The genomic landscape of African populations in health and disease

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Abstract

A deeper appreciation of the complex architecture of African genomes is critical to the global effort to understand human history, biology, and differential distribution of disease by geography and ancestry. Here, we report on how the growing engagement of African populations in genome science is providing new insights into the forces that shaped human genomes before and after the Out-of-Africa migrations. As a result of this human evolutionary history, African ancestry populations have the greatest genomic diversity in the world, and this diversity has important ramifications for genomic research. In the case of pharmacogenomics, for instance, variants of consequence are not limited to those identified in other populations, and diversity within African ancestry populations precludes summarizing risk across different African ethnic groups. Exposure of Africans to fatal pathogens, such as *Plasmodium falciparum*, *Lassa Virus*, and *Trypanosoma brucei rhodesiense*, has resulted in elevated frequencies of alleles conferring survival advantages for infectious diseases, but that are maladaptive in modern-day environments. Illustrating with cardiometabolic traits, we show that while genomic research in African ancestry populations is still in early stages, there are already many examples of novel and African ancestry-specific disease loci that have been discovered. Furthermore, the shorter haplotypes in African genomes have facilitated fine-mapping of loci discovered in other human ancestry populations. Given the insights already gained from the interrogation of African genomes, it is imperative to continue and increase our efforts to describe genomic risk in and across African ancestry populations.

Introduction

Africa is the birthplace of anatomically modern humans and the geographic origin of human expansion across the globe within the last 100,000 years (1-3). Consequently, anatomically modern humans have lived longer on the African continent than anywhere else in the world (4-6). This long evolutionary history has led to several important genetic characteristics, as revealed by the growing engagement of African people in genomic projects such as the International HapMap, the 1000 Genomes, and the African Genome Variation Projects (AGVP) (7-9). Insights provided by these projects include the existence of more haplotypes, lower levels of linkage disequilibrium (LD), more divergent patterns of LD, and more complex patterns of population substructure in Africans compared to other populations. Anthropological and epidemiological studies are providing new understanding of the cultural and social characteristics of African populations, including linguistic diversity representing approximately a third of the world's languages, complex dietary patterns, varied farming practices, and uneven economic development (5, 6). These characteristics have resulted in varying levels of urbanization and differences in the distribution of non-genetic risk factors for disease across African populations.

A high degree of population subdivision across Africa has been observed, with nearly as many ancestries within Africa as in the rest of the world combined (3, 5, 10). On average, African populations display the highest level of within populations genetic diversity such that genetic diversity declines with distance from Africa (6). Consistent with the out-of-Africa model of human origin, the number of variant sites per genome is highest among Africans (~5 million variants) compared to individuals of East Asian, European, or South Asian ancestry (~4.0–4.2 million variants) (8). Genetic differentiation between African ancestries (e.g., F_{ST} is 0.054 between Khoisan and Omotic ancestries) can exceed that between pairs of non-African ancestries (e.g., 0.024 between Southern and Northern European ancestries or 0.042 between Arabian and Indian ancestries) (3, 5). As a function of physical distance, LD decays faster in African populations than in non-African populations, resulting in shorter haplotypes among Africans as illustrated in Figure 1 (8). Admixture has occurred between African ethno-linguistic groups and both Eurasian and

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hunter-gatherer populations in regionally distinctive ways (9). Furthermore, genomes sampled from the Americas display considerable African admixture with average African proportion as high as 80% in populations such as African Americans (AA)(3, 4, 8). Notably, individuals with African admixture show great variability in the number of variants and the degree of variability is roughly proportional to the degree of recent African ancestry in their genomes (8).

Recent genomic studies also show that the current generation of GWAS arrays are inefficient for interrogating African genomes, motivating a major effort by the Human Heredity and Health in Africa (H3Africa) Consortium and Illumina to develop more efficient genome-wide arrays by interrogating whole-genome sequences of thousands of Africans sampled across the continent. Using examples from infectious and cardiometabolic disorders, this review will illustrate how African genomes and environments have shaped the distributions of diseases and variable drug response across the continent, with implications for health disparities among its global diasporan populations, including African Americans. In addition, implications of some the unique characteristics of the African genomes for the performance of imputation and GWAS studies are discussed.

The Impact of Infectious Diseases on Inherited Diseases

Infectious diseases have impacted the human genome. Some mutations, while conferring protection against fatal pathogens, can be associated with costs in the form of inherited diseases. For example, seven loci in the human genome associated with protection against different forms of malaria are associated with several inherited diseases (Table 1).

