Genomics of Cardiometabolic Disorders in Sub-Saharan Africa

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Abstract

Sub-Saharan Africa (SSA) is experiencing a growing burden of cardiometabolic disorders, including diabetes, dyslipidemia, hypertension, obesity, coronary heart disease, and stroke. The increasing trends are expected to accelerate as SSA continues to experience economic progress, population growth, and the shift from communicable to noncommunicable diseases. These complex disorders are caused by multiple, potentially interacting, environmental, and genetic factors. While considerable progress has been made in the identification of the sociocultural, demographic, and lifestyle risk factors for cardiometabolic disorders, many genetic factors that underlie individual susceptibility to these diseases remain largely unknown. Although progress in genomic technologies has allowed for systematic characterization of genome-wide genetic diversity in health and disease in European and Asian ancestry populations, conduct of genetic studies in SSA has been underwhelming until re-

cently. Here, we summarize recent understanding of the body of knowledge and highlight research opportunities on the genomics of cardiometabolic disorders in SSA.

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Introduction

Cardiometabolic disorders including hypertension, diabetes, dyslipidemia, obesity, coronary heart disease (CHD), and stroke have been established as major contributors to the global burden of disease, disability, and mortality. Although cardiometabolic disorders were considered to be primarily prevalent in high-income countries, current indicators identify their increasing public health impact in all regions of the world, particularly in lower middle-income countries (LMIC). Between 2013 and 2100, the populations of 35 countries, most of them LMIC, could triple or more [1]. Among them, the populations of Burundi, Malawi, Mali, Niger, Nigeria, Somalia, Uganda, United Republic of Tanzania, and Zambia are projected to increase at least 5-fold by 2100 [1]. The fast rate of population growth, increase in life expectancy, urbanization, and the shift from communicable to noncom-

municable diseases in these countries suggests an alarming trend of increase in cardiometabolic diseases in Africa in the near future.

Risk factors for cardiometabolic disorders include excess weight gain especially around the abdomen (abdominal obesity), low levels of high-density lipoprotein cholesterol (HDL-C), high levels of triglyceride, fasting blood sugar, and blood pressure. A clustering of at least 3 of these metabolic risk factors, metabolic syndrome [2], is associated with increased risk of stroke by 2- to 3-fold, CHD by 3- to 4-fold [3], and diabetes by 5-fold [4]. Other cardiometabolic risk factors include smoking [5, 6], physical inactivity [7–9], urbanization [10–12], sleep apnea [13–19], western dietary pattern [20, 21], and genetics [22–30]. Variation in lifestyle risk factors operate against a background of genetic susceptibility, to increase the risk of an individual to developing a cardiometabolic disorder. This complex interaction of multiple genetic and nongenetic factors makes understanding the pathogenesis of cardiometabolic traits challenging.

A key advance in the drive to identify the genetic contributions to cardiometabolic diseases is the genome-wide association study (GWAS), an agnostic approach which aims to detect variant frequency differences in cases and controls by interrogating the entire genome. Initially developed as a method for testing association with hundreds of thousands to millions of genotyped single nucleotide polymorphisms (SNPs), its utility has been increased by *in silico* imputation using reference datasets and meta-analytic procedures that can combine association statistics across multiple GWASs. Large-scale GWASs have been remarkably successful in uncovering novel susceptibility loci for a wide range of complex human diseases including obesity-related traits, coronary artery disease, hypertension, dyslipidemia, and diabetes [31, 32]. Table 1 shows GWAS publications which included data from Sub-Saharan Africa (SSA), and Figure 1 shows the number of GWAS publications by ancestry and population.

Africa is the most genetically diverse continent in the world, even though few studies have focused on characterizing the genome-wide genetic diversity of African populations [33]. The International HapMap [34], 1000 Genomes [35], and especially the African Genome Variation Projects (AGVP) [36] have provided remarkable insight into the scope, historic and health implications of the vast genetic variation that exists across African ancestry populations. The AGVP project which generated both genotype and whole-genome sequence data from 20 African ethno-linguistic groups revealed the previously un-

appreciated complex population structure, including regionally distinct patterns of admixture and evidence for substantial “Eurasian” and hunter-gatherer admixture across SSA. African populations are highly subdivided. The population structure across Africa is currently recognized as 11 ancestries that correspond to a combination of geographic and linguistic separation, compared to 12 ancestries detected in the rest of world [37]. Genetic differentiation, measured by F_{ST} , between SSA ancestries can exceed that between pairs of non-African ancestries. The vastness and complexity of genetic variations across African populations have significant implications for human health. For example, genetic adaptations that took place across Africa, particularly against pathogens of fatal diseases 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. Unfortunately, some of these alleles are maladaptive in modern-day environments and 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 [38]. The aim of this review is to highlight how genomics is contributing to our understanding of the patho-biology of cardiometabolic disorders among African ancestry populations.

Hypertension

In 2008, approximately 40% of adults aged 25 and above were diagnosed with hypertension worldwide; the number of people with the condition rose from 600 million in 1980 to 1 billion in 2008 [39]. The increasing prevalence of hypertension is attributed to population growth, aging, and behavioral risk factors, such as unhealthy diet, harmful use of alcohol, salt sensitivity, lack of physical activity, excess weight, exposure to persistent stress, and westernization [40–42]. Overall, high-income countries have a lower prevalence of hypertension (35%) compared to LMIC (~40%). Some countries in Africa have a high prevalence of hypertension among adults [39, 43]. Figure 2 shows the prevalence of raised blood pressure in SSA, by country income group.

