

Supplement: Association of genetic scores related to insulin resistance with neurological outcomes in ancestrally diverse cohorts from the Trans-Omics for Precision Medicine (TOPMed) Program

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Supplementary Methods

Harmonization of phenotypes

1. Glycemic traits

Analysts from each study provided glycemic traits (fasting glucose levels, mmol/L and fasting insulin levels, pmol/L) at baseline (exam at which blood was drawn) following a harmonization plan developed by the TOPMed Diabetes working group. Fasting was defined to be at least 8 h without food or drink. Measurements from blood were converted to plasma values using a 1.13 correction factor. Homeostatic model assessment of insulin resistance (HOMA-IR) was calculated as fasting insulin levels (mU/L) multiplied by glucose levels (mmol/L) and divided by 22.5.

As part of the harmonization process, participants with T2D at the time of glycemic trait measurement (defined by anti-diabetes medication, fasting glucose <7 mmol/L and/or HbA1c $<6.5\%$) were excluded, fasting glucose and fasting insulin were recoded where required to align units, and duplicates were identified and processed using the following strategy: selecting duplicate from sequencing center with highest sequencing percentage, keeping monozygotic twins and choosing duplicate with highest sequencing call rate, dropping duplicate with missing value for trait of interest, and selecting duplicate by prioritizing studies that are population-based or longest running.

2. Neurological diseases and related traits

a) Dementia / AD

Dementia definitions and AD classifications in each cohort (FHS, CHS, and ARIC) are provided below.

ARIC

The second clinical examination in 1990-1992 included a neuropsychological evaluation of all participants. Cognitive function was assessed by three tests and has been described previously (1): 1) the Delayed Word Recall Test (verbal memory); 2) the Digit Symbol Substitution Test (processing speed); and 3) the Word Fluency Test (executive function). The same three tests were also completed by study participants at visit 4 (1996-1998) and visit 5 (2011-2013). In addition, surviving ARIC participants who were examined in person as part of the ARIC Neurocognitive Study (ARIC-NCS) at visit 5 also underwent a more detailed neuropsychological test battery.(2) A subset of those with data from the in-person neurocognitive assessment for whom there was evidence of cognitive decline or who were part of a random sample of cognitively

normal participants were invited for further testing including a neurologic examination, functional activities assessment, and a brain magnetic resonance imaging (MRI) scan.(3) Diagnoses of cognitively normal, mild cognitive impairment (MCI), or dementia were made based on an algorithm. An expert committee of physicians and neuropsychologists then reviewed the records of participants whose algorithmic profiles were either MCI or dementia and gave both a syndromic diagnosis and an etiologic diagnosis of either “Alzheimer’s disease (AD)-related” or “cerebrovascular-disease-related”. AD cases in this study received a syndromic diagnosis of dementia and a reviewer diagnosis of either pure AD, AD with cerebrovascular disease, AD with Lewy body disease, or AD with other diagnoses; dementia cases in this study include ARIC participants who received a syndromic diagnosis of dementia.

CHS

A neurologist or psychiatrist with expertise in the diagnosis of dementia evaluated all potential dementia cases at each of the clinics. Dr. Oscar Lopez, with extensive experience in dementia diagnosis, reviewed each of the cases in the study from every center and classified the cases as dementia, mild cognitive impairment (MCI), or normal.

Records of participants classified as dementia by Dr. Lopez, and all the Pittsburgh cases classified as MCI were then reviewed by a dementia adjudication committee that included Dr. Lopez and other neurologists and psychiatrists from each of the centers in the studies, all having expertise in dementia diagnosis. The neurologists first classified the cases as dementia, MCI, or normal and then, among the dementia cases, by types of dementia. The decision as to whether dementia was present or not was not affected by the results of the MRI. The classification of the specific types of dementia by different categories of classification was done after review of the MRI. Classifications were based on Diagnostic and Statistical Manual of Mental Disorders – ed. 4 (DSM-IV) (4) or National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer’s Disease Related Disorders Association (NINCDS-ADRDA),(5) State of California Alzheimer’s Disease Diagnostic and Treatment Centers (ADDTC),(6) and National Institute of Neurological Diseases and Stroke-Association Internationale pour la Recherche et l’Enseignement en Neurosciences (NINDS-AIREN).(7)

More information on classification of patients at risk of dementia, neuropsychological evaluation, and neurological exams in CHS have been described extensively elsewhere.(8)

FHS

A dementia review panel, consisting of at least one neurologist and a neuropsychologist, reviews every documented case of possible dementia and determines dementia diagnosis as well as dementia type and date of diagnosis, based on data from previously performed serial neurologic and neuropsychological evaluations, telephone interviews with caregivers, medical records, neuroimaging studies, and, when applicable and available, autopsies. Following participant death, medical and nursing records are reviewed postmortem by a separate review panel of FHS physicians to establish date and cause of death, and to review medical records for cardiovascular events and any mention of cognitive impairment. Participants flagged for possible cognitive impairment at postmortem review are referred for postmortem dementia review.