Two genome-wide admixture mapping studies performed in AA identified a locus at chromosome 22q12.3 at which African ancestry conferred increased risk for several forms of end-stage kidney disease (11, 12). Subsequent fine-mapping identified two haplotypes in *APOL1* called G1 and G2 (13, 14). APOL1 carrying G2 affords protection against *Trypanosoma brucei rhodesiense* because the G2 deletion

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prevents binding of a trypanosomal virulence factor called serum resistance-associated protein (15).

Derived allele frequencies for G1 are highest in West-Central Africa, particularly in Nigeria and Ghana, and zero among non-African ancestry populations (16). *APOL1* variants have been associated with increased risk of multiple nondiabetic nephropathies and cardiovascular disease (17-23), accounting for a large proportion of observed disparities in renal disease between individuals with and without African ancestry. However, not all individuals with two copies of the *APOL1* variants develop kidney disease, suggesting the existence of other genetic and/or environmental modifying factors. Understanding the mechanism through which APOL1 influences kidney diseases is a major biomedical priority. A recent study has demonstrated that *APOL1* risk alleles are pathogenic. This study overcame the fact that *APOL1* appears to exist only in a subset of primate lineages by generating transgenic mice with podocyte-specific inducible expression of *APOL1*. This study demonstrated that *APOL1* risk variants adversely affect endosomal trafficking and autophagy, leading to inflammatory-mediated podocyte death and glomerular scarring (24).

Lassa virus, the cause of Lassa fever, has origins in the reservoir of the rodent *Mastomys natalensis* in Nigeria (25). The main cellular receptor for Lassa virus is α-dystroglycan (*DAG1*) (26). Glycosylation of α-dystroglycan by the enzyme LARGE is required for binding of Old World arenaviruses including Lassa virus (27). Signals for natural selection have been detected at *LARGE* in populations with West African ancestry (28-30). Mutations in *DAG1* and *LARGE* are associated with congenital muscular dystrophies (31-34), raising the possibility that an increased risk of congenital muscular dystrophies is a cost for increased resistance to arenavirus infection.

Pharmacogenomics

The vast genetic diversity in African ancestry individuals (8, 9) has pharmacogenomic consequences (16, 35). Not only are there marked differences in allele frequencies at pharmacogenomic loci between

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African vs. other ancestry populations, these variants also differ importantly among African ancestry populations (36, 37). For example, the HLA-B*57:01 allele is strongly associated with serious adverse reactions to the HIV/AIDS drug abacavir. Among the Yoruba in Nigeria, the risk allele is absent, but it is carried by 14% of Kenyan Masai. Importantly, among the Luhya of Kenya, this variant is much less frequent (3%), showing that even the descriptor "Kenyan" is inadequate to describe potential pharmacogenomic risk (38). Although practicing precision medicine may be prohibitively expensive in many parts of Africa, pharmacogenomic discoveries have already been used to improve drug safety in some countries by considering the average frequency of risk alleles in their population before selecting medicines for use (39, 40). Further progress will require a more complete understanding of the genetic diversity of African ancestry individuals at pharmacogenomic loci.

Examples of genomic studies in African and African American populations

Hypertension and blood pressure traits: We conducted the first GWAS of hypertension (HTN) and BP in AA (n=1,017) (41). One of the three significant loci identified is a HTN gene (*CACNA1H*) that is a drug target for a class of calcium channel blockers. Another (*SLC24A4*) is a strong candidate for BP regulation (41). African ancestry individuals have since been included in several other published GWAS and meta-analyses of HTN and blood pressure (BP) traits, including an international study that identified 29 significant loci in over 200,000 individuals of European ancestry with replication in over 70,000 non-European (East Asian, South Asian, and African) ancestry individuals (42). The COGENT Network has conducted a GWAS of systolic blood pressure (SBP) and diastolic blood pressure (DBP) in AA and Nigerians (n=29,378) that identified three novel loci (*EVX1-HOXA*, *RSPO3*, and *PLEKHG1*) in addition to two known loci (*ULK4* and *SOX6*) (43). Another COGENT study used a novel methodological approach that systemically integrated association evidence from multiple traits to identify four loci (*CHIC2*, *EVX1-HOXA*, *IGFBP1/IGFBP3*, and *CDH17*) associated with HTN-related traits, some of which were missed or undetectable in a single-trait analysis (44). A recent investigation of BP traits in

African ancestry individuals from eight cohorts (n=15,914) (45) identified rare variants associated with SBP and DBP in ten genes, including *AFF1, GAPDHS, SLC28A3, COL6A1, CRYBA2, KRBA1, SEL1L3, YOD1, CCDC13,* and *QSOX1*. This study provided important risk information on rare variants that complemented published findings for common variants in AA and continental Africans.

