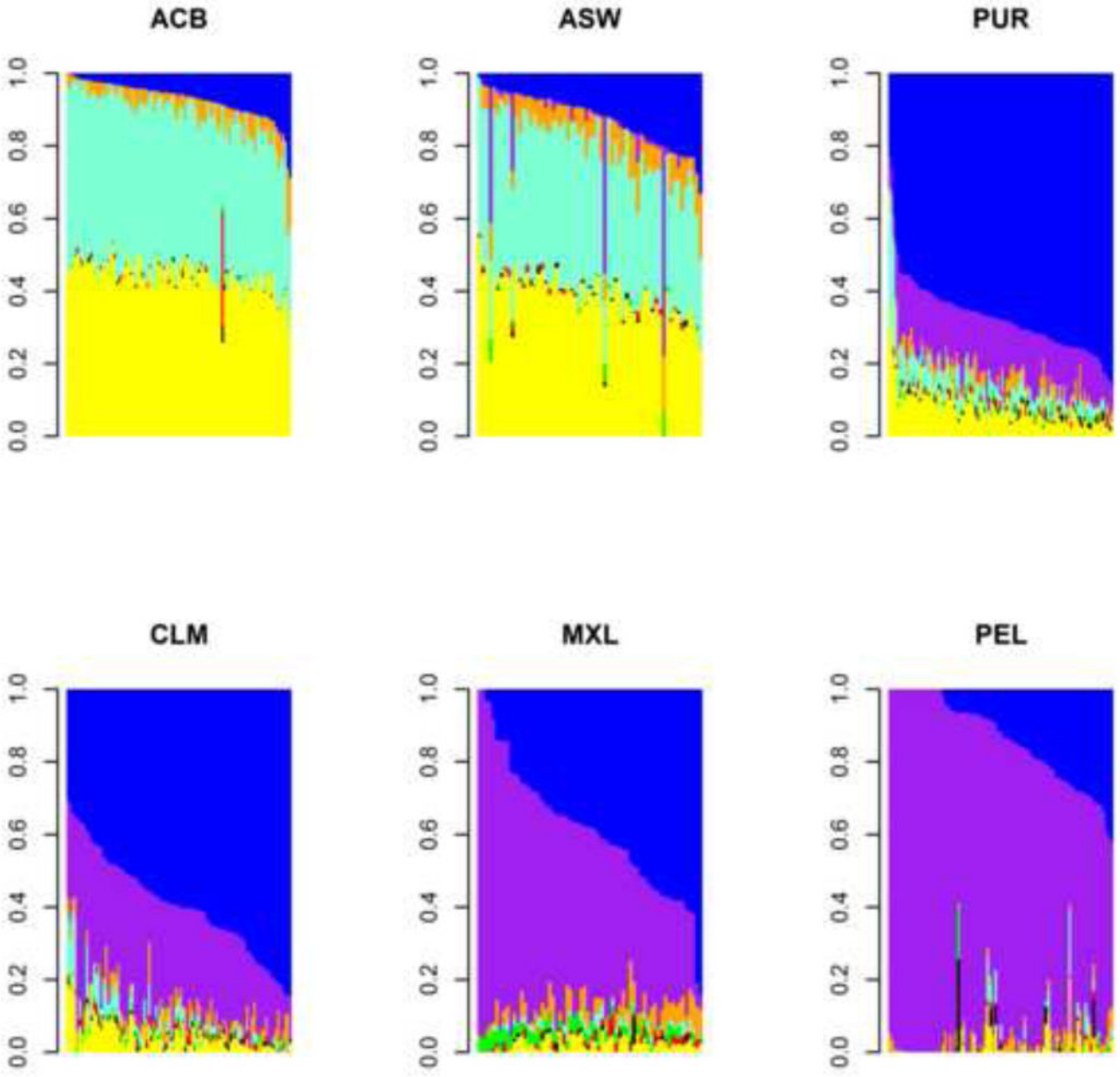