Admixture mapping analysis suggested that African ancestry is associated with increased risk of hypertension [44]. Some studies reported heritability estimates of systolic blood pressure ranging from 34 to 68%, and diastol-

Table 1. GWAS publications including samples from Sub-Saharan Africa, 2009 – October 2016

First author [Ref.], year	Disease/trait	Location(s)	Initial sample	Replication sample
Jallow [173], 2009	Malaria	Gambia	958 Gambian ancestry cases, 1,382 Gambian ancestry controls	1,087 Gambian ancestry cases, 2,376 Gambian ancestry controls
Joubert [174], 2010	HIV (mother-to-child transmission)	Malawi	100 Malawian ancestry infant cases, 126 Malawian ancestry infant controls	
Kang [175], 2010	Anthropometric traits	Nigeria	743 African-American individuals, 1,188 Nigerian ancestry individuals	704 African-American individuals from 306 families, 3,471 African-American and Caribbean individuals
Thye [176], 2010	Tuberculosis	Gambia, Ghana	2,237 Sub-Saharan African ancestry cases, 3,122 Sub-Saharan African ancestry controls	1,462 Sub-Saharan African ancestry cases, 4,604 Sub-Saharan African ancestry controls
Petrovski [177], 2010	HIV-1 susceptibility	Malawi	531 Sub-Saharan African ancestry cases, 848 Sub-Saharan African ancestry controls	
Ziliak [178], 2011	Response to platinum-based chemotherapy in head and neck cancers	Nigeria	90 East Asian ancestry lymphoblastoid cell lines	90 European ancestry lymphoblastoid cell lines, 59 Yoruba ancestry lymphoblastoid cell lines
Fox [53], 2011 ^a	Blood pressure	Nigeria	7,473 African-American individuals	1,188 Sub-Saharan African individuals, 10,694 African-American individuals, 69,899 European ancestry individuals
Ramsuran [179], 2011	Platelet count	South Africa	115 African ancestry HIV-negative individuals	
Haiman [180], 2011	Prostate cancer	Ghana, Senegal	3,425 African-American cases, 3,290 African-American controls	1,500 African-American/Caribbean cases, 1,908 African-American/Caribbean controls, 344 Sub-Saharan African ancestry cases, 1,361 Sub-Saharan African ancestry controls
Wheeler [181], 2011	Chemotherapeutic susceptibility	Nigeria	83 African-American lymphoblastoid cell lines, 176 African ancestry lymphoblastoid cell lines	
Lingappa [182], 2011	HIV-1 viral set point	Kenya, Uganda, Botswana, South Africa	496 African ancestry cases and 302 African ancestry exposed controls from serodiscordant couples	
O'Donnell [183], 2012	Capecitabine sensitivity	Nigeria	Up to 84 East Asian ancestry lymphoblastoid cell lines, up to 164 European ancestry lymphoblastoid cell lines, up to 173 African ancestry lymphoblastoid cell lines, up to 82 African-American lymphoblastoid cell lines	
Thye [184], 2012	Tuberculosis	Ghana	1,329 African ancestry cases, 1,847 African ancestry controls	2,024 African ancestry cases, 5,154 African ancestry controls, 1,025 Indonesian ancestry cases, 983 Indonesian ancestry controls, 4,441 European ancestry cases, 5,874 European ancestry controls
Tekola Ayele [185], 2012	Podoconiosis	Ethiopia	194 African ancestry cases, 203 African ancestry controls	202 African ancestry family trios
Doumatey [186], 2012	C-reactive protein	Ghana, Nigeria	837 African-American individuals	486 West African ancestry individuals
Timmann [187], 2012	Malaria	Gambia, Ghana	1,325 African ancestry, 828 African ancestry controls	2,229 African ancestry cases, 3,526 African ancestry controls
Carty [188], 2012	Height	Nigeria, US	8,149 African-American female individuals	Up to 20,809 African-American and African ancestry individuals
Wheeler [189], 2013	Paclitaxel-induced neuropathy	Nigeria	77 European ancestry lymphoblastoid cell lines, 87 Yoruban ancestry lymphoblastoid cell lines, 83 African-American lymphoblastoid cell lines	
Wheeler [190], 2011	Response to platinum-based chemotherapy (cisplatin)	Nigeria	176 Sub-Saharan African ancestry lymphoblastoid cell lines, 83 African ancestry lymphoblastoid cell lines, 175 East Asian ancestry lymphoblastoid cell lines, 174 European ancestry lymphoblastoid cell lines	
Monda [191], 2013	Body mass index	Ghana, Nigeria	37,956 African-American individuals, 1,188 Nigerian ancestry individuals	27,661 African America/Caribbean individuals, 4,607 Sub-Saharan African ancestry individuals, 123,706 European ancestry individuals
Band [192], 2013	Malaria	Gambia, Kenya, Malawi	5,425 African ancestry cases, 6,891 African ancestry controls	

Table 1 (continued)