The only primary GWAS for HTN/BP in Africans to date used a pathway-focused approach to study Nigerians (n=1,614). Evidence in support of biological relevance was found for the *ADRA1* receptor pathway (46). A recent GWAS for metabolic syndrome (MetSyn) in Africans (n=1,427; described in more detail below) demonstrated that variants in *KSR2* and *MBNL1* displayed significant pleiotropic associations with BP in the single trait analysis (47). Our recent analysis of the GWAS data available through the AGVP (n=1,481) (9) identified several loci under selection in African populations, including a highly differentiated variant (rs1378940) in the *CSK* region which has been reported to be associated with HTN and BP in multiple GWAS (42, 48-50). While these studies provide some evidence in support of the genetic basis of BP regulation in African ancestry populations, the field awaits the publication of the first adequately powered GWAS of BP traits in Africans.

Type 2 Diabetes (T2D) and related traits: T2D is a devastating disease that impacts quality of life and increases risk of complications and cardiovascular disease. In the US, the prevalence of T2D is approximately twice as high among AA compared to European ancestry individuals (EA) (51), and the prevalence of T2D is anticipated to increase by 140% in Africa by 2040 (52). The largest genome-wide study of T2D in Africa included 1,775 West Africans (53), in which 106 previously reported loci across the genome were evaluated. One of these loci, the well-established *TCF7L2* locus (54-56), reached genome-wide significance. There was evidence of transferability for 39% of these loci to West Africans. While it is probable that the proportion of known T2D loci with evidence of transferability to African populations will grow as sample sizes increase, genetic diversity across world populations (particularly for African vs. non-African ancestry individuals) at T2D loci has been noted (57).

Considerably more genomic research has been conducted in AA for T2D (58-63). Notable among these is the largest GWAS of T2D in AA (n=23,827) (60) which identified several significant loci including *TCF7L2*, *HMGA2*, and *KCNQ1* that werepreviously reported and *HLA-B* and *INS-IGF2* that were novel findings. Interestingly, *HLA-B* and *INS-IGF2* have been associated with type 1 diabetes; new research supports some overlap in the pathways underlying susceptibility to both type 1 diabetes and T2D (64). The signal at *INS-IGF2* has since been replicated in Africans [Abstract; 177-OR-ADA 77th Scientific Sessions, June 9-13, 2017, San Diego, CA]. Other studies of common variants have identified two novel signals: *RND3/RBM43* in 1,994 AA (61) and an independent association within the known locus *HMGA2* in 9,681 AA (62). Analyses of low frequency and rare variants have not reported novel discoveries among AA (58, 63).

Studies of T2D-related traits insulin and insulin resistance in African ancestry individuals have also yielded novel findings. A trans-ethnic meta-analysis of fasting glucose and insulin in 20,209 AA and 57,292 EA individuals revealed two novel loci for fasting insulin: *FAM133A* and *PELO* (65). Similar to proportions reported for T2D loci, 43% of EA-identified loci were shared with AA (65). A GWAS of fasting insulin and insulin resistance in 927 non-T2D AA with follow-up and meta-analysis in 570 non-T2D West Africans identified *SC4MOL* and *TCERG1L* as novel loci for these traits (66).

The Metabolic Syndrome (MetSyn) is a clustering of traits that have been shown to dramatically increase risk of T2D and cardiovascular disease. A large study of MetSyn in 15,148 AA was conducted using the Metabochip genotyping array (67). Of the five MetSyn-associated loci, one was in a known glucose locus (*TCF7L2*) and four were in lipids loci (*LPL*, *APOA5*, *CETP*, and *APOC1/APOE/TOMM40*), consistent with previous reports of the contribution of lipids and T2D loci to MetSyn risk. Only one genetic or genomic study of MetSyn in Africans has been reported. This study included participants from Ghana and Nigeria (n=1,427) with replication and meta-analysis in Kenyans (n=174) and in AA (n=2,475). This analysis identified two African ancestry-specific variants that were associated with MetSyn, one near *CA10* and one in *CTNNA3*. The signal at *CA10* was subsequently observed to be associated with T2D in

Africans [Abstract; 177-OR-ADA 77th Scientific Sessions, June 9-13, 2017, San Diego, CA] . Additionally, two variants (near *RALYL* and *KSR2*) that are not unique to African populations were significantly associated with MetSyn. This study also replicated previous MetSyn associations with *LPL* and *CETP* that had been found in EA (47).

Obesity and inflammation: The growing global obesity epidemic is particularly devastating for African ancestry populations on the continent and in the diaspora (68-70). While it is evident that lifestyle changes are the major drivers of the obesity epidemic, it is well established that genetic factors play a role in individual susceptibility to excess weight gain and related metabolic disorders (71). Indeed, the heritability of obesity has been estimated to be as high as 60% (72) and over 300 loci have been identified to be associated with measures of adiposity (47, 72, 73). Several genetic/genomics studies of obesity traits have included African ancestry populations (47, 74-92). Collectively, these studies have identified or replicated variants in *FTO, MC4R, MTCH2, TFAP2A, SEC16B, TMEM18, NEGR1,* and *POMC* in African ancestry populations. Variants in the *FTO* gene are associated with obesity in West Africans (93) and in Black South Africans, suggesting that common genetic variants contribute to obesity risk across populations (82, 94, 95).

