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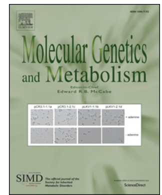

# Genome-wide association study identifies African-ancestry specific variants for metabolic syndrome

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ABSTRACT

The metabolic syndrome (MetS) is a constellation of metabolic disorders that increase the risk of developing several diseases including type 2 diabetes and cardiovascular diseases. Although genome-wide association studies (GWAS) have successfully identified variants associated with individual traits comprising MetS, the genetic basis and pathophysiological mechanisms underlying the clustering of these traits remain unclear. We conducted GWAS of MetS in 1427 Africans from Ghana and Nigeria followed by replication testing and meta-analysis in another continental African sample from Kenya. Further replication testing was performed in an African American sample from the Atherosclerosis Risk in Communities (ARIC) study. We found two African-ancestry specific variants that were significantly associated with MetS: SNP rs73989312[A] near *CA10* that conferred increased risk ($P = 3.86 \times 10^{-8}$, OR = 6.80) and SNP rs77244975[C] in *CTNNA3* that conferred protection against MetS ($P = 1.63 \times 10^{-8}$, OR = 0.15). Given the exclusive expression of *CA10* in the brain, our *CA10* finding strengthens previously reported link between brain function and MetS. We also identified two variants that are not African specific: rs76822696[A] near *RALYL* associated with increased MetS risk ($P = 7.37 \times 10^{-9}$, OR = 1.59) and rs7964157[T] near *KSR2* associated with reduced MetS risk ($P = 4.52 \times 10^{-8}$, $P_{meta} = 7.82 \times 10^{-9}$, OR = 0.53). The *KSR2* locus displayed pleiotropic associations with triglyceride and measures of blood pressure. Rare *KSR2* mutations have been reported to be associated with early onset obesity and insulin resistance. Finally, we replicated the *LPL* and *CETP* loci previously found to be associated with MetS in Europeans. These findings provide novel insights into the genetics of MetS in Africans and demonstrate the utility of conducting trans-ethnic disease gene mapping studies for testing the cosmopolitan significance of GWAS signals of cardio-metabolic traits.

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## 1. Introduction

The metabolic syndrome (MetS) manifests as a clustering of risk factors including abdominal obesity, atherogenic dyslipidemia, elevated blood pressure, insulin resistance, and prothrombotic and proinflammatory states [1,2]. Individuals with MetS have at least a five-fold increased risk of developing type 2 diabetes (T2D), a twofold increased risk of cardiovascular diseases [3], and increased susceptibility to several other disorders including fatty liver disease [4], sleep apnea [5], and some forms of cancer [6].

Recent studies suggest that complex networks of metabolic pathways modulated by interacting genetic and environmental factors underlie MetS [7,8]. Early evidence for the potential contribution of genetics to MetS was provided in a seminal study of twin pairs with 31.6% of monozygotic twin pairs compared to 6.3% of dizygotic pairs displaying concordance for clustering of three MetS components (hypertension, diabetes, and obesity) [9]. Heritability estimates for MetS vary, with estimates as low as 13% in the Dutch [10], 24% in Caribbean-Hispanic families [10,11], and as high as 48% in Omani

*Abbreviations:* cMetS, continuous metabolic syndrome score; GWAS, genome-wide association study; MetS, the metabolic syndrome as defined by the National Cholesterol Education Program; NCEP, the National Cholesterol Education Program; T2D, type 2 diabetes.

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families [12]. Earlier genome-wide linkage studies reported links between MetS and several chromosomal regions including 1p34.1, 10p11.2 and 19q13.4 [13], 1q21–q25 [14], and 1q23–q31 [15]. Candidate gene and whole exome sequencing studies have also identified mutations in patients with rare forms of MetS [16,17]. Meta-analyses of genome-wide association studies (GWAS) in Europeans and Asians have reported associations between MetS and variants in or near several loci including *ZPR1*, *BUD13*, *APOA5*, *LPL*, and *CETP* genes [18–20].

In contrast to the growing success in the identification of variants associated with the individual components of MetS, little progress has been made in the identification of variants underlying the syndromic clustering of the component traits of MetS and variants with pleiotropic effect that may shed light on dysregulated pathways in MetS [21,22]. Furthermore, the prevalence of MetS shows ethnic disparity in individuals of African descent. For example, analysis of the US National Health and Nutrition Survey (NHANES) serial data from the 1999–2000 and 2009–2010 surveys revealed modest decline in prevalence of MetS in Caucasians (25.6% to 21.8%) but a slight increase in African-Americans (22.0% to 22.7%) [23,24]. Paradoxically, the high prevalence of hypertension and diabetes in African-Americans contrasts with the observed low prevalence of high triglyceride levels [25]. Low prevalence of high triglyceride levels is also observed in west Africans, the ancestral populations of African Americans despite dietary and other differences between the two groups. These observed ethnic disparities in the burden of MetS [25] and other cardiometabolic traits [26] persists even after adjustment for modifiable risk factors, implying the role of background genetic predisposition.

In this study, we performed a GWAS of MetS in continental Africans enrolled from Ghana and Nigeria (AF1), and replication testing and meta-analysis with another continental African sample from Kenya (AF2) using ~15 million directly genotyped and imputed single nucleotide polymorphisms (SNPs). Further replication was tested in an African American sample from the Atherosclerosis Risk in Communities (ARIC) study. We also performed a GWAS of MetS in a subset of the samples in the tails of the continuous metabolic syndrome risk scores (cMetS) derived from the sum of standardized residuals of MetS component traits.

