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REVIEW

Pharmacogenomic implications of the evolutionary history of infectious diseases in Africa

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As the common birthplace of all human populations, modern humans have lived longer on the African continent than in any other geographical region of the world. This long history, along with the evolutionary need to adapt to environmental challenges such as exposure to infectious agents, has led to greater genetic variation in Africans. The vast genetic variation in Africans also extends to genes involved in the absorption, distribution, metabolism and excretion of pharmaceuticals. Ongoing cataloging of these clinically relevant variants reveals huge allele-frequency differences within and between African populations. Here, we examine Africa's large burden of infectious disease, discuss key examples of known genetic variation modulating disease risk, and provide examples of clinically relevant variants critical for establishing dosing guidelines. We propose that a more systematic characterization of the genetic diversity of African ancestry populations is required if the current benefits of precision medicine are to be extended to these populations.

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INTRODUCTION

Modern humans evolved in Africa ~200 000 years ago and, although some groups first migrated out roughly 100 000 years ago to populate the world,[1] others remained and eventually inhabited the entire continent.[2] As groups migrated out of Africa they underwent bottlenecks leading to sharp reductions in population size and genetic diversity.[3–5] To this day, African populations retain the most genetic diversity globally.[6] In order to survive both within and out of Africa, early human populations had to adapt to their novel environments including new food resources, colder climates, higher altitudes and, especially, infectious diseases.[7,8] These adaptive requirements, facilitated by natural selection, led to an increased frequency of alleles that were beneficial in that environment. Owing to the fact that these adaptive requirements were driven by local environmental pressures, some of these evolutionarily advantageous alleles display geographic and ancestral specificity as observed in the genomes of present-day humans.[8]

Finding genetic signals of natural selection is becoming increasingly possible as high-throughput biotechnology and novel computational methods are developed.[9,10] The ability to perform genome-wide association studies and large-scale genetic-variation surveys have led to an exponential increase in the amount of publicly available genetic data,[11] and an accompanying explosion in genomic comparisons both within and among populations.[12–14] These data support the clinical significance of identifying genetic outcomes of natural selection such as pinpointing susceptibility loci for infectious diseases plaguing human populations[15] or identifying responses to xenobiotic challenges.[16] These advances have opened the field of genomic medicine, which takes an individual's genetic data into account when planning clinical care[17,18] and is indispensable in the push for personalized, or precision, medicine. In this capacity, genomics has the potential to inform clinicians and contribute to precision medicine on numerous fronts, such as disease prediction, treatment response and avoidance of adverse drug reactions (ADR) or off-target effects.[19]

Unfortunately, most clinical studies remain overwhelmingly European-centered[19–24] and the majority of current drug recommendations were established using data from clinical trials performed in Caucasian or Asian populations and may be inappropriate for African populations.[19,25] This sampling bias is not trivial, as estimates for both disease risk and allele frequencies vary significantly between worldwide populations, as well as between African populations.[26–30] In fact, population-specific studies have established that Africa has the highest genetic diversity in the world,[31] as is reflected culturally in the over 2000 languages spoken on the continent,[32] and genetically in regional allele-frequency differences among African genomes[29,33] and in drug-metabolizing and -transporting genes in particular.[34] As a result of this genetic heterogeneity, it is unsafe to extrapolate results from one African ancestral group to another, as a drug which is found to be in the correct plasma concentration in one group can cause reduced effectiveness or, more troublesome, complete drug toxicity in another.[35,36] The differential metabolism of codeine resulting from genetic variability in *CYP2D6* provides an example. Owing to multiple gene-duplication events, some individuals have several copies of *CYP2D6*, leading to ultra-rapid metabolizing activity.[37] These individuals quickly convert codeine into morphine, a dangerous outcome that can lead to severe ADR, including death. The global distribution of carriers varies widely, from very low rates reported in West Africa, to 3% of Northern Europeans, 5–10% of Southern Europeans, to a high of about 30% of Ethiopians.[37–40] These data, along with a strong warning from

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the US Food and Drug Administration against the use of codeine for the management of pain in children,[41] and the current lack of infrastructure to genotype individuals, led the Ethiopian Food, Medicine and Health Care Administration and Control Authority to ban its use entirely.[42]

Genetic variations in genes involved in the ADME (absorption, distribution, metabolism and excretion) of pharmaceuticals influence drug safety and efficacy, and are the foundation of pharmacogenomic research and development.[43,44] Because genetic variation in ADME genes varies significantly between populations,[29,45] determining allele frequencies of genetic variants associated with known ADR in specific populations is critical for dosing guidelines and avoiding therapeutic failure. If the current benefits of personalized medicine are to be extended to African populations, a more thorough characterization of the diversity of African ancestries will be necessary[33,46–49] and is the motivation for this review. In particular, we will examine Africa's burden of infectious disease, discuss known genetic adaptations to five selected diseases that are prevalent in Africa, and present examples of clinically relevant population-specific variants.