The diagnosis of dementia is based on criteria from the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV).(4) The diagnosis of Alzheimer's disease is based on criteria for possible, probable, or definite Alzheimer's disease from the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA).(5) The diagnosis of vascular dementia is based on criteria for possible or probable vascular dementia from the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS–AIREN).(7) The diagnostic algorithm allows participants to have more than one subtype of dementia. More information on dementia surveillance in FHS has been described elsewhere.(9)

b) General Cognitive Function

General cognitive function scores were calculated by each cohort separately by ancestry/ethnicity except for CARDIA for which PC1 derivation was done in the pooled sample of EA and AA participants. To maintain consistency with previous GWAS,(10) the general cognitive function score was defined as the first unrotated principal component from a principal components analysis (PCA) using at least three cognitive tests that assessed different cognitive domains. Only one score was used from each cognitive domain. Clinical cognitive assessments used as screening instruments for dementia (e.g. MMSE) were only used when three specific domain scores were not available. The general cognitive score was standardized and coded in the direction of higher positive scores indicating higher cognitive function. The cognitive tests used in each cohort are provided in a **Supplementary Excel file**.

c) Brain volumes

MRIs were performed at individual study sites and underwent post-imaging processing by analysts at each study. Details on MRI procedures for each study are provided in a **Supplementary Excel file**. To harmonize phenotypes between studies, we first converted all phenotype measurements to units of milliliters. Analysts from each study provided summaries of which volume segments were used to derive each phenotype. Total cranial and brain volumes were harmonized to include both supra- and infra-tentorial volumes for all studies, and ventricular volumes were excluded from total brain volume. Hippocampal and lateral ventricular volumes reflected summed volumes for the left and right hippocampi and lateral ventricles, respectively.

Total brain volume from two studies did not include the same volumes as the other studies: total brain volume in GeneSTAR included ventricular volumes but did not include infratentorial volume, and total brain volume in GENOA included ventricular volumes. We imputed total brain volume from FHS ($r^2=0.989$), which had ventricular volumes and supra-tentorial total brain volume available and then imputed infratentorial volume in GeneSTAR. This approach amounted to linearly scaling GeneSTAR total brain volume and adding a fixed volume, and the resulting volume was highly correlated with supratentorial total brain volume ($r^2 >0.999$). We then imputed ventricular volume-free total brain volume using FHS or SAFHS data, which had both measures available. Both approaches successfully imputed ventricular volume-free total brain volume ($r^2 >0.999$ between actual and imputed phenotypes) and the coefficients in each model were similar. We chose the model based on SAFHS data to impute total brain volume in GeneSTAR and GENOA.

Study Descriptions

ARIC

The Atherosclerosis Risk in Communities (ARIC) study is a population-based prospective cohort study of atherosclerosis and its sequelae. ARIC included 15,792 individuals, predominantly European American and African American, aged 45-64 years at baseline (1987-89), chosen by probability sampling from four US communities (northwest suburbs of Minneapolis, Minnesota; Washington County, Maryland; Forsyth County, North Carolina; and Jackson, Mississippi). Cohort members completed three additional triennial follow-up examinations, a fifth exam in 2011-2013, a sixth exam in 2016-2017, a seventh exam in 2018-2019, an eighth exam in 2020, a ninth exam in 2021-2022, a tenth exam in 2023, and an eleventh exam is ongoing. The ARIC study has been described in detail previously.⁽¹¹⁾