First author [Ref.], year	Disease/trait	Location(s)	Initial sample	Replication sample
Franceschini [193], 2013 ^a	Blood pressure	Seychelles, Nigeria, Ghana, South Africa	28,190 African-American individuals, 1,188 Nigerian ancestry individuals	69,395 European ancestry individuals, 5,266 African-American individuals, 6,497 African ancestry individuals, 19,601 East Asian ancestry individuals
Chimusa [194], 2013	Tuberculosis	Gambia, Ghana, Malawi, South Africa	642 South African colored cases, 91 South African colored controls	
Willer [195], 2013 ^a	Triglyceride	Seychelles, Uganda, Jamaica, US	94,595 European ancestry individuals	4,420 African ancestry individuals
Cook [196], 2013	Prostate cancer	Ghana	474 West African ancestry cases, 458 West African ancestry controls	5,096 African-American cases, 4,972 African-American controls
Al Olama [197], 2014	Prostate cancer	US, Ghana, Barbados	34,379 European ancestry cases, 33,164 European ancestry controls, 5,327 African ancestry cases, 5,136 African ancestry controls, 2,563 Japanese ancestry cases, 4,391 Japanese ancestry controls, 1,034 Latino cases, 1,046 Latino controls	
Mtatiro [198], 2014	Fetal hemoglobin levels in sickle cell anemia	United Republic of Tanzania, UK	1,213 Tanzanian ancestry cases	321 Caribbean and Sub-Saharan African cases
Aung [199], 2015	Exfoliation syndrome		1,484 Japanese ancestry cases, 1,188 Japanese ancestry controls	1,530 East Asian ancestry cases, 6,230 East Asian ancestry controls, 1,064 Southern Indian ancestry cases, 3,536 Southern Indian ancestry controls, 140 Hispanic cases, 233 Hispanic controls, 347 Middle Eastern ancestry cases, 1,108 Middle Eastern ancestry controls, 3,588 European ancestry cases, 9,012 European ancestry controls, 102 South African Black cases, 379 South African Black controls, 50 Uighur cases, 49 Uighur controls, 80 cases, 180 controls
Curtis [200], 2015	Tuberculosis	Gambia, Ghana	5,530 European ancestry cases, 5,607 European ancestry controls	1,085 Russian ancestry cases, 2,865 Russian ancestry controls, 2,277 Sub-Saharan African ancestry cases, 2,360 Sub-Saharan African ancestry controls
Komatsu [201], 2015	Paclitaxel-induced cytotoxicity	Nigeria	57 Japanese ancestry lymphoblastoid cell lines, 59 Han Chinese ancestry lymphoblastoid cell lines	77 European ancestry lymphoblastoid cell lines, 87 Yoruba ancestry lymphoblastoid cell lines, 83 African ancestry lymphoblastoid cell lines
Band [202], 2015	Severe malaria	Malawi, Ghana, Tanzania, Mali, Cameroon, Burkina Faso, Gambia	5,130 African ancestry cases, 5,291 African ancestry controls	5,535 African ancestry cases, 9,948 African ancestry controls
Kim [203], 2015	Plasma homocysteine	Nigeria	853 African-American cognitively normal individuals, 45 African-American dementia cases, 934 Yoruba ancestry cognitively normal individuals, 26 Yoruba ancestry dementia cases	
Data source: GWAS catalog – accessed November 2016. Location signifies country of recruitment. ^a Cardiometabolic disorders.				

ic blood pressure ranging from 29 to 65% in African populations [45–47]. Early GWASs investigating risk variant associations with hypertension and/or blood pressure traits in Europeans were not very successful [48, 49]. More recently, large-scale GWASs predominantly involving European ancestry study subjects have identified numerous loci associated with blood pressure traits [32, 50]. A recent meta-analysis of gene expression data identified 34 differentially expressed genes for blood pressure and discovered genes, which may explain 5–9% of blood

pressure variability [51]. The first GWAS for hypertension and blood pressure was conducted among 1,017 African-Americans enrolled from the Washington DC metropolitan region of the United States, in the Howard University Family Study. This study identified multiple SNPs reaching genome-wide significance for systolic blood pressure in or near genes *CACANA1H*, *IPO7*, *PMS1*, *SLC24A4*, and *YWHAZ*, with a replication of some of the SNPs in a sample of West Africans. Two of these genes, *SLC24A4* (a sodium/potassium/calcium exchanger) and

Fig. 1. GWAS publications by ancestry of discovery sample. The data used to create this figure was obtained from the GWAS catalog – accessed October 2016 (5,794 GWAS publications after exclusions of unspecified, Oceania, Native Americans). Note that early studies did not consistently label ancestry. Also, some discovery studies used multiple ancestries. Therefore, some ancestry categories may be underestimated. African ancestry includes African-American and Afro-American. *, was used as a population label.

Fig. 2. Prevalence of raised blood pressure among adults in Sub-Saharan Africa by country income groups in 2014. The data used to create this figure were obtained from the Global Health Observatory Data Repository – assessed August 2016. Age-standardized

data for male and female were used. The country income group was based on the World Bank 2014 Classification. Raised blood pressure = systolic ≥ 140 mm Hg or diastolic ≥ 90 mm Hg.

CACNA1H (a voltage-dependent calcium channel), are potential candidate genes for blood pressure regulation and the latter is a drug target for a class of calcium channel blockers [52]. A larger GWAS for blood pressure using the Candidate Gene Association Resource (CARE) consortium consisting of 8,591 African-Americans identified strong signals for blood pressure near *GPR98*, *ARRDC3*, *C21orf91*, *SLC25A42*, and *HLA-B* genes [53]. Although the associations in both of these studies among African-Americans has not been successfully replicated in independent African-American samples [54], some genes associated with blood pressure in other studies, including *SH2B3*, *STK39*, *CDH13*, *TBX3-TBX5*, and *CSK-ULK3*, have been replicated in studies involving African-Americans [52–54].

A genome-wide linkage scan for blood pressure in Nigerian families found evidence of significant linkage to blood pressure on chromosomes 6 and 7 [55]. Further linkage disequilibrium mapping identified at least 7 loci, including an intronic SNP in the *PARK2* gene [56], in the region previously identified by admixture mapping for hypertension in populations of African ancestry [44]. Genetic variation in the *PARK2* gene has also been shown to be significantly associated with blood pressure in Korean populations [57].