Malaria

Transmitted to humans by infected female mosquitos, human malaria is caused by four species of the protozoan parasite *Plasmodium: P. vivax*, *P. malariae*, *P. ovale* and, the parasite that causes the most severe cases of malaria, *P. falciparum*.[50] Malaria is endemic throughout most of the tropics, with *P. falciparum* producing the major burden of disease globally, followed by *P. vivax*.[51] Owing to concerted global efforts, the number of deaths from malaria declined considerably between 2000 and 2015.[50] Despite these significant gains, malaria still poses a significant worldwide public health problem, causing ~438 000 fatalities a year, with 292 000 deaths occurring in African children[50] (Figure 1).

P. falciparum is the leading cause of malaria in Africa, whereas *P. vivax* is the dominant pathogen outside of Africa.[52,53] The Duffy antigen receptor for chemokines (*ACKR1*), commonly known as *DARC*, is the red blood cell receptor for the malaria-causing *P. vivax*.[54] A Duffy-negative phenotype associated with rs2814778 abrogates *DARC* surface expression on red blood cells and confers resistance to *P. vivax*.[55] This genetic variant is found extensively in malaria-endemic regions of sub-Saharan Africa, especially in West African populations (Supplementary Table 1).[53–57] However, *DARC*-independent host cell invasion is apparently possible, as studies in Madagascar[58] and Brazil[59] have identified *P. vivax* parasites that successfully invaded Duffy-negative erythrocytes.

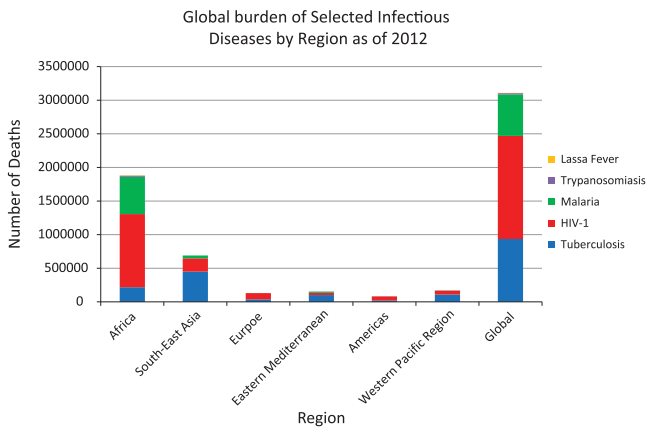

Figure 1. The global burden of the diseases discussed in this review as of 2012. HAT, human African trypanosomiasis.

Upon infection, the parasite incubates in the liver and enters the blood stream infecting red blood cells and causing high fever, sweats, chills and frequently death.[50,60] However, the parasites do not thrive in the presence of sickle-shaped blood cells. Thus, one of the consequences of thousands of years of human co-existence with the malaria pathogen is that inherited red blood cell disorders known as sickle cell disease are maintained as a result of balancing selection.[61] Sickle cell disease is a painful disease caused by abnormal hemoglobin alleles called hemoglobin S (HbS, 'sickle') at rs334 (Supplementary Table 1). Individuals with two sickle alleles (HbSS) produce red blood cells which take the sickle shape, thus severely restricting their oxygen-carrying capacity and interrupting healthy blood flow. Despite the debilitating effects of the homozygous condition, HbS is maintained owing to protection against malaria, as *P. falciparum* cannot thrive in sickled red blood cells.[61–64] In fact, carriers of the sickle allele have 60% protection against overall mortality,[65] resulting in a close geographical overlap of a high sickle allele frequency and malarial endemicity.[66]