CARDIA

The Coronary Artery Risk Development in Young Adults (CARDIA) Study is a study examining the development and determinants of clinical and subclinical cardiovascular disease and their risk factors. It began in 1985-6 with a group of 5115 black and white men and women aged 18-30 years. The participants were selected so that there would be approximately the same number of people in subgroups of race, gender, education (high school or less and more than high school) and age (18-24 and 25-30) in each of 4 centers: Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA. These same participants were asked to participate in follow-up examinations during 1987-1988 (Year 2), 1990-1991 (Year 5), 1992-1993 (Year 7), 1995-1996 (Year 10), 2000-2001 (Year 15), 2005-2006 (Year 20), 2010-2011 (Year 25), and 2015-2016 (Year 30). A majority of the group has been examined at each of the follow-up examinations (91%, 86%, 81%, 79%, 74%, 72%, 72%, and 71%, respectively). While the specific aims of each examination have varied, data have been collected on a variety of factors believed to be related to heart disease. These include conditions with clear links to heart disease such as blood pressure, cholesterol and other lipids, and glucose. Data have also been collected on physical measurements such as weight and body composition as well as lifestyle factors such as dietary and exercise patterns, substance use (tobacco and alcohol), behavioral and psychological variables, medical and family history, and other chemistries (e.g., insulin). In addition, subclinical atherosclerosis has been measured via echocardiography during Years 5, 10, 25, and 30, a chest CT scan during Years 15, 20, and 25, an abdominal CT scan during Year 25, and carotid ultrasound during Year 20. A brain MRI was performed on a subset of participants at Years 25 and 30. The CARDIA cohort, born between 1955 and 1968, has been influenced substantially by the obesity epidemic at ages younger than participants in other established NHLBI cohorts. Further investigation of the mechanisms linking obesity to derangements in cardiovascular structure and function and the etiology of clinical events promises to generate important new knowledge to inform health promotion and disease prevention efforts.

CHS

The Cardiovascular Health Study (CHS) is a population-based cohort study initiated by the National Heart, Lung and Blood Institute (NHLBI) in 1987 to determine the risk factors for development and progression of cardiovascular disease (CVD) in older adults, with an emphasis on subclinical measures. The study recruited 5,888 adults aged 65 or older at entry in four U.S. communities and conducted extensive annual clinical exams between 1989-1999 along with semi-annual phone calls, events adjudication, and subsequent data analyses and publications. Additional data are collected by studies ancillary to CHS. In June 1990, four Field Centers

(Sacramento, CA; Hagerstown, MD; Winston-Salem, NC; Pittsburgh, PA) completed the recruitment of 5201 participants. Between November 1992 and June 1993, an additional 687 African Americans were recruited using similar methods. Blood samples were drawn from all participants at their baseline examination and during follow-up clinic visits and DNA was subsequently extracted from available samples. CHS analyses were limited to participants with available DNA who consented to genetic studies. The baseline examinations consisted of a home interview and a clinic examination that assessed not only traditional risk factors but also measures of subclinical disease, including carotid ultrasound, echocardiography, electrocardiography, and pulmonary function. Between enrollment and 1998-99, participants were seen in the clinic annually, and contacted by phone at 6-month intervals to collect information about hospitalizations and potential cardiovascular events. Major exam components were repeated during annual follow-up examinations through 1999. Cranial MRI scans, retinal photography, and tests of endothelial function were added as new components. Standard protocols for the identification and adjudication of events were implemented during follow-up. The adjudicated events are CHD, angina, heart failure (HF), stroke, transient ischemic attack (TIA), claudication and mortality. Adjudication of cause of death continues using a streamlined protocol; adjudication of other events ended in June 2015. Deep venous thrombosis and pulmonary embolism events from baseline through 2001 were adjudicated in an ancillary study: the Longitudinal Investigation of Thromboembolism Etiology (LITE). Since 1999, participants have been contacted every 6 months by phone, primarily to ascertain health status and for events follow-up. The study was initially approved by institutional review boards at the Field Centers (Wake Forest, University of California – Davis, Johns Hopkins University, University of Pittsburgh), the Core Laboratory (University of Vermont) and at the Coordinating Center (University of Washington). The University of Washington now handles CHS Data Repository approvals.

FHS

The Framingham Heart Study (FHS) is a long-running, ongoing cardiovascular cohort study of residents of the city of Framingham, Massachusetts. FHS was established in 1948 to improve understanding of the common factors or characteristics that contribute to CVD. The first generation referred to as the Original cohort was recruited in 1948 (5209 mostly of European descent residents of the town of Framingham, MA, who have undergone biennial examinations since then),(12) the second generation referred to as the Offspring cohort was recruited in 1971 (5124 offspring of the original cohort and spouse of the Offspring who were examined every 4 to 8 years)(13) and the third generation referred to as Gen 3 (4095 children of the Offspring cohort

enrolled in 2002 and examined periodically with a target interval of 4 years between examinations) was recruited between 2002 and 2005.(14) The first generation has been examined every two years. The second generation has been examined every 4-8 years. A small number of spouse individuals of the second generation were examined at the same time when the third generation had their first examination. To date, the survivors of all three generation cohorts are under active surveillance for cardiovascular events, stroke, and dementia.