We recently published the first GWAS of BMI in Africans (n=1,570), which included replication in independent samples of Africans (n=1,411) and AA (n=9,020). This study identified an African-specific variant (rs80068415) in Semaphorin-4D (*SEMA4D*) that was associated with increased BMI (72). The largest meta-analysis of measures of adiposity that includes African ancestry individuals (n=52,895) (73) identified two novel loci: *TCF7L2/HABP2* (sex-combined analysis) and *SPRYD7/DLEU2* (ancestry-combined analysis). Consistent with observed sexual dimorphism in the genetic determinants of anthropometric markers (96, 97), five additional loci were found to be associated with adiposity in sex-stratified analysis in the African ancestry cohort: *IRX4/IRX2* (women), *INTS10/LPL* (men), *MLC1* (men), *SSX2IP* (women), and *PDE3B* (women)(73).

A number of tissues, including adipose and muscle, are involved in the pathophysiology of obesity and obesity-related traits (98). An epigenome-wide association study of BMI, BMI change, and waist circumference in 2,097 AA identified 15 novel methylation sites near genes implicated in lipid metabolism, immune response, and cytokine signaling (75). An eQTL study in AA identified ~ 2,000 transcripts with at least one significant cis-eQTL in adipose and muscle tissues (75). Comparative transcriptomics between 14 obese AA with T2D and 6 obese AA without T2D in omental adipose tissue identified a number of canonical pathways that were overrepresented and overlaid with T2D signaling pathways including telomere extension by telomerase (*HNRNPA1, TNKS2*), D-myo-inositol (1, 4, 5)-trisphosphate biosynthesis (*PIP5K1A, PIP4K2A*), and regulation of actin-based motility by Rho (*ARPC3*). Additionally, five miRNAs (miR-320b, miR-381-3p, miR-3679-3p, miR-494-3p, and miR-141-3p) were predicted as regulators of the expression changes identified in the omental adipose tissue of obese diabetics (99).

Inflammation is a hallmark of obesity and its complications (100). An association between obesity and circulating levels of adipokines has been observed in Africans (101-103). Serum concentrations of adipokines and inflammatory markers are under genetic control (104-106). Surprisingly, except for C reactive protein levels, serum levels of interleukins IL-10, IL-1RA, and IL-6 appear to be under the control of trans-QTL. Adjusting for BMI did not alter the strength of these associations, suggesting that the identified variants directly influence interleukin levels (105). Adiponectin, the only adipokine known to be decreased in obesity, has an anti-inflammatory property and is associated with obesity in African diasporan populations (102). Paradoxically, in metabolically healthy but obese individuals (MHO), adiponectin is increased compared to metabolically unhealthy individuals (107). The association between high adiponectin and MHO suggests that the absence of inflammation may be protective against the development of obesity-related co-morbidities. Furthermore, our characterization of MHO in AA using shot-gun proteomics revealed that under-expression of inflammatory markers was characteristic of MHO (108). Polymorphisms in adiponectin have been associated with obesity in populations of African

ancestry (83) and this association seems to be modulated by the proportion of European ancestry: the incidence of obesity was higher in individuals with the G allele and a higher proportion of African ancestry (83).

Serum lipids: In contrast to the increased prevalence of HTN, T2D, and obesity observed with increasing degree of westernization, there is remarkable similarity in the distribution of serum lipid parameters across African ancestry populations. In the US, interethnic differences in serum lipid distributions are consistently observed, with AA having a generally healthier lipid profile than European Americans despite differences in lifestyle factors that would be expected to produce a worse lipid profile among AA. This observation, coupled with the relative similarity in distribution of lipids between West Africans and AA with even greater differences in lifestyle characteristics, suggests that the healthier lipid profile among AA has a genetic basis (109).

Primary GWAS of serum lipids have yet to be performed in Africans. However, GWAS conducted in AA have identified a number of novel loci for lipid parameters. Common variant association studies have identified novel loci for low-density lipoprotein in *ICAM1* (110, 111) and for HDL in *CD36* (111) and *EXOC3L1* (112). Large-scale exome sequencing projects in AA have identified associated rare/low-frequency variants in novel loci *COL18A1* and *PCSK7* (113), as well as known loci *APOC3* (114), *PCSK9* (115), *CETP* (113), *LCAT* (113), *APOE* (113), and *ZNF259* (113).