Alternative methods of identifying the genetic underpinnings of hypertension are being explored, including pathway analysis of GWAS results [58] and targeting of candidate genes [59]. A study in Africa which applied a pathway-focused approach to genomic association scans for hypertension found associations between multiple variants in several genes in the adrenergic receptor alpha-1 (*ADRA1*) pathway and hypertension in Yoruba Nigerians [60]. A meta-analysis of genome-wide linkage scans for blood pressure variation in Nigerians and African-Americans reported association in 2 loci: 2p14–p13.1 and 7p21.3–p15.3, the second locus being attributed to the Nigerian sample and suggesting a unique locus for blood pressure variation in people of African ancestry [61].

Most genes near blood pressure GWAS loci are not known to be mechanistically associated with blood pressure regulation [32]. Therefore, further studies are needed to determine whether the genes implicated in GWAS demonstrate functional relations to blood pressure physiology and to uncover the molecular actions and interactions of genetic and environmental factors involved in blood pressure regulation [51]. In a study using a different approach, members of the Framingham Heart Study were screened for variants in genes causing rare diseases

characterized by blood pressure change. This study found rare variants in 3 genes *SLC12A3* (*NCCT*), *SLC12A1* (*NKCC2*), and *KCNJ1* (*ROMK*), which alter renal salt handling, were associated with blood pressure variation in the general population [62].

Diabetes

The rapidly increasing prevalence of type 2 diabetes (T2D) promises to pose a huge public health burden in SSA. It has been projected that the number of people in SSA with diabetes will rise from 7.2 million in the year 2000 to 18.7 million in 2030 representing an alarming 161% increase [63]. This projected increase in the prevalence of diabetes in SSA is much higher than the projected global average of 114% [63]. Figure 3 shows the prevalence of diabetes among adults in SSA.

T2D results from complex interplays between genetic and nongenetic factors including lifestyle, sociocultural, ecological, and demographic characteristics [64]. Genomic studies that employed the GWAS approach have identified more than 100 genetic loci associated with T2D in predominantly European-ancestry study subjects [31]. In continental Africans, the only published study to date that applied a genome-wide approach in T2D research is the Africa America Diabetes Mellitus (AADM) study that enrolled participants recruited from Ghana, Kenya, and Nigeria [65]. Multipoint linkage analysis in the AADM study revealed suggestive evidence of linkage on chromosomes 12, 19, and 20, the strongest evidence for linkage being on chromosome 20q13.3, a locus that had also been reported to be linked to T2D in non-Africans [30]. No T2D GWAS involving continental African populations has been published to date (Table 2). However, our group recently published the first large-scale transferability of T2D loci in continental Africans. In a replication study of 1,775 unrelated Africans genotyped on the Affymetrix Axiom PanAFR SNP array, 38% of 106 known T2D GWAS loci showed transferability, and the majority of the loci that showed replication were fine mapped [66]. An extensive review of published genome-wide and candidate-gene studies of T2D in SSA has been published elsewhere [28].

The gene transcription factor 7-like 2 (*TCF7L2*), particularly the intronic SNP rs7903146, has been one of the strongest and most widely reproduced associations with T2D across diverse ethnic groups [67]. This *TCF7L2* association was first reported by the deCODE group of investigators [68], followed by successful fine mapping and

Fig. 3. Prevalence of diabetes among adults in Sub-Saharan Africa in 2014. The data used to create this figure was obtained from the Global Health Observatory Data Repository – assessed August 2016. Crude prevalence estimates for male and female were used.

evidence for recent selection in West African populations (621 cases and 448 controls) enrolled in the AADM study [68, 69]. This study fine mapped the association between the *TCF7L2* rs7903146 T allele and T2D leveraging on the weaker linkage disequilibrium in African genomes. This study was among the earliest empirical demonstrations of trans-ethnic fine mapping of a disease locus [69]. The frequency of rs7901695 C allele ranges from 0.01 to 0.49 in global populations with African-ancestry populations having up to 40-fold higher frequency [70].

Currently ongoing studies are applying genome-wide approaches such as whole-genome genotyping and sequencing in larger samples of subjects recruited from Africa to enhance our understanding of the genetic basis of T2D unique to Africans and shared among diverse population groups. It is anticipated that large-scale genomic projects including those supported by the Human Heredity and Health in Africa (H3Africa) initiative [71] co-funded by the US National Institutes of Health and the UK Wellcome Trust will generate data that shed new light onto the genetic architecture of T2D. The H3Africa T2D

project is designed to study the burden, etiology, and spectrums of diabetes in Africa. The study is projected to enroll and examine 12,000 cases of T2D and 12,000 ethnically matched controls from 12 centers across 9 countries in SSA (www.h3africa.org).

Dyslipidemia

Dyslipidemia is characterized by a spectrum of qualitative lipid abnormalities reflecting perturbations in the structure, metabolism, and biological activities of both atherogenic lipoproteins and antiatherogenic HDL-C. These abnormalities include an elevation of lipoproteins containing apolipoprotein B, elevated triglycerides, increased levels of low-density lipoprotein (LDL), and low levels of HDL-C [72]. Data from recent studies showed that the prevalence of low HDL-C was ~13%, high LDL was ~23%, and high triglyceride was 7–21% in SSA [73–75] compared to the US where the prevalence of low HDL was 17% [76], high LDL was 32%, and high triglyceride

Table 2. Genes associated with cardiometabolic disease traits identified in Sub-Saharan Africa versus other populations

