135

Exome-wide study identifies loci displaying pleiotropic associations with multiple cardiometabolic traits in continental Africans.

F. Tekola-Ayele[1], A. Adeyemo[1], A.R. Bentley[1], A.P. Doumatey[1], J. Zhou[1], G. Chen[1], D. Shriner[1], C. Adebamowo[2], J. Achaempong[3], J. Oli[4], O. Fasanmade[5], T. Johnson[5], A. Amoah[6], K. Agyenim-Boateng[3], B.A. Eghan Jr.[3], D. Ngare[7], C.N. Rotimi[1]. 1) Center for Research on Genomics and Global Health, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD; 2) School of Medicine, University of Maryland, MD; 3) University of Science and Technology, Kumasi, Ghana; 4) University of Nigeria Teaching Hospital, Enugu, Nigeria; 5) University of Lagos, Lagos, Nigeria; 6) University of Ghana Medical School, Accra, Ghana; 7) Moi University, Eldoret, Kenya.

Clustering of cardiometabolic abnormalities displays high heritability. However, the underlying physiological dysregulations behind these shared abnormalities remain unresolved. Here we aim to identify genetic loci with pleiotropic effects on cardiometabolic traits and inflammation markers in the largest sample (n=4,218) of continental Africans genotyped to-date on the Illumina HumanExome BeadChip v1.1 and the Affymetrix Axiom Exome 319® Array. After filtering-out variants that were non-exonic, with minor allele frequency <0.01, genotype call rate <0.98, and Hardy-Weinberg equilibrium $P<=10^{-6}$, a total of 32,889 exonic variants in 11,049 genes were retained for analysis. Gene-based analysis was performed with SKAT on 16 quantitative traits (including levels of albumin, creatinine, HDL, LDL, cholesterol, BMI, glucose, insulin, urea, uric acid, triglycerides, total protein, waist circumference, waist to hip ratio, systolic blood pressure, and diastolic blood pressure), each adjusted for age, sex, the first three principal components and genotyping chip. We found that *A2ML1*, *COL4A1*, *PARVB*, *TTN*, and *CDK5RAP2* genes showed Bonferroni-corrected significant associations ($P<4.53 \times 10^{-6}$) with five or more traits including albumin, HDL, insulin, triglycerides, systolic blood pressure, and uric acid levels. The encoded proteins of these genes have important cardiometabolic roles: A2ML1 is a ligand of the well-known low density lipoprotein receptor-related protein 1 (LRP1) that plays an important role in lipid metabolism; over-expression of PARVB enhances PPARG activity and lipogenesis; COL4A1 is expressed in the vascular tissue. Three of these loci (*COL4A1*, *TTN* and *PARVB*) were previously reported to be associated with coronary artery disease and arterial stiffness (*COL4A1*), hip circumference and lipid traits (*TTN*), and non-alcoholic fatty liver disease and serum triglycerides (*PARVB*) in Europeans and Asians. In all, we identified five loci displaying pleiotropic associations with several cardiometabolic traits providing insight into the pathogenesis of the clustering of metabolic disorders in Africans and other human populations.