A predominant focus in the published work on the genomics of serum lipids in African ancestry individuals, however, is not in discovery analyses, but in establishing the transferability of loci discovered primarily in EA studies (59, 111, 116-118). It has been estimated that 42% of lipids loci have replicated in AA (116). Despite modest statistical replication, analyses have noted a consistent direction of effect for most loci (111, 119-121), suggesting that replication may be achieved with increased sample sizes. However, effect sizes may appear diluted in AA compared to EA, due to interethnic differences in LD between the tag and causal SNP (121).

An efficient strategy that has been used to address the issue of trans-ethnic replication in the presence of interethnic differences in LD patterns and minor allele frequencies is first sequencing the gene of interest in African ancestry individuals to identify variants present before conducting analyses. We sequenced five lipids loci (*LPL*, *ABCA1*, *PON1*, *LCAT*, and *SERPINE1*) in 48 AA, with follow-up in 1,694 AA. As expected, *LPL* was associated with serum lipids; however, the ancestral background on which this variant occurred modified this association. The associations were much stronger among those with European ancestry at this locus, and not significant among those with only African ancestry, in whom the associations were strikingly similar to those in West Africans (122). Sequencing of known lipids genes has also been performed in studies of Africans, identifying novel associations in *LDLR* (123), *APOB* (124), *CETP* (125), *SCARB1* (126), and *LPL* (127).

Examples of fine-mapping of loci using reduced LD in African genomes

As discussed above, the demographic histories of African ancestry individuals have resulted in shorter segments of linked alleles compared to the relatively longer segments observed in other human populations (Figure 1). The distinct patterns created by these relative segmental lengths can be leveraged in genomic studies for fine-mapping loci associated with disease and non-disease traits (128). One of the earliest demonstrations of this principle was for the refinement of the association between variants in *TCF7L2* and T2D (55). The considerable interest and enthusiasm accompanying the discovery was tempered by the observation that the association spanned over many markers and a fairly broad region due to the strong LD in European ancestry populations. Using the weaker LD in West Africans, we were able to refine initial association between T2D and three markers (the composite allele X of microsatellite DG10S478 and the T alleles of SNPs rs12255372 and rs7903146) which were in strong LD in European ancestry populations (54). In the West African sample, the association was not significant for DG10S478, weaker for rs12255372 and statistically significant for rs7903146, indicating that either rs7903146 is the risk variant or its closest known correlate (55). Using sequence data on this region from the 1000 Genomes Project shows how critical the finer-grained LD in West Africans was in refining the original

association (Figure 2). Another notable example is the fine-mapping of the *SLC2A9* locus originally reported to be associated with serum uric acid concentrations in European ancestry populations. In our GWAS in African Americans, four variants in this locus achieved genome-wide significance for association with uric acid (129). Using an r^2 cutoff of ≥0.5, the 10 top ranking SNPs fall within the 263 kb range in CEU but remarkably 9 of the 10 top ranked SNPs lie within the 37 kb interval and 3 out of the 4 SNPs that achieved genome-wide significance lie in an approximately 1.3 kb interval. We also found other notable examples of fine-mapping (Figure 3) from our genome wide studies of African ancestry cohorts of Africans or African Americans in the *CYP7A1* locus for LDL-cholesterol (116) and in the *CRP* promoter locus for C-reactive protein (104). A recent trans-ethnic fine-mapping study of over 54,000 individuals of diverse ancestries reduce the region of interest for three known lipid loci (*LIPC*, *PLTP*, and *APOA5*) to a single variant by taking advantage of the reduced LD in the African Americans included in the analyses (130). Lastly, attempt to fine-map genetic association signals using expression quantitative trait loci (eQTL) in six 1000 Genomes populations (CEU, CHB, GIH, JPT, LWK, and YRI) demonstrated how African sampes can facilitate improved localization (8). Overall, between 17.5–19.5% of the top eQTL variants overlapped annotated transcription factor binding sites (TFBSs) within each population. However, a meta-analysis approach that combined pairs of populations resulted in an increase in the proportion of top eQTL variants overlapping TFBSs to 19.2–21.6% consistent with improved localization. Notably, the inclusion of an African population facilitated the greatest increase in overlap between top variants and TFBSs (8).