	African	African-American	European	Asian
Hypertension	ADH7, ALDH1A2	SLC12A9, IGSF5, ADH7, KLHL29, ALDH1A2, ZBTB38, LOC105377436, OPRM1, TIAM1, UBE3AP2, LOC105377369-CCDC34P1, IGSF5	AN06, ATP2B1, PLCE1, BAT2, ZFAT, TMEM133, BAT5, XRCC4, CACNB2, CBLN2, FLJ32810, EBF1, CDH13, SLC12A9, NPR3, GNAS, GPR39, EDN3, C5orf23, CHRM3, ZP4, RYR2, HFE, MACROD2, MSRA, MYO6, MOV10, ZNF831, RANBP3L, FES, FURIN, SLC39A8	UMOD, FSTL4, FGF5, NR, CACNA1D, MOV10, CASZ1, CYP21A2, MED13L, SLC4A7, GUCY1A3, SOX6, ATP2B1, ALDH2
Diabetes	INS-IGF2, TCF7L2, TCF2, FTO, SLC308A	SLC44A3, F3, RBM43, RND3, GALNTL4, CPA6, LOC729013, BARX2, TMEM45B, HLA-B, GALNT14, CAPN13, HECW1, INTS8, ASCL2, INS-IGF2, TCF7L2, TH, KCNQ1, ANXA2, HMG2A, TMEM175, SLC12A9, KLHL29, SLC30A1, RNA5SP110, RNA5SP111	ADAMTS9, ADCY5, ANK1, AP3S2, ARL15, DCD, BCL11A, C10orf35, C14orf70, C2CD4A, DGKB, C2CD4B, C6orf173, CDC123, CDC123, DUSP9, ETV1, FAF1, CAMK1D, CDKAL, CDKALI, FTO, GIPR, GLIS3, GRB14, HMG20A, CDKN2A, HHEX, IDE, HMG2A, HNF1A, HNF4A, CDKN2B, LGR5, TSPAN8, CENTD2, ARAP1, CHCHD9, HNF1B, TCF2, IGF2BP2, IL20RA, IRS1, JAZF1, KCNJ11, KCNK16, KCNQ1, KLF14, KLHDC5, LGR5, TP53INP1, TSPAN8, LPP, LYPLAL1, MC4R, NOTCH2, ADAM30, PLEKHA1, PPARG, MPHOSPH9, MTNR1B, PCBD2, PRC1, PROX1, PLEKHA1, PTEN, RNF6, RREB1, SSR1, SLC30A8, SPRY2, ST6GAL1, SYN2, PPARG, TCF19, POU5F1, TCF7L2, THADA, TLE1, TLE4, TMEM154, VEGFA, WFS1, ZBED3, ZFAND6, ZMIZ1, CRHR2, UBE2E2, TMEM18, TMEM75	ANK1, AP3S2, CMIP, GCC1, GPSM1, PTPRD, DUSP9, GLIS3, KCNK16, MAEA, C2CD4B, C2CD4A, CDKAL1, CDKN2A, CDKN2B, FITM2, R3HDM1, HNF4A, HMG20A, HNF1B, HNF4A, IGF2BP2, KCNQ1, ZFAND3, MGC21675, MIR129, LEP, NXN, PEPD, PALM2, PAX4, AKAP2, GCC1, PSMD6, SGCG, SACS, RHOU, WWOX, SLC16A13, SLC30A8, SRR, ST6GAL1, SRR, SYK, TCF7L2, UBE2E2, VPS26A, WISP1
Dyslipidemia			ABCA1, ABCG8, ANGPTL4, APOB, APOA1, XKR6, APOC3, APOA4, APOA5, APOC2, APOE, APOC4, APOC1, CELSR2, PSRC1, SORT1, CETP, GALNT2, FADS1, FADS2, FADS3, GCKR, HMGCR, HNF1A, HNF4A, LCAT, LDLR, LIPC, LIPG, LPL, MAFB, MVK, MMAB, MLXIPL, PCSK9, NCAN, CILP2, PBX4, PSRC1, CELSR2, PLTP, TRIB1, TTC39B, AMAC1L2	
Obesity			ADCY3, POMC, ADCY9, ADCY9, ARG1, TNNT3K, UBE2E3, WWOX, ZZZ3, TCF4, SLC8A1, TFAP2B, TMEM18, SCN1A, SDCCAG8, SEC16B, SH2B1, ASAH1, BC041448, BDNF, C5orf37, CADM2, CAMK1G, CCDC77, CMYA5, ETV5, FANCL, FAT1, MTNR1A, FARS2, FLJ39743, GPRC5B, HNF4G, HOXB5, HS6ST3, INHBB, KC6, KCNMA1, LEPR, LHFPL3, LINGO2, RABEP2, SH2B1, RPL27A, RPTOR, LOC144233, MAF, MAP2K5, MC4R, MRPS33P4, MSRA, TNKS, NCAM2, NEGR1, PRL, PRMT6, PTER, RGS6, RMST, NINJ1, NPC1, NRXN3, OLFM4, PACS1, PCDH9, OTUD1, KIAA1217, PITPNB, PRKCH	MDFIC, PROX1, FTO
CAD/CHD		CELSR2, PSRC1, SORT1, CRYGN, WDR86-AS1, LINC00333, LOC105360289, LOC101926941-RPS12P10	ABO, ADAMTS7, ANKS1A, CXCL12, FN, ANRIL, CDKN2A, CDKN2B, FHL5, FNDCl, C12orf43, HNF1A, GPC5, HHIPL1, ILR6, KIAA1462, LDLR, COL4A1, COL4A2, LIPA, LPA, LRFN2, HCG27, HLA-C, MIA3, MRAS, MRPS6, ZNF259, APOA1, APOC3, APOA4, APOA5, SNF8, GIP, UBE2Z, ATP5G1, WDR12, SLC22A3, LPAL2, LPA, VEGFA, ZC3HC1, RASD1, SMCR3, PEMT, SORT1, TCF21, PHACTR1, PSRC1, SH2B3, SMAD3, NT5C2, CNM2, CYP17A1, MTAP, PCSK9, MTHFD1L, PHACTR1, PPAP2B	CDKN2A, RPL6-PTPN11, TTC32, WDR35, GUCY1A3 ATP2B1, C12orf51, TCF21, CUX2, CDKN2B, ALDH2, MYL2, FLT1, ACAD10, PHACTR1
Stroke		ALDH1A2, GAPDHP71, C21orf81, AGBL1, TSG1, WDFY4, UBASH3B, CDCSL, CHD3, ELTD1, CLDN17, GATA3, FLRT2, TRNAK27, GLULP3, LIPC, HDAC9, HPS4, IL1RN, IL1F10, IL36RN, LIP1, LOC100507163, MSX2, NKX2-5, ABCC13, TGFB1, SPINK2, SUMO2P6, PTPRG, MICAL2, RNU6-36, MIR135A2, AQP9	AIM1, ALDH2, HDAC9, IMPA2, NR, FOXF2, FOXQ1, PITX2, SPSB4, ZFH3	
Data source: GWAS catalog – accessed February 2017.				