G6PD (glucose-6-phosphate dehydrogenase) deficiency is an inherited enzyme abnormality and, similar to other red blood cell disorders, is prevalent in countries where malaria is historically endemic,[67] signifying that the deficiency may confer some protection.[68–70] Primaquine is the only drug licensed for the prevention and, in combination with other drugs, treatment of *P. vivax*. Unfortunately, the drug can cause severe hemolytic anemia in G6PD-deficient patients.[71,72]

Malaria prophylaxis and treatment is challenging because the *Plasmodium* parasite is capable of generating drug resistance in a relatively short time.[73] Therefore, an increasing number of African countries are heeding the recommendations of the World Health Organization for treating malaria by administering artemisinin-based combined treatments, which combines a form of artemisinin (either artemether or artesunate) with a longer-acting drug such as lumefantrine, amodiaquine, mefloquine or sulfadoxine-pyrimethamine.[74,75] Artemisinins work by quickly removing parasites from the blood, leaving fewer numbers upon which the partner drug must act.[76] The implementation of combination therapy is intended to reduce parasite resistance, as it should be more difficult for *P. falciparum* to become resistant to two drugs with unrelated modes of action.[77] However, resistance against the limited number of effective drugs is the foremost impediment to successfully treating malaria.[78,79]

The artemisinin-based combined treatments presently recommended for treatment of uncomplicated malaria are substrates of CYP enzymes. These highly polymorphic enzymes metabolize >80% of the commonly used therapeutic drugs[80] and influence individual variability in drug efficacy.[34] It is well-known that allele frequencies in the corresponding CYP genes differ between African populations, translating into differences in drug response.[81] For example, amodiaquine is regularly used in conjunction with artesunate, and, to a lesser extent, with sulfadoxine-pyrimethamine.[82] The enzyme CYP2C8 metabolizes amodiaquine, as well as another malaria medication, chloroquine.[83,84] A variant of this enzyme, CYP2C8*2, results in the poor metabolizer phenotype, where individuals with at least one copy of CYP2C8*2 experience a longer drug half-life and increased adverse side effects.[85] Allele frequencies of CYP2C8*2 differ between East and West Africa.[84] Establishing an individual's pharmacogenetic profile with respect to these artemisinin-based combined treatment combinations will allow practitioners to better tailor treatment outcomes and improve rational drug use. A comprehensive list of the known CYP450 enzymes involved in the metabolism of antimalarial drugs includes: Artemether: CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4 and CYP3A5; Lumefantrine: CYP2D6, CYP3A4 and CYP3A5; Amodiaquine; CYP1A1, CYP1B1 and CYP2C8; Mefloquine: CYP3A4 and CYP3A5; Chloroquine: CYP2C8, CYP2D6, CYP3A4 and CYP3A5; Sulfadoxine-

Table 1. Frequency of G allele at rs73885319

Population	*Sample size*	*Frequency*	*Reference*	*Population*	*Sample size*	*Frequency*	*Reference*
Western Africa				*Eastern Africa*			
Esan	99	0.495	6	Sena	51	0.122	199
Ibo	411	0.488	200	Malawi	50	0.120	199
Edo	14	0.464	200	Baganda	100	0.080	33
Akan	361	0.436	200	Barundi	97	0.077	33
Asante	35	0.409	199	Banyarwanda	100	0.075	33
Yoruba	563	0.342	200	Kikuyu	55	0.064	200
Ga-Adangbe	158	0.247	200	Luhya	99	0.056	6
Mandinka	113	0.243	6	Sandawe	19	0.050	201
Jola	79	0.234	33	Iraqw	19	0.050	201
Ewe	45	0.189	200	Hadza	19	0.050	201
Mende	85	0.124	6	Bantu Kenya	12	0.045	112
Wolof	78	0.122	33	Sudanese	24	0.042	202
Fula	73	0.116	33	Kalenjin	99	0.020	200
Bulsa	22	0.114	199	Anuak	76	0.020	199
				Wolayta	24	0	33
Southern Africa				Tygray	21	0	202
Zulu	100	0.130	33	Somali	38	0	33
Sotho	86	0.081	33	Sengwer	19	0	201
Bantu South Africa	8	0.070	112	Oromo	26	0	33
San	7	0	112	Maale	76	0	199
				Gumuz	24	0	33
Central Africa				Borana	18	0	201
Somie	65	0.164	199	Ari Cultivator	24	0	202
Congo	55	0.109	199	Ari Blacksmith	17	0	202
Bakola	19	0.050	201	Amhara	42	0	33
Biaka Pygmy	36	0.042	112	Afar	76	0	199
Mada	19	0.030	201				
Cameroon	64	0.008	199	*Northern Africa*			
Mbuti Pygmy	15	0	112	Mozabite	30	0.018	112
Lemande	18	0	201	Kordofan	30	0	199
Fulani	19	0	201				

pyrimethamine: CYP2C9 and CYP2D6; Primaquine: CYP1A1, CYP1A2, CYP3A4 and CYP3A5; and Quinine: CYP1A1, CYP1A2 and CYP3A5.[81]

