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GENETICS (AP MORRIS, SECTION EDITOR)

# Genetic Basis of Obesity and Type 2 Diabetes in Africans: Impact on Precision Medicine

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## Abstract

**Purpose of Review** Recent advances in genomics provide opportunities for novel understanding of the biology of human traits with the goal of improving human health. Here, we review recent obesity and type 2 diabetes (T2D)–related genomic studies in African populations and discuss the implications of limited genomics studies on health disparity and precision medicine.

**Recent Findings** Genome-wide association studies in Africans have yielded genetic discovery that would otherwise not be possible; these include identification of novel loci associated with obesity (*SEMA-4D*, *PRKCA*, *WARS2*), metabolic syndrome (*CA-10*, *CTNNA3*), and T2D (*AGMO*, *ZRANB3*). *ZRANB3* was recently demonstrated to influence beta cell mass and insulin response. Despite these promising results, genomic studies in African populations are still limited and thus genomics tools and approaches such as polygenic risk scores and precision medicine are likely to have limited utility in Africans with the unacceptable possibility of exacerbating prevailing health disparities.

**Summary** African populations provide unique opportunities for increasing our understanding of the genetic basis of cardiometabolic disorders. We highlight the need for more coordinated and sustained efforts to increase the representation of Africans in genomic studies both as participants and scientists.

**Keywords** Type 2 diabetes · Obesity · Genome-wide association studies · Genetic risk score · Precision medicine · Africa

## Introduction

Obesity and type 2 diabetes (T2D) prevalence have been steadily increasing worldwide with the highest increase expected in Africa in the coming two decades [1]. Disturbingly, it is predicted that about 40 million Africans will be diagnosed with T2D by 2045, an increase of 156% [2]. Obesity is a major risk factor for T2D and the correlation between the two disorders explains the concomitant increase in prevalence of both disorders [3]. While both obesity and T2D are strongly influenced by lifestyle changes (e.g., diet, lack of physical activity, and urbanization), they also display strong genetic components with heritability of obesity ranging from 40 to 70% and about 60% for T2D [4, 5]. Several approaches, including genome-wide linkage and candidate genes studies, have been implemented to shed light on the genetic basis of these comorbid conditions [6–10]. However, most of the gains in understanding the genetics of obesity and T2D have come from the recent availability of more efficient genomic technologies especially genome-wide genotyping arrays for the conduct of genome-wide association studies (GWAS). These newer genomic technologies have not been evenly deployed across global populations raising the real possibility of exacerbating already unacceptable disparities in inequalities in genomic-driven health care strategies.

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To date, most GWAS for common complex traits such as T2D have been conducted in European ancestry populations with remarkable successes [11, 12]. The current limited engagement of other human ancestry populations in genomics has both social justice and scientific implications. From the social justices' perspective, the health and economic gains from genomic driven approaches are likely to disproportionately benefit those in high-income countries; as a scientific imperative, the lack of diversity in genomics hinders scientific discoveries and thus limits understanding of biology. For example, it is well documented that African-ancestry populations harbor greater genetic variation, more complex patterns of linkage disequilibrium (LD), and more haplotype diversity compared with other human populations. These unique genomic characteristics have been shown to facilitate fine-mapping of genetic loci identified in populations of European descent thus improving localization of putative causal variants in gene-trait mapping. A demonstration of this approach was the use of the low LD in West Africans to more efficiently localize the most likely causal variant for *TCF7L2* in the context of T2D that was originally discovered in Icelandic individuals [13]. This collaboration between our lab and that of deCODE genetics provided some of the earliest evidence for how diverse populations, such as those of West Africa, could facilitate fine-mapping of loci originally identified in relatively homogeneous populations (such as those of European ancestry) characterized by larger regions of strong LD [12, 13].