Considerations for future studies

In the context of the growing success stories of the genomics of African ancestry populations, we highlight some issues for consideration for the design of future initiatives. First, a careful review of the literature shows that the sampling of African ancestry populations remains a patchwork process, with efforts ranging from collecting convenience samples (.i.e., samples that are easy to get or already available) to the more systematic approaches implemented by the 1000 Genomes, AGVP and the

H3Africa projects, among others. In the context of sub-Saharan Africa, the 1000 Genomes Project focused on populations genetically close to the Yoruba (8). The African Genome Variation, Egypt Genome, and H3Africa Projects have contributed samples from populations in Benin, Botswana, Burkina Faso, Cameroon, Côte d'Ivoire, Democratic Republic of the Congo, Egypt, Ethiopia, The Gambia, Ghana, Guinea, Kenya, Mali, Nigeria, South Africa, Uganda, and Zambia. These samples are predominantly from Niger-Congo-speaking populations, largely as a consequence of the Bantu Expansion. Many linguistic groups are poorly or not represented, including speakers of Afroasiatic, Khoisan, and Nilo-Saharan languages, as well as other populations such as Central African Pygmies, Hadza, Laal, and Sandawe. In the past, for reasons including ongoing wars, it has been extremely difficult to sample some regions of the African continent. Resolution of some of these human conflicts are presenting us with new opportunities to filling these gaps. However, the achievement of this goal must include robust community engagements and involvement of local scientists as true partners and address local ethical issues that are likely to arise.

A second issue for consideration is what sample sizes are needed. The answer, of course depends on the question being asked. For association analysis of single variants, the sample size is inversely proportional to r^2 between the tag and causal variants (131). Thus, genotyping arrays that provide higher correlation between typed tag variants and untyped causal variants will be more efficient, requiring smaller sample sizes. Larger sample sizes are needed for lower frequency alleles or haplotypes and for smaller effect sizes. For diversity projects, sample sizes are inversely proportional to F_{ST}. Given the lower LD in African ancestry populations, a more efficient GWAS array, such as the H3Africa consortium array under development, will provide better opportunities to identify susceptibility loci.

A third issue is the adequacy of available reference panels for imputation in African ancestry populations. It is heartening to observe that this issue has received considerable attention from the genomic scientific community such that available reference panels are constantly improving. However, based on whole-genome sequencing, we demonstrated recently that the inclusion of more genetic diversity from the AGVP to the 1000 Genomes reference panels resulted in substantial improvement in imputation accuracy

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for Sotho population from South Africa (9). This result suggested poor representation of some haplotypes (e.g., Khoe-San haplotypes in Sotho) in the 1000 Genomes Project reference panel and calls for the inclusion of more diverse whole-genome sequenced samples in public genomic reference panels (9). A recent contribution to this effort was made by the Southern African Human Genome Programme (SAHGP), which is at the forefront of whole-genome sequencing in Africa of Africans by Africans. Although limited in scope, the SAHGP is demonstrating the feasibility of major sequencing effort led by continental scientists with local funding (132). However, larger future efforts such as GWAS based on whole-genome sequences in Africa will require a substantially higher commitment of resources from national and international funding agencies.

Conclusions

Genomic science is contributing novel insights into biology and human history, especially in EA populations. The engagement of Africans and it's diasporan populations in genomic science is still limited but growing (Figure 4). Some of the challenges facing a broader understanding of the genomics of African people are highlighted in Box 1. While the ability to summarize the transferability of loci identified in other populations is a notable advance, genomic diversity among African populations offers the potential to identify novel loci that could enhance our understanding of pathophysiology and prompt new treatment strategies that could benefit at-risk Africans as well as worldwide populations. As exemplified in this review, the successes proceeding from the still limited genomic research in African ancestry populations should motivate the field to promote and support the increased efforts into this area.

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Legends to Figure

Figure 1. Haplotype diversity in the 1000 Genomes Project. Haplotypes were counted over windows of six consecutive diallelic SNPs, with a slide of one SNP. For each sample, all counted haplotypes have a frequency ≥1%. See Supplementary Information Table 1 in (8) for the sample descriptors.

Figure 2. **Fine-mapping of *TCF7L2*.** A. Regional plot of *TCF7L2* rs7903146 association among West Africans (55). B. LD plot of region in 1000 Genomes CEU. C. LD plot of 1000 Genomes YRI. Consistent with the original report based on genotyping a few SNPS around the locus (54), both sequence and genotype data showed a much smaller haplotype around the lead SNP in the African samples. Note the fine-grained haplotype structure across the whole region in the African ancestry compared to the European ancestry sample.

Figure 3. Fine-mapping examples. Examples from studies of C-reactive protein(104), serum uric acid (129), serum lipids(116), and T2D(53) showing how smaller haplotype blocks in African ancestry populations helped refine genome-wide significant loci. Data are shown for fine-mapping analyses conducted in sub-Saharan Africans from Nigeria, Ghana and Kenya (AADM) and in African Americans from the Washington DC region in the United States (HUFS).