GeneSTAR

The Genetic Study of Atherosclerosis Risk (GeneSTAR) is an ongoing European- and African American- family-based study to investigate mechanisms of stroke and coronary heart disease. GeneSTAR was conducted initially in healthy adult siblings of probands with documented early onset coronary disease under 60 years of age from 1983-2007 in one of ten Baltimore, Maryland hospitals. Apparently healthy siblings of the probands and offspring of the siblings and probands were screened for traditional coronary disease and stroke risk factors from 2003-2006, during which time GeneSTAR enrolled 2,194 participants from 568 families who had no coronary disease, vascular thrombotic events, peripheral vascular disease, serious gastrointestinal disorders, autoimmune diseases, bleeding disorders, or hemorrhagic events. A subset of this study population participated in an MRI study between 2009 and 2013.

GENOA

The Genetic Epidemiology Network of Arteriopathy (GENOA) study, a part of the Family Blood Pressure Program (FBPP Investigators,2002), consists of hypertensive sibships that were recruited for linkage and association studies to identify genes that influence blood pressure and its target organ damage (Daniels, 2004). In the initial phase of the GENOA study (Phase I: 1996-2001), all members of sibships containing ≥ 2 individuals with essential hypertension clinically diagnosed before age 60 were invited to participate, including both hypertensive and normotensive siblings. In the second phase of the GENOA study (Phase II: 2000-2004), 1,239 non-Hispanic white and 1,482 African American participants were successfully re-recruited to measure potential target organ damage due to hypertension.

GOLDN

The Genetics of Lipid-Lowering Drugs and Diet Network Study (GOLDN) is a family-based study of European descent individuals recruited in Minneapolis and Salt Lake City (two of the NHLBI Family Heart Study sites). Contributions of genes shared and individual environments, and

behaviors to variations in risk factors, preclinical atherosclerosis, and CHD were estimated in the study. It aims to uncover genetic predictors of variability in lipid phenotypes, which include both fasting and postprandial lipids quantified using traditional methods, NMR, and high throughput lipidomics.

HCHS/SOL

The Hispanic Community Health Study/Study of Latinos (HCHS/SOL) is a prospective, population-based cohort study of 16,415 Hispanics/Latino adults (ages 18-74 years) who were selected using a two-stage probability sampling design from four US communities (Chicago, IL; Miami, FL; Bronx, NY; San Diego, CA).^(15,16) During the enrollment phase, standardized clinical visits were conducted during 2008-2011 at dedicated study field centers by bilingual interviewers and medical technicians. Data collection followed a uniform protocol implemented in the four field centers, overseen by a Coordinating Center, Central Laboratory, and specialized Reading Centers.

HyperGEN

The Hypertension Genetic Epidemiology Network Study (HyperGEN) - Genetics of Left Ventricular (LV) Hypertrophy is a familial study aimed to understand genetic risk factors for LV hypertrophy by conducting genetic studies of continuous traits from echocardiography exams. As part of HyperGEN study, four field centers recruited African American and white hypertensive siblings, aged 23 to 87 years. The current study includes only African Americans from HyperGEN. Data from detailed clinical exams as well as genotyping data for linkage studies, candidate gene studies and GWAS have been collected and is shared between HyperGEN and the ancillary HyperGEN - Genetics of LV Hypertrophy study.

JHS

The Jackson Heart Study (JHS) is a large, community-based, observational study whose participants were recruited from urban and rural areas of the three counties (Hinds, Madison and Rankin) that make up the Jackson, MS metropolitan statistical area (MSA). Participants were enrolled from each of 4 recruitment pools: random, 17%; volunteer, 30%; currently enrolled in the Atherosclerosis Risk in Communities (ARIC) Study, 31% and secondary family members, 22%. Recruitment was limited to non-institutionalized adult African Americans 35-84 years old, except in a nested family cohort where those 21 to 34 years of age were also eligible. The final cohort of 5,306 participants included 6.59% of all African American Jackson MSA residents aged 35-84