Although genomic studies that include African populations are increasing in numbers, these studies remain small in size compared with the studies conducted in other populations [12]; furthermore, most of the African samples included in genomics to date were for replication rather than for discovery. For example, over 400 risk loci have been associated with T2D in Europeans and Asians but only a few of these loci have been investigated in African populations to determine their transferability [14–16]. While at least 39% of T2D-associated loci showed transferability in Africans and other populations (i.e., same risk alleles and consistent direction of effect) [12, 14, 17–19], there is evidence of differentiation at these loci; this is especially true in sub-Saharan African populations [17] with the frequencies of 12 T2D-associated gene variants decreasing with migration out of Africa [20]. Although deserving further investigations, Africans have been reported to display the highest T2D genetic risk compared with other ancestral populations [19, 21]. Similar trends have been reported for obesity traits with GWAS for body mass index (BMI), waist-to-hip ratio (WHR), and other adiposity traits yielding more than 300 loci [4] to date. Notable among these are association signals located in the *FTO* locus, arguably the most replicated obesity locus across human populations though the most significant single-nucleotide polymorphisms (SNPs) vary across populations [22].

The current limited engagement of Africans in genomics studies, both as participants and scientists, has been recognized by the scientific community and efforts have been mounted to reverse this trend [11, 23]. An aspect of the growing recognition of the lack of diversity in genomics is the acknowledgment of the tremendous efforts and coordination needed from all stakeholders to close the enormous gap between developed and developing countries, especially those on the African continent. Significant clinical applications have been developed or are in development based mainly on the genetic discoveries in populations of European ancestry, thus unintentionally exacerbating disparities that could be referred to as "genomic driven-health disparities." An illustrative example is the recent emergence of genetic risk scores (GRS), which are estimates of the joint contribution of genetic factors to specific outcomes of an individual that take into account the reported risk alleles to predict disease risk [24–33]. Given that most reported risk alleles and their effect sizes are more representative of European ancestry populations, their predictive values will have to be tested in other populations. This is important because while European-discovered alleles will be common in European ancestry populations, they could be rare in other populations, especially in Africans. Moreover, shorter-range LD means that SNPs reported in European ancestry GWAS may not be a good tag for causal variants in African populations [34•]. Therefore, GRS tailored to individuals of African ancestry will be needed as more GWAS become increasingly available in these populations. While the issues related to GRS are relevant to all phenotypes, its implications are particularly profound for metabolic disorders and other non-communicable diseases that are outpacing the traditional communicable diseases previously known to be the most pressing health issues in Africa [1]. In this review, we provide comprehensive updates of the genomic studies related to obesity and T2D in Africa and discuss the implications of underrepresentation of African populations in genomic studies of metabolic disorders for precision medicine on the African continent.

## An Update on Genome-Wide Association Studies in Polygenic Obesity and Related-Traits in Africans

Several loci have been associated with obesity and related traits [4] with some replicating in African populations [35]. About 300 polymorphisms in approximatively 40 genes, previously identified in other populations, were tested in Africans using a candidate gene approach and included SNPs and indels in genes such as adiponectin, leptin and its receptor, calpain10, *MC3R*, *MC4R*, *FTO*, *SGIP1*, and *ACE* [35]. These genes encode proteins that appear to interact and are involved in inter-related functions including glucose and lipid metabolism (mainly represented by the red cluster), energy balance and body weight control (red and green clusters),