Figure 4. Inclusion of African ancestry individuals in genome-wide association studies. A. Percentage of studies including individuals with African ancestry *vs*. non-African ancestry individuals in the discovery sample. B. Percentage of studies including individuals with African ancestry *vs*. non-African ancestry individuals in the replication sample. C. Average sample size of individuals with African ancestry *vs*. non-African ancestry individuals in the discovery sample. D. Average sample size of individuals with African ancestry *vs*. non-African ancestry individuals in the replication sample. Whiskers indicate 95% confidence intervals. Data compiled from the NHGRI-EBI GWAS Catalog (https://www.ebi.ac.uk/gwas) from 2015 to 2017.

Box 1. Key challenges to the improved understanding of the genomics of African peoples

- Too few African ancestry scientists in genomics

- Limited funding opportunities, especially from national governments

- Inadequate genomic research infrastructure

- Lack of optimum genomics tools (e.g., GWAS arrays) and methodologies for the interrogation of African genomes

- Need for more discovery- vs. replication-focused analyses

- Larger studies of common, complex traits needed

- Insufficient characterization of diverse African ethnicities

- Further characterization of pharmacogenomic loci across the vast genomic diversity of African ancestry populations essential for clinical care

- Appropriately considering environmental background in studies of complex diseases, given vast environmental heterogeneity across African ancestry populations