during the baseline exam (N=76,426, US Census 2000). Among these, approximately 3,700 gave consent that allows genetic research and deposition of data into dbGaP, with 3406 participants with post-QC TOPMed whole genome sequencing data. Major components of three clinic examinations (Exam 1 – 2000-2004; Exam 2 – 2005-2008; Exam 3 – 2009-2013) include medical history, physical examination, blood/urine analytes and interview questions on areas such as: physical activity; stress, coping and spirituality; racism and discrimination; socioeconomic position; and access to health care. Exam 4 is ongoing. Extensive clinical phenotyping includes anthropometrics, electrocardiography, carotid ultrasound, ankle-brachial blood pressure index, echocardiography, CT chest and abdomen for coronary and aortic calcification, liver fat, and subcutaneous and visceral fat measurement, and cardiac MRI. At 12-month intervals after the baseline clinic visit (Exam 1), participants have been contacted by telephone to: update information; confirm vital statistics; document interim medical events, hospitalizations, and functional status; and obtain additional sociocultural information. Questions about medical events, symptoms of cardiovascular disease and functional status are repeated annually. Ongoing cohort surveillance includes abstraction of medical records and death certificates for relevant International Classification of Diseases (ICD) codes and adjudication of nonfatal events and deaths.

MESA

The Multi-Ethnic Study of Atherosclerosis (MESA) is a study of the characteristics of subclinical cardiovascular disease (disease detected non-invasively before it has produced clinical signs and symptoms) and the risk factors that predict progression to clinically overt cardiovascular disease or progression of the subclinical disease. MESA researchers study a diverse, population-based sample of 6,814 men and women aged 45-84 and free of clinically recognized cardiovascular disease. Thirty-eight percent of the recruited participants are White, 28 percent Black, 22 percent Hispanic, and 12 percent Asian, predominantly of Chinese descent. Participants were recruited from six field centers across the United States: Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; New York, New York; and St. Paul, Minnesota. Participants are being followed for identification and characterization of cardiovascular disease events, including acute myocardial infarction and other forms of coronary heart disease (CHD), stroke, and heart failure; for cardiovascular disease interventions; and for mortality. In addition to the six Field Centers, MESA involves a Coordinating Center, a Central Laboratory, and Central Reading Centers for Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Ultrasound, and Electrocardiography (ECG). The first examination took place over two years, from

July 2000 - July 2002. It was followed by six examination periods that were 17-20 months in length. Participants have been contacted every 9 to 12 months throughout the study to assess clinical morbidity and mortality.

SAFHS

The San Antonio Family Heart Study (SAFHS) began in 1991 and included 1,431 individuals in 42 extended families at baseline. Probands were 40- to 60-year-old low-income Mexican Americans selected at random without regard to presence or absence of disease, almost exclusively from Mexican American census tracts in San Antonio, Texas. As part of ongoing studies, new family members were recruited to the original families, expanding the cohort to almost 3,099 individuals primarily from 73 families.

WHI

The Women's Health Initiative (WHI) cohort is a prospective national health study focused on identifying optimal strategies for preventing chronic diseases that are the major causes of death and disability in postmenopausal women. The WHI initially recruited 161,808 women between 1993 and 1997 with the goal of including a socio-demographically diverse population with racial/ethnic minority groups proportionate to the total minority population of US women aged 50-79 years. The WHI consists of two major parts: a set of randomized Clinical Trials and an Observational Study. The WHI Clinical Trials (CT; N=68,132) includes three overlapping components, each a randomized controlled comparison: the Hormone Therapy Trials (HT), Dietary Modification Trial, and Calcium and Vitamin D Trial. A parallel prospective observational study (OS; N = 93,676) examined biomarkers and risk factors associated with various chronic diseases. While the HT trials ended in the mid-2000s, active follow-up of the WHI-CT and WHI-OS cohorts has continued for over 25years, with the accumulation of large numbers of diverse clinical outcomes, risk factor measurements, medication use, and many other types of data.(17)

TOPMed acknowledgements by study

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NHLBI TOPMed: Atherosclerosis Risk in Communities Study VTE cohort (ARIC)

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NHLBI TOPMed: Coronary Artery Risk Development in Young Adults (CARDIA)

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NHLBI TOPMed: Cardiovascular Health Study (CHS)

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NHLBI TOPMed: Framingham Heart Study (FHS)

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NHLBI TOPMed: Genetic Studies of Atherosclerosis Risk (GeneSTAR)

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NHLBI TOPMed: Genetic Epidemiology Network of Arteriopathy (GENOA)

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NHLBI TOPMed: Genetics of Lipid Lowering Drugs and Diet Network (GOLDN)

GOLDN biospecimens, baseline phenotype data, and intervention phenotype data were collected with funding from National Heart, Lung and Blood Institute (NHLBI) grant U01 HL072524. Whole-genome sequencing in GOLDN was funded by NHLBI grant R01 HL104135 and supplement R01HL104135-04S1. All GOLDN participants provided informed consent, and the study was approved by the Institutional Review Board of the University of Kentucky.