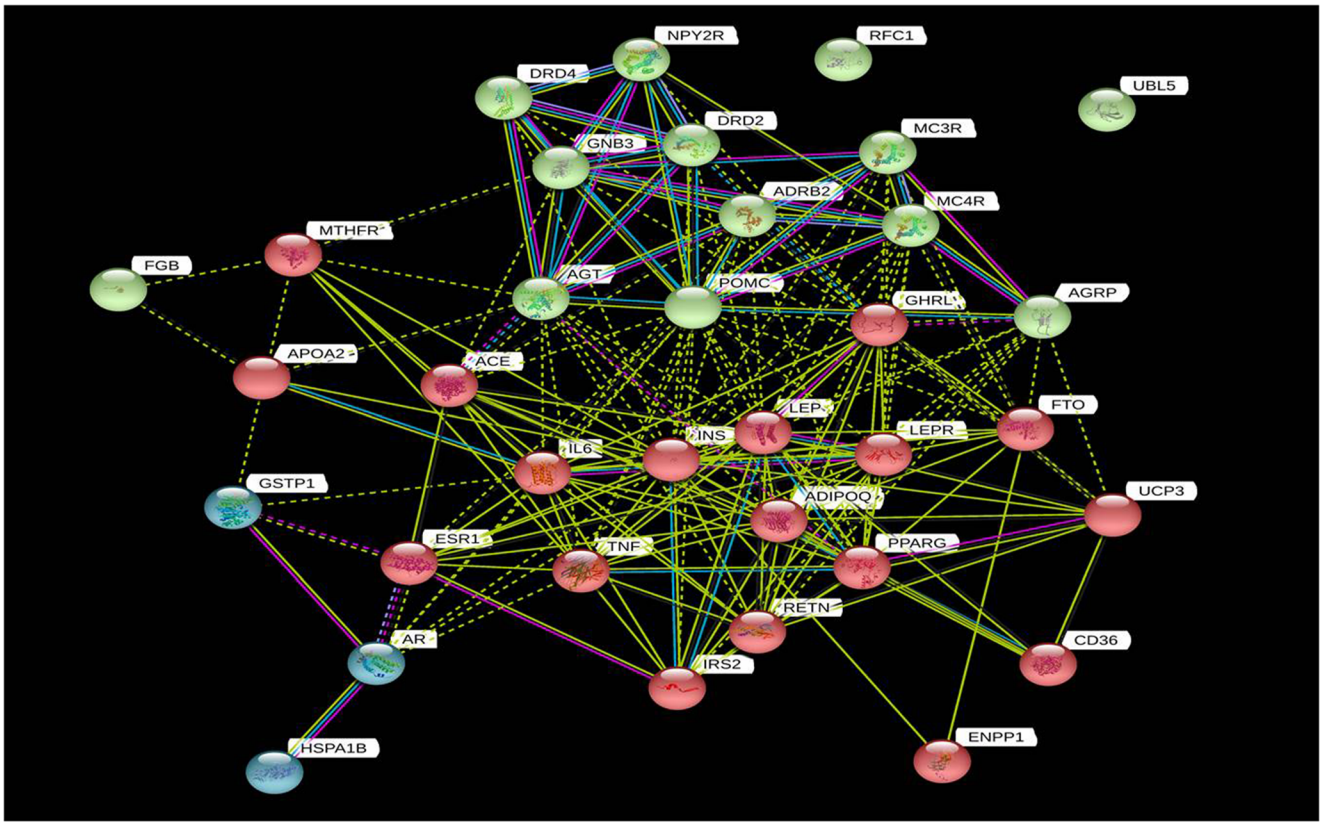


**Fig. 1** Network of proteins encoded by obesity-related genes tested in African populations using a candidate gene approach. *Circles* represent proteins; each color defines a cluster of related proteins (k-means clustering). *Lines* between proteins showed known interactions (experimentally determined or curated). Cluster 1 (*red*) consists of 18 proteins. Cluster 2 (*green*) consists of 13 proteins. Cluster 3 (*dark cyan*) consists of three proteins

and appetite control (green cluster) as shown by String cluster analysis [36] (Fig. 1, Supplemental Table 1).The identified loci explain less than 3% of the variance in BMI suggesting that there are more loci to be discovered. Yang Jian et al. showed that SNPs could account for up to 27% of BMI variance [37] based on studies in populations of European ancestry; these estimates may not however directly apply to African populations because they do not account for variants that may be specific to Africans as identified in recent GWAS for BMI and metabolic traits in African populations [38••, 39••].