Abbreviations

AA: African Americans

AGVP: African Genome Variation Project

BMI: Body Mass Index

BP: Blood Pressure

DBP: Diastolic Blood Pressure

EA: European Ancestry

eQTL: Expression Quantitative Trait Loci

GWAS: Genome-wide Association Study

H3Africa: Human Health and Heredity in Africa

HTN: Hypertension

LD: Linkage Disequilibrium

MetSyn: Metabolic Syndrome

MHO: Metabolically Healthy Obese

QTL: Quantitative Trait Loci

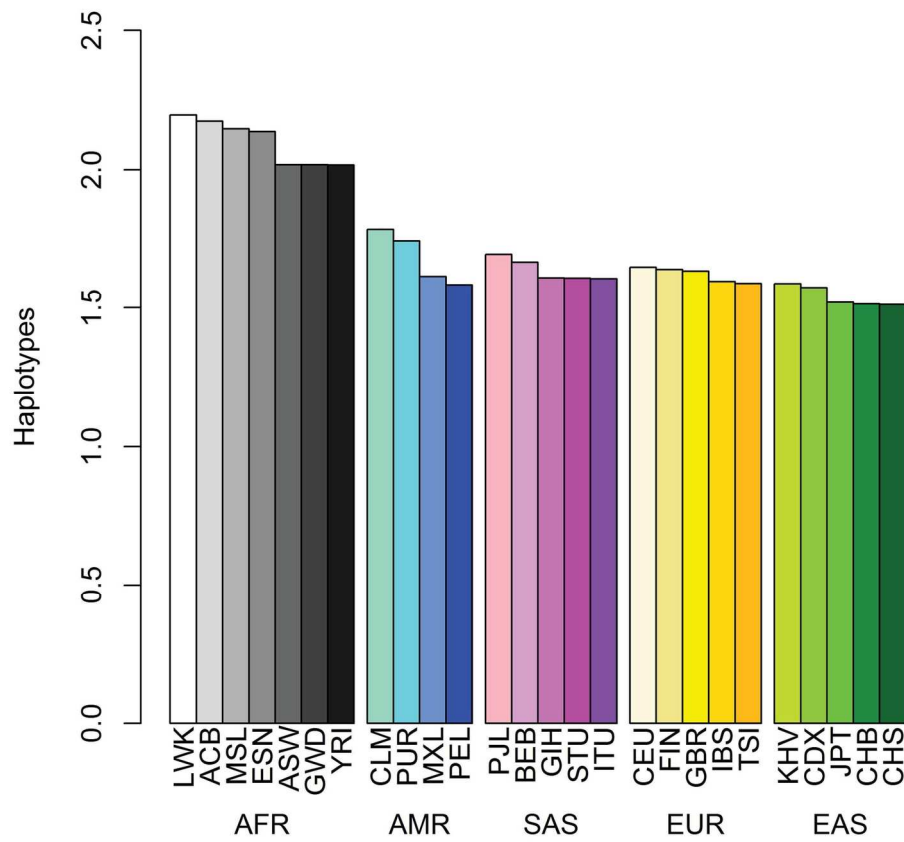SBP: Systolic Blood Pressure

T2D: Type 2 Diabetes

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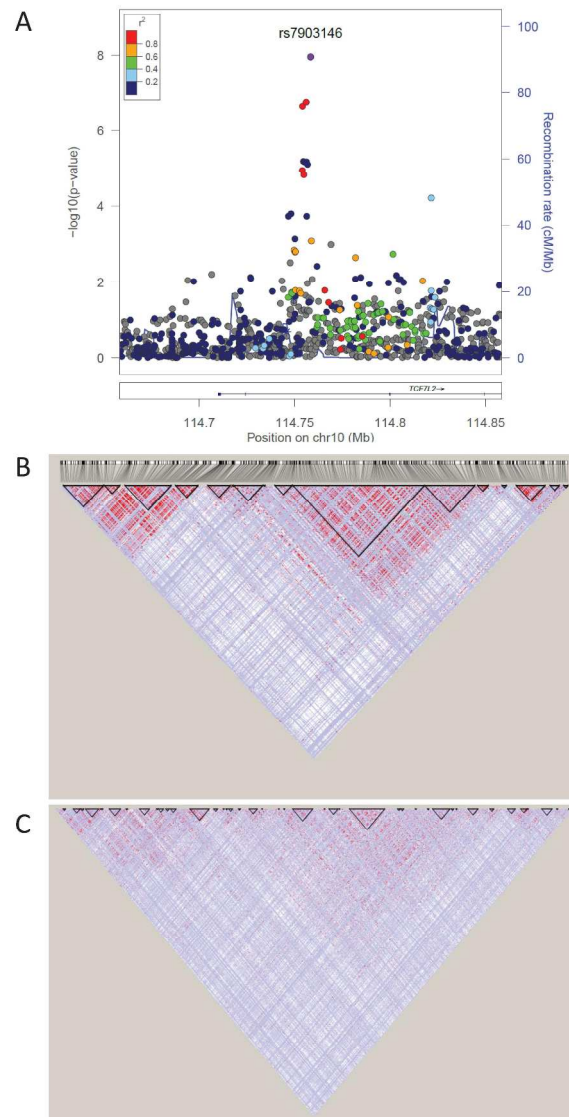
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Figure 2. Fine-mapping of TCF7L2. A. Regional plot of TCF7L2 rs7903146 association among West Africans (55). B. LD plot of region in 1000 Genomes CEU. C. LD plot of 1000 Genomes YRI. Consistent with the original report based on genotyping a few SNPS around the locus (54), both sequence and genotype data showed a much smaller haplotype around the lead SNP in the African samples. Note the fine-grained haplotype structure across the whole region in the African ancestry compared to the European ancestry sample.
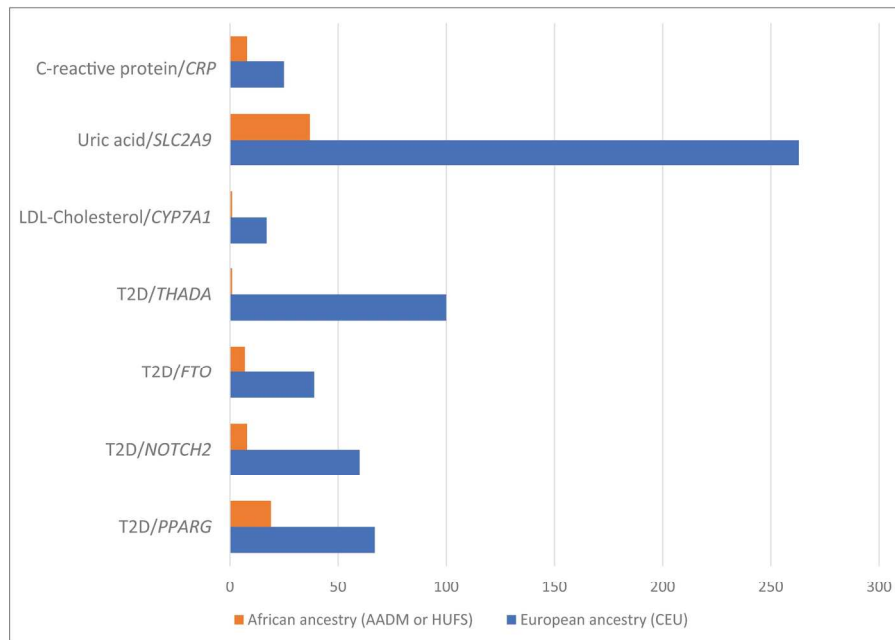
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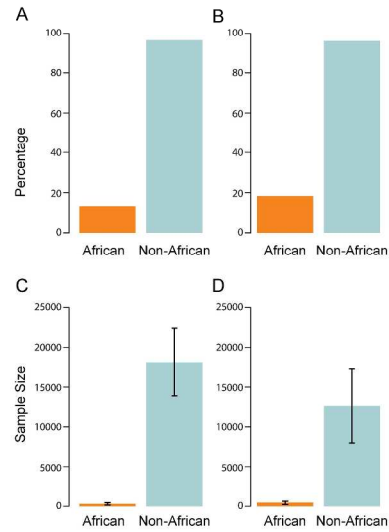
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