Human african trypanosomiasis

Human African trypanosomiasis (HAT), also known as African sleeping sickness, is spread by blood-feeding tsetse flies infected with one of two protozoans, *Trypanosoma brucei* (*TB*) *rhodesiense* and *T.b. gambiense*.[86,87] *T.b. rhodesiense* causes East African (or Rhodesian) trypanosomiasis and accounts for 3% of cases annually, whereas two types of *T.b. gambiense*, termed groups 1 and 2, cause West African (or Gambian) trypanosomiasis and account for 97% of cases annually.[87,88] Primarily confined to remote rural areas of Sub-Saharan Africa,[89,90] incidences of the two illnesses generally map respectively to the east and west side of the African Rift Valley,[91] although this historically defined boundary is shifting in Uganda as infected cattle move northwards, taking *T.b. rhodesiense* with them.[92] Fortunately, disease prevalence has been steadily dropping since systematic global data collection began in 1940, reaching an all-time low of 3796 diagnosed cases in 2015,[93] down from 30 000 diagnosed and an estimated 300 000 undiagnosed cases in 1995.[94,95]

T.b. gambiense causes a prolonged chronic disease that can take decades before becoming fatal, whereas *T.b. rhodesiense* causes a more acute illness that progresses rapidly and can lead to death within weeks or months after infection.[96–98] Regardless of the infecting agent, clinical progression of the illness is divided into two stages,[96] (1) the early or hemolymphatic stage, characterized by nonspecific inflammatory symptoms similar to those associated with malaria or enteric fever, making diagnosis and treatment a challenge,[99] and (2) the late meningoencephalitic stage, characterized by weight loss, behavioral changes, stupor and coma.[96,100] If left untreated, both can be fatal.[98]

There is an unequal incidence of HAT cases among people living in close geographical proximity to each other, suggesting a genetic component to HAT susceptibility.[89] Thus far, genes associated with the susceptibility and severity of HAT include *FAS* and *FASLG*,[101,102] *IL23R*,[103] *SIGLEC6* and *SIGLEC12*,[104] *RNASEL*, *CXCR6* and *IFIH1*,[105] *APOL1*,[106] and *OAS2/3*.[33]

Although the burden of HAT on the African continent has plummeted in recent years, evolutionary signatures of the arms race between humans and trypanosomes are still evident in their genomes.[86,107,108] For example, humans have a trypanosome lytic factor, which includes the key component APOL1. When trypanosome lytic factor is taken up by trypanosomes, APOL1 localizes to the lysosome and forms a pore that leads to osmotic swelling and rupture of the trypanosome. However, *T.b. rhodesiense* has evolved a serum resistance-associated virulence factor which, when expressed as a protein in trypanosome lytic factor-resistant lines, binds and inactivates APOL1.[86] Variants in the *APOL1* gene evade serum resistance-associated inactivation, restoring protection from HAT.[109] In fact, the frequency of the HAT-protective G allele at rs73885319 is 26% among the 1000 Genomes AFR populations and as high as nearly 50% among the Esan in Nigeria (Table 1), whereas this variant is absent among non-African ancestry populations.[6] Furthermore, using a different resistance mechanism, group 2 *T.b. gambiense* can also overcome APOL1, an adaptive strategy that reflects the ability of *T.b.* to continually evolve and infect new hosts.[86] Curiously, the protective G allele at

rs73885319 is common in Western Africa and rare to absent in Eastern Africa; the advantages conferred by *APOL1* variants are not fully explained, although it has been suggested that protection may be conferred against other pathogens besides trypanosomes.[109]