## 2. Materials and methods

### 2.1. Study samples

Individuals included in this study were participants enrolled in the Africa America Diabetes Mellitus (AADM) study with centers in Ghana and Nigeria (AF1) and Kenya (AF2) [27]. The AADM study has been ongoing for over a decade, and most of participants included in the present analysis were recruited in the year 2008. The study populations, data collection procedures, and ethical processes have been described in detail elsewhere [27,28].

For developing continuous metabolic syndrome scores and testing their predictive accuracy, we analyzed all 4820 individuals in the cohorts with non-missing phenotype values (4023 AF1 and 797 AF2). The discovery genome-wide association analysis was done in 1427 AF1. Independent replication of genome-wide significant loci was tested in 174 AF2 and 2475 African Americans enrolled in the ARIC study.

### 2.2. MetS phenotypes

Based on the definition of the National Cholesterol Education Program (NCEP) improved threshold, an individual was considered to have MetS if they have the following measures for three or more of the five component traits [1]: waist circumference ≥102 cm for men or ≥88 cm for women; fasting plasma glucose ≥100 mg/dL; plasma triglyceride levels ≥150 mg/dL; HDL cholesterol <40 mg/dL for men or <50 mg/dL for women; systolic BP ≥ 130 mm Hg or diastolic BP ≥ 85 mm Hg. In our analysis, cases were individuals with MetS and controls were individuals without MetS. We also developed a continuous metabolic syndrome risk scores (cMetS). Previous studies used different approaches including Z-scores, principal components, and percentile rankings to derive cMetS; the scores obtained by using these methods displayed strong correlation with one another [29]. We developed cMetS using the sum of the standardized scores from the components of MetS. Prior to deriving cMetS, normality of each trait was assessed using descriptive statistics and distribution plots (histograms and scatter plots). Plasma glucose and triglyceride values were $\log_{10}$-transformed because their distributions did not conform to normality. Next, standardized residuals were obtained by regressing each trait on age, sex, and broad ethnicity. The sign of the standardized residuals for HDL was reversed so that higher values indicate greater risk of metabolic syndrome. Finally, all standardized residuals of MetS component traits were summed to form cMetS. The higher the cMetS, the higher the tendency for the components to cluster indicating a higher MetS risk. To evaluate the accuracy of cMetS, we developed another continuous metabolic syndrome score based on principal components analysis of MetS component traits. Previous studies have shown that the power of detecting pleiotropic effects of genetic variants on correlated traits can be enhanced by reducing the dimension of the original traits into a single trait using principal components analysis and subsequent analysis of the top principal component in place of the original traits [30,31]. We used the loadings of the first principal component (PC1) that explain most of the total trait variance as PC-based continuous metabolic syndrome score (pc1MetS).

### 2.3. Genotyping, quality control, and imputation

The discovery GWAS was done using 1637 unrelated AF1 in the AADM study genotyped on the Affymetrix Axiom® PANAFR SNP array. The array was chosen because it offers ≥90% genetic coverage of variants with minor allele frequency (MAF) > 2% of the Yoruba (West African) genome and >85% coverage of the Luhya and Maasai (East African) genome. DNA sample preparation and quality control were done in our laboratory at the National Institutes of Health (NIH). We excluded 210 samples (one duplicated, three sex discordant, and 206 with one or more missing MetS component trait values), leaving 1427 AF1 for the discovery GWAS. Replication of top signals and meta-analysis were done using 185 unrelated AF2 genotyped on the Affymetrix Axiom® PANAFR SNP array. We excluded 11 samples (10 sex discordant, and one with one or more missing MetS component trait values), leaving 174 AF2 for independent replication and meta-analysis. Additional replication was done using 2612 African Americans in the ARIC study with ~24 million imputed SNP dosage data accessed through the Database of Genotypes and Phenotypes. We excluded 137 samples with one or more missing MetS component trait values, leaving 2475 ARIC study individuals for replication.

Of the 2,217,748 SNPs in the raw genotype data of the AADM cohort, we excluded 46,562 SNPs that had a minor allele frequency (MAF) of <1%, 22,509 that were missing in more than 10% of individuals, 10,282 that had a Hardy-Weinberg $p$-value $<1 \times 10^{-6}$, and 61,087 non-autosomal SNPs. The remaining 2,077,552 SNPs that passed quality filers were used as the basis for imputation. Imputation was performed using the 1000 Genomes Consortium phase 1, version 3 cosmopolitan reference using the programs *MaCH* [32]/*MaCH-ADMIX* [33]. The resulting imputed dosage data were filtered for imputed allelic dosage frequency < 0.01 and $r^2 < 0.3$, yielding ~15 million SNPs for analysis.

We generated principal components (PCs) from multi-dimensional scaling analysis of a pruned set of uncorrelated genome-wide SNPs (i.e., $r^2$ threshold of 0.2, and a sliding window of 50 SNPs by skipping 5 SNPs between consecutive windows) as implemented in the program *PLINK*. A plot of the first three PCs is shown in Fig. S1. To minimize the effect of population structure in the GWAS, all analyses were adjusted for the first three PCs in AF1 and AF2 and the first two PCs in AA. Quantile-quantile plot of the distribution of the test statistic was

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