## African-Specific Variants Associated with Obesity and Obesity-Related Traits

### Semaphorin-4D and BMI

The first GWAS for BMI in West Africans (WA) identified a genome-wide significant variant (rs80068415 [C], $p = 2.10 \times 10^{-8}$) located in an intronic region of semaphorin-4D (*SEMA-4D*). This variant, which is African-specific, was successfully replicated in an independent cohort of WA and in about 9000 African Americans (AA) (Table 1). Interestingly, carriers of the risk allele [C] were about 6 pounds heavier than homozygotes for the protective allele [T]. Additionally, serum soluble SEMA-4D (sSEMA-4D) was associated with an increased risk of obesity with an odds ratio of 4.22 (95% CI 3.05, 5.83). The SNP rs80068415 was also nominally associated with sSEMA-4D ($p = 5.37 \times 10^{-2}$). The biological mechanism underlying this association is complex and may be mediated through regulatory processes that modulate other obesity-related genes. Obesity is characterized by increased accumulation of T cells [42]. Notably, SEMA-4D plays a role in activation and differentiation of T cells as well as promotion of T-helper cells. This study underscores the need to conduct more genomic studies in populations other than those of European ancestry with the promise of generating new hypotheses to elucidate the pathophysiology of obesity.

## Protein Kinase C Alpha, Tryptophanyl tRNA Synthetase 2, Mitochondrial (*WARS2*), and Body Composition Measures

Body composition measures including fat mass (FM), percentage fat mass (PFM), lean mass (LM), and waist and hip circumferences are used in research settings to estimate the degree of obesity [43, 44]. Furthermore, waist circumference

**Table 1** African-specific and low-frequency variants associated with obesity, MetS, and T2D in GWAS conducted in continental Africa

| Phenotype/disease | Gene name[#] | Gene location | SNP/risk allele | Discovery populations | Risk allele frequency (RAF) in study | RAF in other populations[&] | | | Reference |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | AFR | EUR | EA/SA | |
| Obesity* | *SEMA-4 D* | 9q22.2 | rs80068415 [C] | West Africa (Nigeria, Ghana) | 0.008 | 0.007 | 0 | 0/0 | [38] |
| | *WARS2* | 1p12 | rs56750694 [T] | Black South Africans | 0.050 | 0.066 | 0 | 0/0 | [40] |
| | | 1p12 | rs17023092 [T] | Black South Africans | 0.070 | 0.095 | 0.006 | 0/0 | [40] |
| | *PRKCA* | 17q24.2 | rs115012414 [C] | Black South Africans | 0.040 | 0.067 | 0.001 | 0.005/0 | [40] |
| MetS | *CA-10* | 17q21.33-q22 | rs73989312 [A] | West Africa (Nigeria, Ghana) | 0.016 | 0.017 | 0 | 0/0 | [39] |
| | | 17q21.33-q22 | rs73989319 [C] | West Africa (Nigeria, Ghana) | 0.016 | 0.017 | 0 | 0/0 | [39] |
| | *CTNNA3* | 10q21.3 | rs77244975 [C] | Meta-analysis − West Africa (Nigeria, Ghana) and East Africans (Kenya) | 0.017 | 0.020 | 0 | 0/0 | [39] |
| | *MBNL1* | 3q25.1-q25.2 | rs146816516 [G] | West Africa (Nigeria, Ghana) and East Africa (Kenya) | 0.040 | 0.030 | 0 | 0/0 | [39] |
| T2D | *AGMO* | 7p21.2 | rs73284431 [G] | Meta-analysis South Africans (Zulu) + West Africa (Nigeria, Ghana) and East Africans (Kenya) | 0.093 | 0.110 | 0 | 0/0 | [18] |
| | *ZRANB3* | 2q21.3 | chr2:136064024 [T] | West Africa (Nigeria, Ghana) and East Africa (Kenya) | 0.035 | NA | NA | NA | [41] |
| | | 2q21.3 | rs1465146591 [A] | West Africa (Nigeria, Ghana) and East Africa (Kenya) | 0.068 | NA | NA | NA | [41] |

*AFR*, African/African American population; *EUR*, Europeans, populations of 1000 genome project; *EA*, East Asian population dataset assembled by the Exome Aggregation Consortium (ExAC); *SA*, South Asian population dataset assembled by the Exome Aggregation Consortium (ExAC)

[#] The closest gene or within gene

*Anthropometric measurements: BMI, percent fat mass (PFM), hip circumference (HP), waist-to-hip ratio (WHR)