was 25% [77]. Blood lipid levels are influenced by multiple environmental and genetic factors. Heritability estimates for blood lipids are high, including ~40–60% for HDL-C, ~40–50% for LDL, and ~35–48% for triglycerides [78], suggesting that genetic factors play a significant role in determining the variation of blood lipid levels.

Most of our knowledge of lipoprotein genetics stems from monogenic familial disorders of lipoprotein metabolism with extreme phenotypes [79]. For example, familial hypercholesterolemia (FH), an inherited disorder of lipoprotein metabolism, which is characterized by highly elevated serum levels of LDL [80]. FH is the most common dominantly inherited disorder in humans, affecting 1 in about 250 people [81, 82]. Most people with the disease have mutations in the LDL receptor [83], apolipoprotein B [84], or *PCSK9* genes [85]. However, in most studies, despite next-generation sequencing, no mutation could be identified in up to 20% of patients with a clinical diagnosis of definite heterozygous FH [86]. In a small sample of FH patients in central and southern Tunisia, 2 novel mutations in the LDL gene were identified, the CYS127S and the D245N [87].

A combined analysis of the AADM cohort and other population datasets revealed that the relationship between HDL-C and kidney function varies by ancestry with observed inverse relationship in African ancestry populations (West Africans and African-Americans) and positive relationship in East Asians (Han Chinese) and European Americans [88]. The observed inverse relationship between HDL-C and kidney function in African ancestry populations was strongest in individuals with the nephropathy risk genotype of SNP rs73885319 in the *APOL1* gene. Higher HDL-C was significantly associated with worse kidney function in subjects with the risk genotype but not in those without this genotype. It is believed that the *APOL1* risk variant rose to high frequency in West African populations presumably to provide protection against a deadly form of African sleeping sickness [88, 89].

Loci associated with dyslipidemia have been identified in several populations. GWASs involving up to 20,000 individuals of European ancestry have identified over 30 genetic loci contributing to variation in serum and lipid concentrations [90–93]. Meta-analyses of GWASs among 100,000 individuals of European descent ascertained in the United States, Europe, and Australia, showed 95 significantly associated loci with lipid traits, which in aggregate, may explain 10–12% of the total variance [94]. In individuals of African descent, sequence variants in individual genes shown to be consistently related to blood

lipid phenotypes include *PCSK9* [95], C679X [96], and apolipoprotein E [97] with LDL; *LPL*, *CETP* [98], and apolipoprotein E [97] with HDL-C; and apolipoprotein A5 with triglycerides [99].

Obesity

Obesity is a major global health challenge. Worldwide, the number of overweight and obese individuals increased from 857 million in 1980 to 2.1 billion in 2013, with higher prevalence among women compared to men in developed and developing countries [100]. In Africa, there are marked variations in the rate of obesity across countries, with distinct regional patterns. The age-standardized prevalence of obesity ranged from 4.4% (4.2–4.6) in the Eastern to 11.7% (10.9–12.4) in the Southern regions for men; and from 8.8% (8.4–9.1) in the Eastern to 37.0% (35.9–38.1) in the Southern regions for women, in 2013; while the rates were higher than 25 and 45% for men and women, respectively, in some Northern African countries [100]. Increased economic growth and sedentary lifestyles may explain the regional variations of obesity in Africa. Furthermore, increased levels of physical inactivity and consumption of calorie-dense foods may explain the upward trend of obesity in SSA [101–107].

The association between variants in the fat mass and obesity-associated (*FTO*) gene and BMI is well-established in populations of European descent, and GWASs have identified several strongly correlated SNPs in intron 1 of *FTO* associated with increased BMI and increased risk of obesity, with subsequent replication in other studies [108, 109]. Although the *FTO* gene is the most replicated gene for obesity in humans, its association with obesity and BMI has not been consistently replicated in all populations [110–112] and the mechanistic basis of this association remains unclear. A recent study provided some evidence that the association of *FTO* with obesity does not involve the *FTO* gene but a repressor binding site that resides within an intron in the *FTO* gene. Among Africans, the *FTO*-rs17817449 was associated with higher BMI among black South Africans ($p = 0.022$) [113], but no association was observed among Gambians [111]. In another study, SNPs in the *FTO* gene previously reported to be associated with obesity in Europeans, including rs9939609, rs1121980, rs17817449, and rs7204609, were tested among populations of African ancestry [27]. The association with obesity was replicated for 2 SNPs, rs1121980 and rs7204609, at $p < 0.05$ in West Africans but not in African-Americans [27]. The *FTO* region harbors

the strongest genetic association with obesity, yet the mechanistic basis of this association remains elusive.