Importantly, however, the protection from infectious disease that *APOL1* variants confer appear to come at the cost of chronic disease risk. HAT-protective *APOL1* variants have been strongly associated with kidney disease and, to a lesser degree, cardiovascular disease.[110,111] This association has been confirmed for nephropathies including focal segmental glomerulosclerosis,[106,112] HIV-associated nephropathy,[112,113] hypertension-attributed end-stage kidney disease,[106] severe lupus nephritis[114] and chronic kidney disease progression.[115] Analyses of *APOL1* HAT-protective/kidney disease risk variants have yielded some of the highest recorded odds ratios for a common variant: 29 and 89 for risk of HIV-associated nephropathy in African Americans[112] and South African Blacks,[113] respectively, and 17 for focal segmental glomerulosclerosis.[112] The magnitude of effect suggested by these associations coupled with the relatively high prevalence of the risk alleles have been suggested to underlie the huge public health burden of kidney diseases among African ancestry individuals. The *APOL1* story is a notable example of how the shaping of the genome in response to infectious disease can have an impact on chronic disease risk.

According to the CDC, four drugs are currently prescribed for the treatment of HAT, namely: pentamidine, suramin, melarsoprol and eflornithine,[116] and some of the pharmacogenomics properties of some of these drugs have been described. For example, pentamidine is transported within the body by human OCT1, a broad selectivity transporter encoded by the highly polymorphic *SCL22A1* gene,[117,118] variants of which affect the efficiency of uptake, distribution, and excretion of clinically relevant drugs.[117,119,120] Furthermore, CYP450 enzymes with roles in the metabolism of pentamidine include CYP1A1, CYP1A2, CYP2C8, CYP2C19, CYP2B6, CYP3A4, CYP3A5 and CYP4A11.[81]

Human immunodeficiency virus

Sub-Saharan Africa accounts for 70% of the global burden of HIV, with nearly one out of every twenty-five adults infected with the virus[121] (Figure 1). HIV is a retrovirus that causes the immune system to become weaker as infection progresses, eventually leading to the most advanced stage of infection, AIDS. There are two types of HIV, HIV-1 and HIV-2, of which the former is the predominant virus worldwide and is highly pathogenic.[122] Because the virus affects the immune system, an HIV-positive individual is more susceptible to infections and complications from other illnesses, especially tuberculosis (TB), which are often the ultimate cause of death.[123]

Early research suggested that host genetic polymorphisms affect individual susceptibility to HIV-1, viral load (indicative of infectiousness), and the speed of disease progression.[124–126] Although HIV-1 is not believed to have been in the human population long enough to have shaped the human genome, susceptibility to HIV-1 does depend in part on an individual's genetic architecture shaped by the evolutionary history of exposure to other infectious diseases.

A fully functioning receptor called CCR5 is required for HIV-1 virus entry.[127,128] A 32-base-pair deletion termed *CCR5* Δ32 (rs333) leads to a frameshift in the coding sequence, resulting in a non-functional protein that is not expressed in the cell membrane.[129–131] Individuals homozygous for *CCR5* Δ32 do not express functional receptors and are resistant to HIV-1 infection.[132,133] In addition, heterozygosity for the deletion provides a reduction in functional CCR5, thereby conveying partial resistance to HIV-1 infection; when an infection does occur, the viral loads are lower, slowing the progression to AIDS.[134]

Data suggest that the *CCR5* Δ32 deletion arose ~ 2900 years ago from a single mutation event[135] and was subsequently subjected to positive selection,[136,137] resulting in a geographical distribution where it is more prevalent in Europeans and largely absent from Asian and African populations (Supplementary Table 1).[129,130,136,138–140] A twentieth century disease, HIV-1 has not been around long enough for selection pressure to drive *CCR5* Δ32 from 0 to 10% in European populations.[141] Another pathogen, *Yersinia pestis*, the cause of the bubonic plague, was proposed as an agent of positive selection for *CCR5* Δ32.[137] However, the variola virus, which causes smallpox, generates a stronger selective pressure than plague on pre-reproductive members of a population and therefore appears to be a more plausible candidate.[142] In addition, both the variola virus and HIV-1 use chemokine receptors to enter white blood cells,[143] whereas the plague bacterium has an entirely different mode of entry.

Selection pressure from two infectious agents, both flaviviruses, provides the best evidence thus far to explain why this deletion is not observed in Africa. First, individuals homozygous for *CCR5* Δ32 are at higher risk for tick-borne encephalitis.[144] Second, fully functional CCR5 reduces symptoms from infection with West Nile virus,[145] named for the West Nile district of Uganda where it was first isolated in 1937.[146] These data suggest that infectious agents had a role in shaping the genome. Whether *CCR5* Δ32 is beneficial or deleterious in the context of a given infection (for example, HIV-1 infection versus West Nile virus) is contingent upon complex interactions between an infecting pathogen and the host immune system.