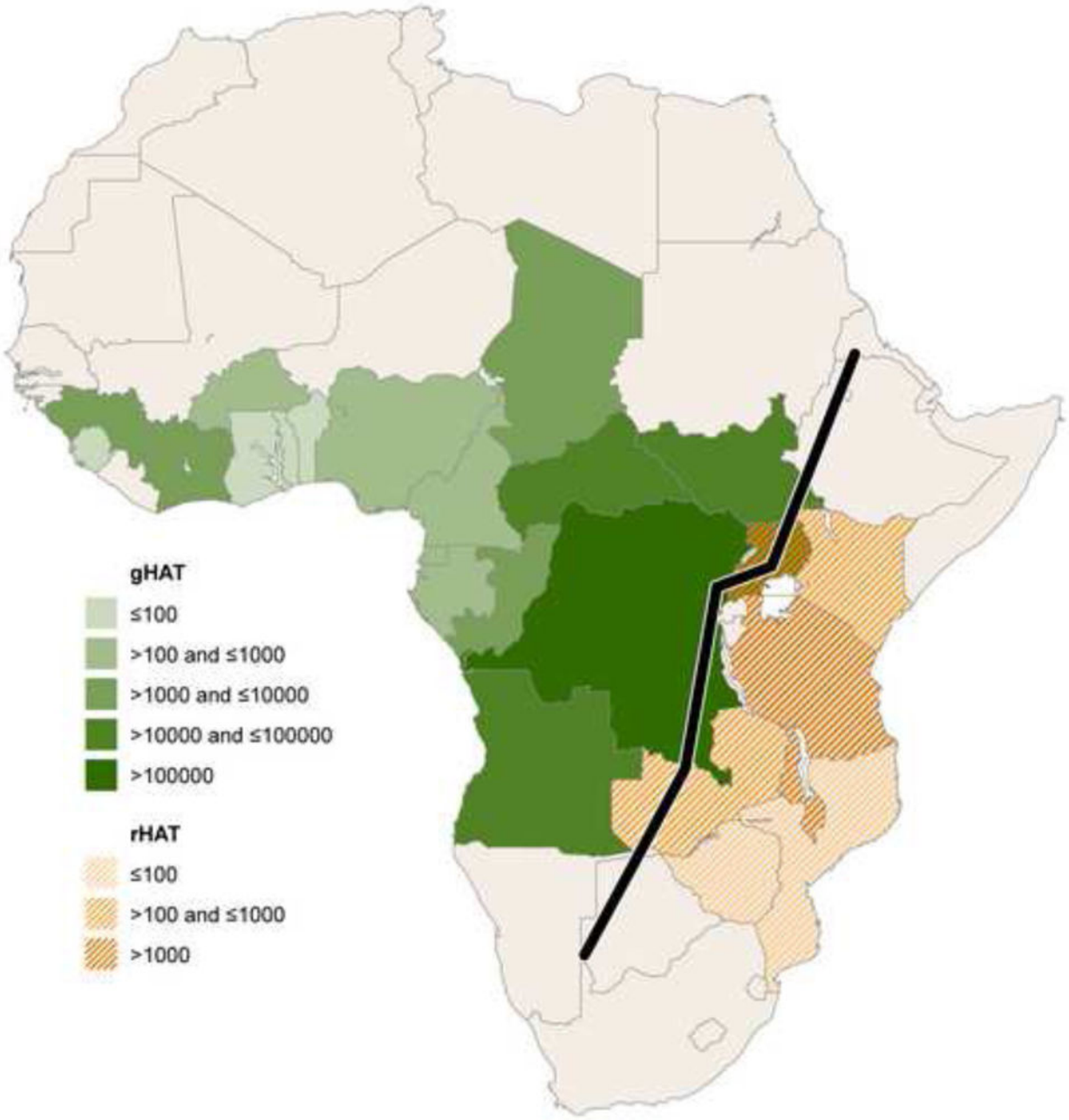