Several other polymorphisms have been found to be associated with obesity or BMI in some African populations but were not subsequently replicated. The leptin receptor (*LEPR*) gene rs1137101 was significantly associated with BMI or obesity risk in some Tunisian populations, but not among South Africans [113–115]. Likewise, although the *ENPP1*-rs1044498 was associated with obesity in Moroccans, no significant association was observed among South Africans [116]. However, the *RETN*-rs1862513 and rs3745367 have been found to be positively associated with obesity risk among several African populations [117, 118].

A recent systematic review on genomics of obesity in Africa, based mostly on studies which used the candidate gene approach reported that the majority of polymorphisms investigated by single studies in genes such as *ACE*, *ADIPOQ*, *ADRB2*, *AGRP*, *AR*, *CAPN10*, *CD36*, *C7orf31*, *DRD4*, *FTO*, *MC3R*, *MC4R*, *SGIP1*, and *LEP* were found to be associated with various measures of obesity (BMI, waist circumference, and percentage fat mass) in different ethnic groups [119]. Among these loci, *FTO*, *LEP*, *MC3R*, *MC4R*, and *SGIP1* were associated with lower measures of obesity indices. Some of the SNPs investigated in the same population group and located in one gene had opposite effects on obesity indices. Of the 17 genes reported to be significantly associated with obesity in Africa, only *FTO* and *MC4R* polymorphisms have been previously validated by GWASs that showed a directionally consistent association with obesity in non-African populations [119]. Further replication studies and large-scale genomic studies are needed to validate and ascertain the role of polymorphisms and the underlying genetic mechanisms of obesity in African populations.

Coronary Artery Disease/CHD

Coronary artery disease (CAD) is a heart disorder which results from interaction between multiple environmental and genetic factors. CHD, a result of CAD, was the leading cause of death globally among men and women in both 1990 and 2013 [120]. In 2013, CHD was responsible for nearly half of all deaths from cardiovascular diseases, causing as many deaths as chronic obstructive pulmonary disease, diabetes mellitus, cirrhosis, lung cancer, and liver cancer combined [120]. Although SSA experiences the world's lowest CHD death rates [121], the number of deaths due to CHD increased by 87% from 1990 to

2013 in SSA, likely due to aging and growth of the SSA population [122].

Several GWASs among individuals of European descent have reported a strong association between common variants on chromosome 9p21 and risk of CAD, and this association has been replicated in populations from North Africa [123–125]. Chromosome 9p21 locus is also associated with other cardiovascular disease phenotypes including abdominal aortic aneurysm and intracranial aneurysm [126]. A study of the haplotype diversity and allelic history of the 9p21.3 region among unrelated individuals from 51 populations of non-European origin (Human Genome Diversity Project) found that variants rs10116277 and rs2383207 located in the intron of cyclin-dependent kinase inhibitor 2B antisense RNA 1 (*CDKN2B-AS1/ANRIL*) gene were by far most common in populations from SSA [127].

A meta-analysis of 14 CAD GWASs, including thousands of cases and controls, validated the association of 10 previously reported loci and identified 13 new variants associated with heart disease [128]. Few candidate-gene studies have been conducted on CAD in North Africa. Results from recent studies show that there is an independent association between rs699 located in exon 2 of the angiotensinogen (*AGT*) gene and CAD among Tunisians [129] and Egyptians [130]. The *AGT* rs699 SNP is a well-characterized genetic polymorphism of the renin-angiotensin system (RAS) and is associated with known risk factors of heart disease [131, 132]. Other RAS polymorphisms associated with CAD in Africans include rs4762 in *AGT* gene, rs5186 in ADP-ribosyltransferase 1 (*ATR1*) gene and Glu298Asp polymorphism in exon 7 of the endothelial nitric oxide synthase 3 (*eNOS3*) gene [129, 130, 133]. It is possible that RAS polymorphism and hypertension play a role in CAD [134, 135].

Chronic kidney disease (CKD) is an independent risk factor for the development of CAD [136]. Recently, the apolipoprotein L1 (*APOL1*) gene was identified as a risk locus for CKD in African-Americans; these findings were confirmed in Nigerian Yoruba CKD patients [89, 137]. Identified *APOL1* genetic variants, G1 and G2, are both very frequent on African-derived chromosomes and strongly associated with FSGS and HIV-associated nephropathy [89, 138]. G1 and G2 alleles appear to be most frequent in West Africa, with the highest allele frequencies reported in Nigeria and Ghana [138–140]. It was hypothesized that the *APOL1* renal disease risk variants evolved in SSA thousands of years ago to confer protection against the trypanosome parasite that causes African sleeping sickness [89]. Furthermore, some studies have

shown an associations between *APOL1* genotype and cardiovascular disease, among African-Americans [141, 142]. While one study showed that *APOL1* nephropathy variants were associated with lower levels of subclinical atherosclerosis in African-Americans with T2D [142], another showed that *APOL1* genotype was associated with subclinical atherosclerosis and incident myocardial infarction, and concluded that *APOL1* trypanolytic variants may account for a substantial proportion of the excess risk of chronic disease in African-Americans [141]. Large-scale studies to examine the association between *APOL1* and CAD among Africans are warranted.

Stroke

Stroke is a focal neurological deficit resulting from disruption of cerebral blood supply. About 80% of strokes are ischemic, resulting from an obstruction of blood flow, whereas 15–20% are hemorrhagic, due to bleeding into the brain [143]. In 2010, the worldwide prevalence of stroke was 33 million, with 16.9 million people having a first stroke [144]. The majority of global stroke burden is in LMIC [145]. In these countries, 2.8 million individuals died of ischemic stroke and 3 million of hemorrhagic stroke; 39.4 million DALYs were lost because of ischemic stroke and 62.8 million because of hemorrhagic stroke in 2010 [145]. Data from Africa suggest that about 66% of strokes are ischemic while 34% are hemorrhagic stroke [146]; the number of deaths from stroke nearly doubled from 1990 to 2013, but overall age-adjusted stroke mortality rates decreased by 1% in SSA (increased by 9% for ischemic stroke and decreased by 10% for hemorrhagic stroke) [122].