For those who have access to healthcare in Africa, treatment of HIV/AIDS with highly active antiretroviral therapy has drastically increased life expectancy for infected individuals,[147–149] transforming a once certain fatal disease into a chronic condition. Because patients are now receiving continuing treatment, much of African pharmacogenetic research is focused on optimizing therapeutic responses and preventing ADRs[150] by identifying clinically relevant genetic variants.[151–156]

Drug efficacy disparities between African populations treated with same active antiretroviral therapy regimen have been reported. For example, efavirenz is metabolized to 8-hydroxyefavirenz mainly by CYP2B6.[157] A specific variant of this enzyme, CYP2B6*6, is associated with a higher plasma efavirenz concentration. The frequency distribution of the CYP2B6*6 variant allele is significantly higher in Tanzanians (41.9%) than Ethiopians (31.4%)[151] and has also been shown to vary between Zimbabweans (49%) and Ugandans (35%).[158,159]

As we observed in the malaria discussion, many CYP450 enzymes are involved in the metabolism of drugs used to fight HIV. A comprehensive list includes: Efavirenz: CYP2B6, CYP3A4, and CYP3A5; Saquinavir: CYP3A4 and CYP3A5; Maraviroc: CYP3A4 and CYP3A5; Nevirapine: CYP2B6; Indinavir: CYP3A4 and CYP3A5; Nelfinavir: CYP3A4 and CYP3A5; Ritonavir: CYP3A4 and CYP3A5; and Lopinavir: CYP3A4 and CYP3A5.

Another example is the *HLA-B*5701* allele, which is strongly associated with abacavir hypersensitivity syndrome.[160] Abacavir causes serious ADR in 4–8% of patients.[160] Screening for the *HLA-B*5701* allele has been shown to greatly reduce the frequency of abacavir hypersensitivity syndrome.[161,162] There are clear frequency differences of the *HLA-B*5701* allele between African populations, ranging from 0% in the Nigerian Yoruba to 3.3% in the Kenyan Luhya and 13.6% in the Kenyan Maasai.[163] Such differences for a clinically relevant variant validates the importance of individual screening and demonstrates the inadequacy of group identity such as 'African' in medical decision making at the individual level. In fact, the U.S. Food and Drug Administration currently recommends that screening for *HLA-B*5701* be completed prior to administration of abacavir for all patients.[163] Increasingly, genomic data can help predict immunological response to HIV/AIDS therapeutic medicine, as was observed in

HIV infected women in Kenya[164] and Zimbabwe[165] taking nevirapine-based antiretroviral therapy.

Lassa fever

Lassa fever is a severe viral hemorrhagic fever caused by the Lassa virus. This RNA virus of the Arenaviridae family resides in the rodent vector *Mastomys natalensis* that lives in close contact with humans and sheds the virus in urine.[166,167] First described in 1969 in the town of Lassa, Nigeria,[168,169] Lassa fever is endemic in the West African countries of Guinea, Liberia, Nigeria and Sierra Leone,[170,171] although it does occur in other countries as well, such as Mali and Côte d'Ivoire.[172,173] The virus infects an estimated 300 000–500 000 people annually, resulting in thousands of deaths in the region.[174,175]

The virus enters the cell via its cell-surface receptor, alpha-dystroglycan (*DAG1*), replicating in a wide variety of cell types.[176] The glycosyltransferase *LARGE* is required for viral entry as it post-translationally modifies *DAG1*[174] by producing a protein the virus needs to infect an individual.[177] A genome-wide screen for recent selective sweeps identified a signal for positive selection at a 300 kb region exclusively within the *LARGE* gene in populations with West African ancestry.[178] Further data supporting the hypothesis of this virus as a driver of selection was subsequently reported for *LARGE* as well for another gene biologically connected to Lassa fever, *IL21*.[174,179] For both genes, the signal has been localized to putative regulatory regions,[174] a potentially important fact in the development of future therapies.