[&] Other populations include AFR, EUR, and SA

(WC) and WHR are markers of abdominal obesity that has been demonstrated to be the most pathogenic form of obesity [45–48]. The genetic basis of these body composition markers has been well documented in European ancestry populations with limited data in African populations [5, 48]. Efforts to use the candidate gene approach [49–55] to replicate variants discovered in non-African populations have achieved limited success. In contrast, a recent GWAS of Black South Africans (BSA) was more successful in replicating loci identified in non-African populations [40]. The study, which included about 1900 adolescents and female adults, reported several notable findings. First, population structure analysis showed that these South Africans formed distinct clusters from WA and East Africans (EA), but formed a tight cluster with other south eastern Bantu speakers. These observations underscored the genetic diversity that exists within the African continent and the need to conduct genomic studies in as many African populations as possible. Second, the study replicated several loci previously associated with measures of body-shape in Europeans including *SEC16B*, *FTO*, and *NEGR1* [56–63]. At the *BRINP2/SEC16B* locus (rs6664268 [C]), minor allele frequency ((MAF) = 22%) was associated with both FM and PFM and is in the same LD block as previously reported SNPs (rs543874 and rs10913469) for anthropometric measures in other African populations [56, 58, 64–67] highlighting the trans-continental effect of these variants. Third, the study also identified novel variants with suggestive associations including protein kinase C alpha (*PRKCA*) (rs115012414 [C], MAF = 4%) associated with PFM, BMI, and hip circumference (HC), an intronic variant (rs56750694 [T], MAF = 5%) in *WARS2* associated with HC, and a variant in 3′UTR region of *WARS2* (rs17023092 [T], MAF = 7%, $r^2$ = 0.65 with rs56750964) associated with WHR. Other SNPs in *PRKCA* have been linked to food addiction [68] and height [69] in Europeans but the genomic regions encompassing the signals identified in BSA and Europeans appear to be independent given low LD between them [70]. Similarly, other SNPs in *WARS2*, distinct from the two identified in BSA, were associated with WHR adjusted for BMI or for BMI and smoking behavior or BMI and physical activity in other populations [43, 64, 67, 71]. Interestingly, a mutation in *WARS2* resulting in L53F WARS2 protein variant in animal models of spontaneous hypertension revealed a key role of the gene in brown adipose tissue function with implications for lipid and glucose metabolism and predisposes to visceral adiposity [72].

## Carbonic Anhydrase-Related Protein 10, Catenin Alpha-3, and Metabolic Syndrome

Metabolic syndrome (MetS) is a clustering of clinical factors including obesity, insulin resistance (IR), and dyslipidemia [73]. Obesity and IR are highly correlated with MetS and usually precede the development of T2D in many individuals. The risk of developing T2D in individuals with MetS is 5-fold higher than in individuals without MetS [39••, 73]. MetS heritability varies across populations and can be as low as 13% in Dutch and as high as 48% in individuals from the Middle East [74, 75]. Previously reported trans-ethnic differences in the prevalence of MetS suggest that the syndrome may have genetic predisposition or susceptibility.