NHLBI TOPMed: Hispanic Community Health Study - Study of Latinos (HCHS/SOL)

The Hispanic Community Health Study/Study of Latinos is a collaborative study supported by contracts from the National Heart, Lung, and Blood Institute (NHLBI) to the University of North Carolina (HHSN268201300001I / N01-HC-65233), University of Miami (HHSN268201300004I / N01-HC-65234), Albert Einstein College of Medicine (HHSN268201300002I / N01-HC-65235), University of Illinois at Chicago (HHSN268201300003I / N01-HC-65236 Northwestern Univ), and San Diego State University (HHSN268201300005I / N01-HC-65237). The following Institutes/Centers/Offices have contributed to the HCHS/SOL through a transfer of funds to the NHLBI: National Institute on Minority Health and Health Disparities, National Institute on Deafness and Other Communication Disorders, National Institute of Dental and Craniofacial Research, National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Neurological Disorders and Stroke, NIH Institution-Office of Dietary Supplements.

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This study was approved by the institutional review boards (IRBs) at each field center, where all participants gave written informed consent, and by the Non-Biomedical IRB at the University of North Carolina at Chapel Hill, to the HCHS/SOL Data Coordinating Center. All IRBs approving the study are: Non-Biomedical IRB at the University of North Carolina at Chapel Hill. Chapel Hill, NC; Einstein IRB at the Albert Einstein College of Medicine of Yeshiva University. Bronx, NY; IRB at

Office for the Protection of Research Subjects (OPRS), University of Illinois at Chicago. Chicago, IL; Human Subject Research Office, University of Miami. Miami, FL; Institutional Review Board of San Diego State University. San Diego, CA.

NHLBI TOPMed: Hypertension Genetic Epidemiology Network (HyperGEN)

The HyperGEN Study is part of the National Heart, Lung, and Blood Institute (NHLBI) Family Blood Pressure Program; collection of the data represented here was supported by grants U01 HL054472 (MN Lab), U01 HL054473 (DCC), U01 HL054495 (AL FC), and U01 HL054509 (NC FC). The HyperGEN: Genetics of Left Ventricular Hypertrophy Study was supported by NHLBI grant R01 HL055673 with whole-genome sequencing made possible by supplement -18S1. All HyperGEN participants provided informed consent, and the study was approved by the Institutional Review Board of the University of Kentucky.

NHLBI TOPMed: Jackson Heart Study (JHS)

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NHLBI TOPMed: Multi-Ethnic Study of Atherosclerosis (MESA)

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NHLBI TOPMed: Whole Genome Sequencing to Identify Causal Genetic Variants Influencing CVD Risk - San Antonio Family Studies (SAFHS)

Collection of the San Antonio Family Study data was supported in part by National Institutes of Health (NIH) grants R01 HL045522, MH078143, MH078111 and MH083824; and whole genome sequencing of SAFHS subjects was supported by U01 DK085524 and R01 HL113323. We are very grateful to the participants of the San Antonio Family Study for their continued involvement in our research programs. All SAFHS participants provided informed consent, and the study was approved by Institutional Review Board at the University of Texas Rio Grande Valley.