Although there are no approved vaccines for Lassa virus infection, the antiviral therapeutic ribavirin increases survival if given early in infection.[180] The pharmacogenomics of ribavirin are well-known in relation to another infectious disease, as pegylated interferon-a and ribavirin-based regimens are the mainstay for treatment of patients with chronic hepatitis C virus genotype 1 infection. In this case in point, a patient's interleukin 28B (*IL28B*) genotype predicts drug response;[181–184] the same genotype is predicted to affect drug response when given to patients with Lassa Fever, although to date the literature is devoid of any Lassa Fever pharmacogenomic studies.

Tuberculosis

Africa carries the highest overall burden of TB, with 281 cases per 100 000 population in 2014, whereas the global average is 133 per 100 000 population.[185] Approximately one-third of the global population has latent, asymptomatic TB,[185] and although those individuals only have a 10% chance of developing active TB disease,[186] risk is larger in individuals with compromised immune systems owing to conditions such as diabetes or HIV infection. Caused by the bacteria *Mycobacterium tuberculosis*, TB begins with fever, weight loss and coughing. Coughing progressively becomes worse with sputum and bloody coughs, chest pain and ultimately death.[185,187]

Human genetic variation affects susceptibility to mycobacterial infections, and candidate gene-association studies have suggested roles for several genes and pathways.[188] A recent genome-wide linkage study in Gambia and South Africa found suggestive linkage on 15q and Xq.[189] Many studies have reported associations between susceptibility and resistance to TB and several HLA loci and/or alleles[190–193] and allele frequencies of these markers are known to vary between ethnic groups.[194] One recent study from Uganda suggests the HLA-DQB1*03:03 allele may be associated with resistance to TB,[186] but much work needs to be done between African populations to assess population-specific allele-frequency differences and/or corresponding pharmacogenomic outcomes. Moreover, the contributions of rare variants with potentially large effects or multiple genes of small effect warrant systematic investigation.[188]

Isoniazid, rifampicin and pyrazinamide are the most commonly used drugs to fight TB and, as we observed in previous examples, the highly polymorphic CYP450 enzymes are involved in metabolism of these drugs. For example, CYP1A2, CYP2C19 and CYP2E1 affect the metabolism of isoniazid. Metabolism of rifampin involves the actions of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP3A4 and CYP3A5, CYP2C9, CYP2C19 and CYP2E1 affect the metabolism of ethambutol and the metabolism of pyrazinamide is affected by CYP1A2 and CYP3A4.[81]

Isoniazid, rifampicin and pyrazinamide can cause serious ADR in some individuals.[195] The most serious is anti-TB drug-induced hepatotoxicity, which can lead to treatment failure and interruption, drug resistance, morbidity and mortality.[196,197] An increased risk of ADR is associated with SNPs rs1799929 and rs1495741 in *NAT2*.[197] Ethiopian populations have significantly higher frequencies of these variants when compared with African ancestry 1000 Genomes populations (Supplementary Table 1),[36] providing yet another example of the genetic diversity between different African ancestries. In a 2011 study,[198] researchers examined the distribution of the *SLCO1B1* rs4149032 polymorphism that is associated with low blood concentrations of rifampicin (Supplementary Table 1). They found that the variant allele occurred at a lower frequency in Caucasians or Asians than in African populations. The presence of rs4149032, and subsequent lower rifampicin concentration, means a higher dosage of the drug is required for African populations to obtain the target concentration.[198] These two examples demonstrate again how African genetic diversity extends to clinically important genetic variants and supports the urgency of working to identify ancestry-specific pharmacogenomic variants.

CONCLUSION

This review details the complex history of infectious diseases in Africa and demonstrates how they have shaped African genomes. Documenting the vast genetic variation observed among African populations demonstrates the inadequacy of such group labels as 'Blacks' or 'Africans' in biomedical research, especially in the context of pharmacogenomics and medicine. It also calls for the need to engage more diverse populations across the continent to better document the scope and extent of genetic diversity in Africans to ensure they reap the benefits of the global efforts to use genomics to improve the precision of medicine for individuals. Given the extent of disease in Africa, combined with the monetary and human costs incurred from ADRs or ineffectiveness, the necessity for economical approaches to limit disease burden on the continent is evident. Although individualized screening prior to the selection of therapy is currently cost-prohibitive, comprehensive pharmacogenetic profiling of many African populations will produce data that will improve patient care by identifying populations at risk for developing drug toxicity or non-responsiveness until such time as truly personalized medicine can become a reality.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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