Our group performed the first GWAS of MetS in about 4800 Africans. In this study, MetS was defined based on the National Cholesterol Education Program (NCEP) improved threshold as follows: MetS cases were individuals who have at least three or more of the five component traits—i.e., WC ≥ 102 cm for men or ≥ 88 cm for women; fasting plasma glucose ≥ 100 mg/dL; plasma triglyceride levels ≥ 150 mg/dL; high-density lipoprotein (HDL) cholesterol < 40 mg/dL for men or < 50 mg/dL for women; systolic blood pressure (BP) ≥ 130 mmHg or diastolic BP ≥ 85 mmHg [39••]. This study discovered two African-ancestry-specific variants that were significantly associated with MetS; SNP rs73989312 near *CA10* ($p = 3.86 \times 10^{-8}$, OR = 6.80) and SNP rs77244975 in catenin alpha-3 (*CTNNA3*) ($p = 1.63 \times 10^{-8}$, OR = 6.67). This study also identified two variants that were not African-specific (rs76822696) near *RALYL* associated with MetS risk ($p = 7.37 \times 10^{-9}$, OR = 1.59) and rs7964157 near *KSR2* ($p = 4.52 \times 10^{-8}$, OR = 1.89). The *KSR2* locus showed pleiotropic associations with triglyceride and blood pressure and, importantly, rare *KSR2* mutations have been shown to influence early onset obesity and IR [39••]. The use of a continuous MetS risk scores yielded an additional significant association signal that was African-specific near *MBNL1* (rs146816516, MAF ≈ 4%). The *MBNL1* variant also exhibited pleiotropic proprieties as it was associated with more than 2 cardiometabolic traits. These African-specific variants are near genes that have credible biological roles in MetS. The carbonic anhydrase-related protein 10 (*CA-10*), *CTNNA3*, and *MBNL1* genes have been implicated in brain function, and cardiac muscle contraction. This African GWAS also replicated the *LPL* and *CETP* loci previously linked with MetS in Europeans. In all, these results provide new insights into the pathogenesis of MetS in Africans while demonstrating the advantages of conducting trans-ethnic disease gene mapping studies.

## Type 2 Diabetes–Associated Variants in African Populations

In addition to a previously reported genome-wide linkage study in Nigerians and Ghanaians, which identified significant linkage peaks on 20q13.3 and 12q24 [9], multiple attempts have been made to replicate GWAS loci discovered mainly in Europeans [15, 76, 77]. *TCF7L2 and CDKAL1* are among the most replicated loci in African populations with limited

contribution to explained T2D variance [14–16, 49, 78–82]. Although the *TCF7L2* association was discovered in an Icelandic cohort, the locus was fine-mapped in West Africans [13], establishing for the first time the usefulness of the low LD present in African populations to refine GWAS loci identified in more homogeneous ancestral group such the Europeans and Asians. Previous reviews by us and others have described genetic findings related to T2D in Africans [6, 12, 50], and here we update these reviews by describing GWAS findings in African populations since their publications.

## A Novel Variant in Alkylglycerol Monooxygenase Is Associated with T2D

A recent T2D meta-analysis published by our group identified a novel association with a variant in alkylglycerol monooxygenase (*AGMO*). This collaboration included about 4350 sub-Saharan Africans enrolled from two South African studies (the Zulu Durban Diabetes Case-Control study (DCC) and the Durban Diabetes study (DDS)) and participants enrolled in the AADM study with study sites in Ghana, Nigeria, and Kenya. In addition to replicating the known *TCF7L2* variant (rs7903146 [T], $p = 5.30 \times 10^{-13}$, OR = 1.32) as the most significant T2D association, the study identified an independent African-specific *TCF7L2* variant, rs17746147 ($r^2 =$ 0.009 with lead *TCF7L2* variant rs7903146). A novel variant near the *AGMO* locus (rs73284431 [G], ($p = 5.20 \times 10^{-9}$, MAF = 9.5%, OR = 1.48) was associated with T2D in this meta-analysis [70]; this variant is monomorphic in non-African-ancestry populations. The genomic region encompassing *AGMO* has been associated with other metabolic traits (blood glucose levels, rs1558318): obesity-related traits (rs12531027 [G]) and diabetic kidney disease (rs12531478 [A]) [83–85]. The biological function of *AGMO* is not well defined but it seems to be involved in fatty acid, triacylglycerol, and ketone body metabolism and it is highly expressed in the liver (www.ncbi.nlm.nih.gov/gene/392636).