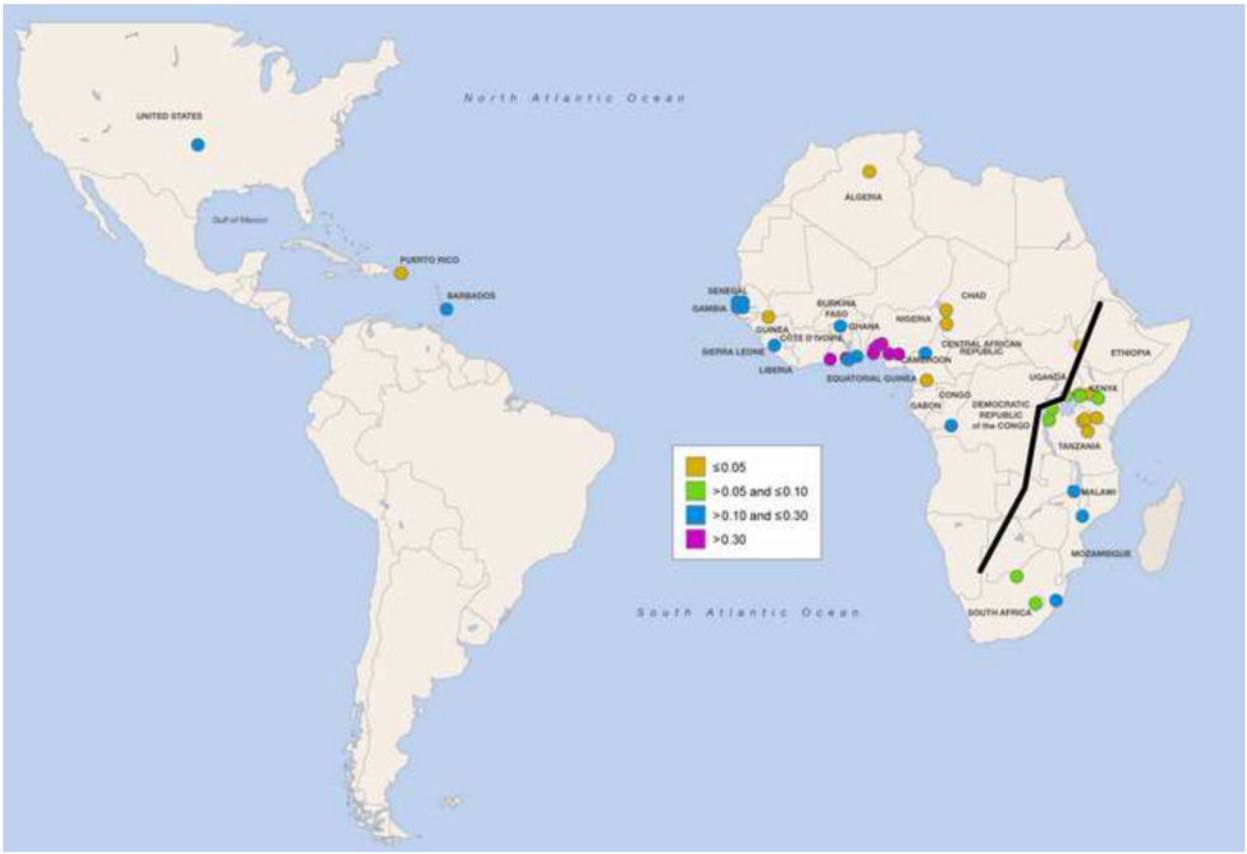