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Supplementary References

- (1) Cerhan JR, Folsom AR, Mortimer JA, Shahar E, Knopman DS, McGovern PG, et al. Correlates of cognitive function in middle-aged adults. Atherosclerosis Risk in Communities (ARIC) Study Investigators. *Gerontology* 1998;44(2):95-105.
- (2) Schneider ALC, Sharrett AR, Gottesman RF, Coresh J, Coker L, Wruck L, et al. Normative data for 8 neuropsychological tests in older blacks and whites from the atherosclerosis risk in communities (ARIC) study. *Alzheimer Dis Assoc Disord* 2015 March 01;29(1):32-44.
- (3) Knopman DS, Gottesman RF, Sharrett AR, Wruck LM, Windham BG, Coker L, et al. Mild Cognitive Impairment and Dementia Prevalence: The Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS). *Alzheimers Dement (Amst)* 2016;2:1-11.
- (4) American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, ed 4. Washington, American Psychiatric Association. ; 1994.
- (5) McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984 Jul;34(7):939-944.
- (6) Chui HC, Victoroff JI, Margolin D, Jagust W, Shankle R, Katzman R. Criteria for the diagnosis of ischemic vascular dementia proposed by the State of California Alzheimer's Disease Diagnostic and Treatment Centers. *Neurology* 1992 March 01;42(3 Pt 1):473-480.
- (7) Roman GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology* 1993 February 01;43(2):250-260.
- (8) Lopez OL, Kuller LH, Fitzpatrick A, Ives D, Becker JT, Beauchamp N. Evaluation of dementia in the cardiovascular health cognition study. *Neuroepidemiology* 2003;22(1):1-12.
- (9) Satizabal C, Beiser AS, Seshadri S. Incidence of Dementia over Three Decades in the Framingham Heart Study. *N Engl J Med* 2016 Jul 7;375(1):93-94.
- (10) Davies G, Lam M, Harris SE, Trampush JW, Luciano M, Hill WD, et al. Study of 300,486 individuals identifies 148 independent genetic loci influencing general cognitive function. *Nat Commun* 2018 May 29;9(1):2098-x.
- (11) Wright JD, Folsom AR, Coresh J, Sharrett AR, Couper D, Wagenknecht LE, et al. The ARIC (Atherosclerosis Risk In Communities) Study: JACC Focus Seminar 3/8. *J Am Coll Cardiol* 2021 June 15;77(23):2939-2959.
- (12) Dawber TR, Kannel WB. The Framingham study. An epidemiological approach to coronary heart disease. *Circulation* 1966 Oct;34(4):553-555.

- (13) Feinleib M, Kannel WB, Garrison RJ, McNamara PM, Castelli WP. The Framingham Offspring Study. Design and preliminary data. *Prev Med* 1975 Dec;4(4):518-525.
- (14) Splansky GL, Corey D, Yang Q, Atwood LD, Cupples LA, Benjamin EJ, et al. The Third Generation Cohort of the National Heart, Lung, and Blood Institute's Framingham Heart Study: design, recruitment, and initial examination. *Am J Epidemiol* 2007 Jun 1;165(11):1328-1335.
- (15) Lavange LM, Kalsbeek WD, Sorlie PD, Aviles-Santa LM, Kaplan RC, Barnhart J, et al. Sample design and cohort selection in the Hispanic Community Health Study/Study of Latinos. *Ann Epidemiol* 2010 August 01;20(8):642-649.
- (16) Sorlie PD, Aviles-Santa LM, Wassertheil-Smoller S, Kaplan RC, Daviglus ML, Giachello AL, et al. Design and implementation of the Hispanic Community Health Study/Study of Latinos. *Ann Epidemiol* 2010 Aug;20(8):629-641.
- (17) Design of the Women's Health Initiative clinical trial and observational study. The Women's Health Initiative Study Group. *Control Clin Trials* 1998 Feb;19(1):61-109.

Supplementary Tables Titles:

Table S1: Description of studies included in the validation set (~17K) used to derive the cross-population polygenic score

Table S2: Description of studies included in the testing set (~21K) used for association analyses with the cross-population polygenic score

Table S3 Comparison of association results of the cross-population FI PSs with HOMA-IR under different weighting strategies

Table S4: Description of clustering analyses used to derive partitioned polygenic scores related to insulin resistance (IR)

Table S5: Description of TOPMed participants with neurological outcomes

Table S6: Association results of the IR-related partitioned polygenic scores (set 1-Kim, PMID: 36538063) with HOMA-IR in the pooled sample of TOPMed studies or by population groups

Table S7: Association results of the IR-related partitioned polygenic scores (set 2-Smith, Deutsch, PMID: 38443691) with HOMA-IR in the pooled sample of TOPMed studies or by population groups

Table S8: Association results of the IR-related partitioned polygenic scores (set 3-Suzuki, PMID: 38374256) with HOMA-IR in the pooled sample of TOPMed studies or by population groups

Table S9: Association results of the IR-related partitioned polygenic scores (set 4-Sevilla, PMID: 40089507) with HOMA-IR in the pooled sample of TOPMed studies or by population groups