## ZRANB3, a Modulator of Beta-Cell Mass and Insulin Response

Our group conducted a discovery GWAS in ~5000 African samples as part of the AADM study with replication in the South African Zulu T2D case-control studies [41••]. Of the three identified significant loci, two were known diabetes risk variants: *TCF7L2* (rs7903146 [T], MAF = 33.1%, $p = 7.29 \times 10^{-13}$) and *HMGA2* (rs138066904, deletion frequency = 9.6%, $p = 2.5 \times 10^{-9}$). The third signal, which included two intronic variants in *ZRANB3*—Zinc 94 Finger RANBP2-Type Containing 3 (chr2:136064024 [T], MAF = 3.4%, $p = 2.83 \times 10^{-9}$; rs1465146591 [A], MAF = 6.9%, $p = 5.80 \times 10^{-9}$), has not been previously associated with T2D in any human population. These *ZRANB3* variants are in moderate LD ($r^2 = 0.66$) and seem to be only polymorphic in African populations (Table 1). Given the novelty of this locus in the context of T2D and a successful replication of the signal in an independent African cohort, we conducted functional studies in model organism (Zebrafish) to determine the potential role of *ZRANB3* in the pathophysiology of T2D.

Using Zebrafish as a model, and focusing on the pancreas as a tissue relevant to T2D, we showed that a *ZRANB3* ortholog was expressed by beta cells (pancreatic islets), and the disruption of *ZRANB3* by CRISPR/CAS at exon 4 or disruption of splicing of the endogenous *ZRANB3* transcript at the same exon 4 resulted in about 30% reduction in beta cells of the mutants compared with the wild-type. The observed reduction was due to apoptosis as shown by increased expression of Caspase-3 in Zebrafish larvae beta-cells. siRNA suppression of *ZRANB3* in mammalian beta-cell line (MIN6 beta-cells) showed decreased insulin secretion in response to high glucose load, suggesting a role for *ZRANB3* in beta-cell response to hyperglycemic conditions.

Other variants upstream of and in *ZRANB3* have been reported to be associated with anthropometric markers (BMI with rs7570971 and rs1988235 and HC with rs1561277) [57, 64], suggesting a pleiotropic effect of this locus in metabolic disorders.

## Genetic Risk Score in Metabolic Disorders and Its Utility in Precision Medicine in the African Context

The paucity of GWAS and other genomic studies in diverse populations directly affects the downstream applications of genetic/genomic discoveries in populations that may be disproportionately more burdened by cardiometabolic diseases. The underrepresentation of African-ancestry populations in genomics limits the extent to which they can benefit from genomic discoveries including, but not limited to, risk prediction in the context of precision medicine.

Genome-wide studies have identified variants associated with metabolic disorders including obesity and T2D [86]. To take advantage of these findings in the context of an individual, GRS have been designed to capture the cumulative predictive ability of all genetic variation at known loci on the trait of interest [24, 86]. As indicated above, notable genomic discoveries have largely occurred in individuals of European ancestry, and the applicability of a GRS constructed from these results in non-European populations, especially in Africans, is limited [50]. Given that GRS are calculated by including summary information of multiple risk alleles across the genome, it is important that these alleles are well defined in all populations for the prediction to be accurate and clinically useful across the globe.

In addition to the problem of lack of diversity, discovered genetic variants only explain a modest fraction of the variation in complex phenotypes including metabolic disorders and therefore have a partial predictive power for disease occurrence [87].

It has been estimated that 39% of T2D loci are transferable in populations of African descent, especially West Africans [12], and about 25% of previously identified BMI-associated lead SNPs are transferable in trans-ethnic analyses that included individuals of African descent [88]. Although there is evidence of transferability of these loci across populations, it is widely reported that the frequency of the risk allele and the effect size can differ across populations [14, 18••]. This implies that the predictive value of GRS is likely to be dependent on the variant discovery population. Additionally, as shown throughout this review, several variants are African-specific and have not been available in the literature, and therefore have not been accounted for in GRS estimation. These "missing" variants again underscore the sub-optimal predictive utility of GRS derived from currently available genomic data in African-ancestry populations. For example, a South African study that evaluated the cumulative predictive utility of 66 variants associated with T2D in European and Asian populations showed that only the GRS based on a subset of the variants that were replicated in South Africans had predictive power in that population [89]. Similarly, a T2D trans-ethnic GRS derived from 102 loci showed that only variants directly replicated in the African cohort had predictive power [18••]. These findings show that while there is a shared genetic contribution to T2D at established loci across populations, the predictive utility of the GRS derived from such loci is likely to be more accurate and clinically useful for African-ancestry populations if those associations of African ancestry are taken into account in the construction of the GRS. This concern was clearly expressed by Martin et al. when they showed that GRS computed for T2D across populations differed depending on whether the summary statistics used in the construction of GRS were derived from European ancestry or diverse cohorts. The biases inherent to current estimations of GRS may impact health outcomes in diverse populations if genomic tools are made part of routine health assessment [34•, 90•].