Figure 1.

Individual admixture proportions from New World samples [12]. The six samples are African Caribbean in Barbados (ACB), People with African Ancestry in Southwest USA (ASW), Puerto Ricans in Puerto Rico (PUR), Colombians in Medellín, Colombia (CLM), People with Mexican Ancestry in Los Angeles, California (MXL), and Peruvians in Lima, Peru (PEL). Conditional on eight ancestries, yellow corresponds to Western African ancestry, aquamarine corresponds to West-Central African ancestry, blue corresponds to Southern European ancestry, orange corresponds to Northern European ancestry, purple corresponds to Native American ancestry, red corresponds to South Asian ancestry, green corresponds to East Asian ancestry, and black corresponds to Southeastern Asian ancestry.

Summing the Western and West-Central African ancestries, the range of individual admixture proportion across these six samples goes from 0% to 97.8%. Similarly, the range of individual admixture proportion for Native American ancestry goes from 0% to 100%.





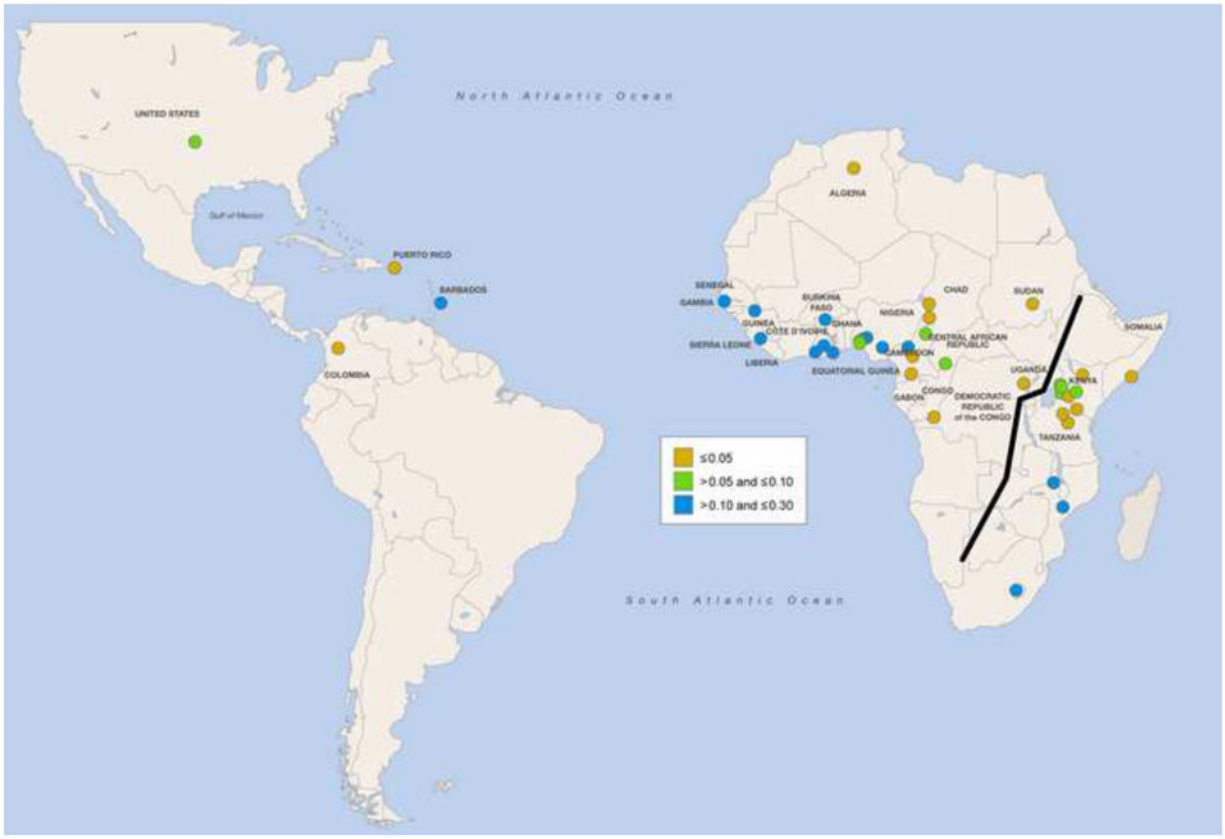


Figure 2.

Geographic distribution of *Trypansoma brucei* and *APOL1* risk variants. (A) Cumulative incidence from 1990 to 2014 of human African trypanosomiasis due to *Trypansoma brucei gambiense* (gHAT) and *Trypanosoma brucei rhodesiense* (rHAT) [75]. Uganda is the only country reporting trypanosomiasis due to both subspecies, with a higher cumulative incidence of gHAT. (B) Global frequency distribution of the G allele of the S342G mutation [11,12,28,49,76–78]. The Esan in Nigeria have the highest frequency (49.5%). (C) Global frequency distribution of the G2 deletion [12,28,32,49,77]. Bantu-speaking people in South Africa (Herero, Ovambo, Pedi, Sotho, Tswana, and Zulu) have the highest frequency (21.4%).

Table 1

Examples of natural selection with implications for human health

Adapted Genes	Beneficial Trait	Negative Outcome	References
APOL1	Protection against Human African Trypanosomiasis (HAT)	Kidney disease	[27–36,49]
ATP1A1, AQP2, CSK	Climate adaptation	Hypertension and osmoregulation	[11,37,38]
PPARA	Energy metabolism during prolonged food deficiency	None known to date	[50]
CIC, PAFAH1B3, LIPE, BHLHE41	High altitude adaptation	None known to date	[25,26]
LARGE, IL21	Confers protection against the Lassa virus	None known to date	[51]
DMD	Confers protection against the Lassa virus	1) Increased replication of vaccinia virus. 2) Duchenne and Becker muscular dystrophy	[52]
DARC	Confers resistance to *P. vivax*	Benign ethnic neutropenia	[53–59]
HBB	Confer incomplete resistance to lethal forms of malaria	Sickle Cell Trait and Sickle Cell Disease	[60–65]
Regulatory deficiencies of *HBA* and *HBB*	Confers incomplete resistance to lethal forms of malaria	α and β thalassemia	[66,67]
CCR5 Δ32 deletion	Confers HIV protection	1) CCR5 Δ32 are at higher risk for tick-borne encephalitis. 2) Fully functional CCR5 reduces symptoms from infection with West Nile virus	[68–71]
LCT	Lactase persistence	None known to date	[21,72,73]
AMY1	Increased copies of the gene in areas where starch is consumed	None known to date	[74]