Evidence from studies of family history suggests that genetic predisposition is important [26]. These studies have consistently found that a family history of stroke is more common in individuals with ischemic stroke compared with controls [147]. In the Framingham Heart Study, a documented parental ischemic stroke by the age of 65 years was associated with a 3-fold increase in ischemic stroke risk in offspring, even after adjustment for other known stroke risk factors [148]. Studies evaluating the familial risk of hemorrhagic stroke demonstrate that in first-degree relatives, a subject's odds of having a stroke increase as much as 2- to 6-fold [149]. Limited data from twin studies suggest stroke is more common in monozygotic compared with dizygotic twins [150].

Some monogenic disorders can cause stroke. Sickle cell disease is one of the most common severe monogen-

ic disorders worldwide [151]. A hereditary blood disorder, it is an established risk factor for stroke. The global distribution of this disease is indicative of 2 factors: selection for carriers through their survival advantage in malaria-endemic regions and subsequent migration [152]. Although the scarcity of diagnostic facilities means that precise data are not available; a recent estimate suggests that more than 230,000 affected children are born in this region every year (0.74% of the births in SSA), which is about 80% of the global total [153]. First-stroke incidence was reported to be 1.02 per 100 patient-years between the ages of 2 years and 5 years, and 11% of patients with sickle cell disease have had a stroke by the age of 20 years [154]. Mutations in the glucose-6-phosphate dehydrogenase (*G6PD*) gene and certain SNPs, including *ANXA2*, rs11853426, *TEK* rs489347, and *TGFBR3* rs284875 variants, have been associated with increased stroke risk in sickle cell disease [155]. Other monogenic disorders that can cause stroke include cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) [26], autosomal dominant retinal vasculopathy, and homocystinemia [143, 156].

Linkage studies for stroke were successfully conducted, with the identification of *STRK1* gene in the Icelandic population as phosphodiesterase 4D (*PDE4D*) [157]; however, this association could not be replicated in other European populations [158]. Nonetheless, the rs918592 SNP variant of *PDE4D* was found to be significantly associated with stroke in a small sample of young African-American women [159]. A further linkage study in Iceland found a 13q12 locus associated with both stroke and myocardial infarction. Within this region, a candidate gene, lipoxxygenase-activating protein (*ALOX5AP*), was proposed as the underlying gene [160].

Mutations in *eNOS3* were found to be associated with ischemic stroke risk in some, including African-Americans and French [161, 162], but not all populations [163, 164]. *IL6* SNP rs2069832 [165] and *CSN3* [166] were also significantly associated with ischemic stroke in African-Americans. Certain SNPs, including *ANXA2* rs11853426 *TEK* rs489347, and *TGFBR3* rs284875 variants, have been associated with increased stroke risk, in sickle cell disease [155].

Genes with significant polymorphisms related to hemorrhagic stroke include the *APOE* ϵ 2, *APOE* ϵ 4 methylenetetrahydrofolate reductase (*MTHFR*), *IL6*, tumor necrosis factor (TNF)- α , angiotensin-converting enzyme (ACE), factor VII, factor XIII, platelet activating factor, and β -tubulin [167–169].

Various GWASs have identified a few associated loci including a risk variant on 4q25, possibly on *PITX2*, and another variant associated with atrial fibrillation in the *ZFHX3* gene at 16q22 [170, 171]. A recent whole-exome sequencing study identified 2 modifier mutations *GOLGB1* (Y1212C) and *ENPP1* (K173Q) associated with protection from stroke in a cohort of children with sickle cell anemia [172]. Larger stroke GWASs are underway, including the NIH-funded Stroke Investigative Research and Education Network (SIREN) project, which proposed to explore genomic factors in stroke in 6,000 native West Africans (3,000 case-control pairs) in comparison with 1,000 African-Americans (80% of whom are of West African ancestral origin) and 12,000 Americans of European ancestry in the REasons for Geographic and Racial Differences in Stroke (REGARDS) study.

Future Directions

The global burden of cardiometabolic diseases is increasing at an alarming rate and is projected to surpass the burden of infectious diseases such as HIV/AIDS in developing countries. While lifestyle and environmental modifications are important to control various diseases, genetic factors, which are not easily translatable, play an important role in the risk of cardiometabolic disorders. The brunt of the cardiometabolic disease epidemic will have disproportionate public health and economic impact in SSA because the health-care infrastructure and policy framework is not adequately prepared to prevent disease occurrence, screen for early disease diagnosis, and clinically manage chronic diseases and associated comorbidities. Thus, the outcome of genomics studies on cardiometabolic disorders in SSA and lessons learned from other populations promise to help alleviate these concerns and facilitate implementation of precision medicine strategies.

Given the role of the complex interactions between genetic, lifestyle, sociocultural, and other environmental

factors in cardiometabolic diseases, genetic research in African populations is likely to shed novel insights into the pathogenesis of this group of disorders. The genetic diversity and reduced linkage disequilibrium structure present in African genomes will be advantageous to fine map disease loci identified in European and Asian ancestry populations and will aid discovery of novel genetic loci associated with cardiometabolic diseases. To drive these efforts forward, it will be important to expand recruitment of large population-based cohorts from diverse African populations; perform deep phenotyping of research subjects; link genomics research with health-care programs and epidemiological surveys; integrate multi-omics studies in tissues relevant to specific diseases; and develop new statistical genetics analysis approaches, continuously improve genotyping arrays and other genomic technologies to efficiently capture and utilize the diversity of African genomes.

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