GRS have also been developed for obesity and obesity-related traits to identify individuals at high risk of obesity [91–95]. GRS estimated from the most comprehensive genetic study of obesity to date displayed considerable discrimination accuracy between obesity categories, predicted obesity trajectories, and were associated with differences in cardiometabolic diseases as well as overall mortality in older individuals. While the GRS derived from this study appears to outperform a previously constructed GRS, its extension, generalization, or application in diverse populations is likely to be limited because the genotyping array used was based on variants discovered mostly in Europeans and the population used to derive and validate its predictability was also mainly of European ancestry [96, 97].

Given that the definition of precision medicine can vary widely, we highlight the definition used by the precision medicine initiative, expressed as "an emerging approach for disease treatment and prevention that considers individual variability in genes, environment, and lifestyle for each person" [98]. The growing implementation of precision medicine in developed countries has been driven by the combined successes of biomedical research, data analytics, and health infrastructures [99]. While we acknowledge that, in developing countries, most of the pillars of precision medicine are still in their infancy, it is important to point out potential issues that can hinder its application in populations underrepresented in research. Many precision medicine components can be discussed in the African context, but in this review, we will only address the genomic component.

Genomics is an important part of precision medicine and risk prediction, as shown in studies conducted for many diseases including cancers and cardiovascular disease [100, 101]. As discussed previously in this review, the variants being used to establish GRS were derived from populations of European descent, which raised the question of their accuracy, applicability, and usefulness in other populations. Although GRS could be used to improve health outcomes, they may well have the opposite effect in underrepresented populations. GRS prediction accuracy for different traits varies widely across populations [34•]. Therefore, specific and thoughtful steps must be taken to avoid the ineffective use of ancestrally mismatched GRS in diverse populations: (1) increase and prioritize the inclusion of diverse populations in genomic studies; (2) develop population-specific GRS; and (3) test derived GRS for accuracy in populations other than the discovery populations. Failure to strategically evaluate GRS before their implementation in clinical settings serving diverse populations will not only be detrimental to populations that are already deeply affected by health disparity but also delay the reality of precision medicine in these populations.

## Conclusion

Genomics of obesity and T2D in Africans has evolved from linkage, candidate gene, and replication studies to discovery GWAS in small to moderately sized samples. These studies have led to the discovery of novel loci, some of which are African-specific, and facilitated fine-mapping of signals initially discovered in European populations, thereby contributing to our understanding of the pathophysiology of cardiometabolic disorders. For example, our recent discovery of the T2D *ZRANB3* locus in West and East Africans provides new insights into beta-cell mass, maintenance, and insulin response. While we acknowledge recent efforts to address the

limited representation of Africans in genomic science (e.g., the H3Africa initiative and the Trans-Omics for Precision Medicine (TOPMed) program), the balance is still tilted in favor of European-descent populations, which constitute more than 70% of all GWAS. Given the highlighted discoveries in this review in Africans, there is a pressing scientific imperative and social justice need to increase genomic studies in diverse populations. We emphasize that failure to rapidly include diverse populations in genomics is a missed opportunity for scientific discoveries with strong consequences for the equitable implementation of precision medicine in all human populations, thus intensifying the real possibility of genomic exacerbation of health disparity.

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## Compliance with Ethical Standards

**Conflict of Interest** Ayo P. Doumatey, Kenneth Ekoru, Adebowale Adeyemo, and Charles N. Rotimi declare no conflict of interest.

**Human Rights and Informed Consent** All human research was conducted according to the Declaration of Helsinki. The study protocol (AADM including WA and EA) was approved by the institutional ethics review board of each participating institution. Written informed consent was obtained from each participant prior to enrollment.

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- • Of importance
- •• Of major importance

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