Table S10: Association results of the metabolic syndrome GWAS polygenic score [PMID: 35983957] with HOMA-IR in the pooled sample of TOPMed studies or by population groups

Table S11: Association results of the fasting insulin (FI) polygenic scores (PSs) with neurological outcomes in the pooled sample of studies included in the testing set and stratified by population group

Table S12: Association results of the metabolic syndrome GWAS polygenic score (N=318 genetic variants, PMID: 35983957) with neurological outcomes in TOPMed European population

Table S13: Overlap of genetic variants included in the partitioned polygenic scores and polygenic scores related to insulin resistance

Table S14: Cluster trait definitions extracted from clustering/GWAS analyses papers

Table S15: Comparison of Hispanic/Latino populations in TOPMed FI phenotype file for HCHS/SOL (included in the validation set) and MESA (included in the testing set)

Excel files provided separately:

Association_GSs_NeuroTraits_Suppl_Tables.xlsx
GenCog_BV_Description.xlsx

Table S1: Description of studies included in the validation set (~17K) used to derive the cross-population polygenic score

Validation set	GOLDN	HyperGEN	JHS	WHI	HCHS/SOL
N	834	1429	2283	6042	6088
Age, mean (SD)	46.11 (15.96)	44.97 (12.57)	52.82 (13.00)	66.54 (6.98)	44.16 (13.83)
Males, N (%)	396 (47.48)	543 (37.99)	885 (38.76)	0 (0)	2570 (42.21)
Population group					
N _{EA} (%)	834 (100)	0	0	4706 (77.9)	0
N _{AA} (%)	0	1429 (100)	2283 (100)	983 (16.3)	0
N _{HA} (%)	0	0	0	234 (3.9)	6088 (100)
N _{AS} (%)	0	0	0	119 (2.0)	0
Log HOMA-IR, mean (SD)	1.03 (0.52)	0.53 (0.76)	1.12 (0.57)	0.51 (0.64)	2.60 (0.71)

GOLDN: The Genetics of Lipid Lowering Drugs and Diet Network cohort; HyperGEN: The Hypertension Genetic Epidemiology Network; JHS: The Jackson Heart Study; WHI: The Women's Health Initiative; HCHS/SOL: The Hispanic Community Health Study / Study of Latinos

EA: Non-Hispanic White, AA: Black/African American, HA: Hispanic/Latino American, AS: Asian American

HOMA-IR: The Homeostatic Model Assessment for Insulin Resistance

Table S2: Description of studies included in the testing set (~21K) used for association analyses with the cross-population polygenic score

Testing set	ARIC	CARDIA	CHS	FHS	GeneSTAR	GENOA	MESA	SAFHS
N	5950	2555	2880	3083	500	627	4186	849
Age, mean (SD)	53.51 (5.72)	45.20 (3.58)	72.63 (5.38)	48.49 (12.01)	48.14 (7.98)	55.78 (10.92)	60.60 (9.82)	44.47 (15.56)
Males, N (%)	2523 (42.40)	1148 (44.93)	1171 (40.66)	1429 (46.35)	191 (38.2)	191 (30.46)	1984 (47.40)	324 (38.16)
Population group								
N _{EA} (%)	4844 (81.4)	1480 (57.9)	2356 (81.8)	3083 (100)	214 (42.8)	0	1735 (41.5)	0
N _{AA} (%)	1106 (18.6)	1075 (42.1)	516 (17.9)	0	286 (57.2)	627 (100)	1085 (25.9)	0
N _{HA} (%)	0	0	0	0	0	0	844 (20.2)	849 (100)
N _{AS} (%)	0	0	0	0	0	0	522 (12.5)	0

ARIC: The Atherosclerosis Risk in Communities Study; CARDIA: The Coronary Artery Risk Development in Young Adults Study; CHS: The Cardiovascular Health Study; FHS: The Framingham Heart Study; GeneSTAR: The Genetic Study of Atherosclerosis Risk; GENOA: The Genetic Epidemiology Network of Arteriopathy Study; MESA: The Multi-Ethnic Study of Atherosclerosis; SAFHS: The San Antonio Family Heart Study

EA: Non-Hispanic White, AA: Black/African American, HA: Hispanic/Latino American, AS: Chinese American

Table S3: Comparison of association results of the cross-population FI PSs with HOMA-IR under different weighting strategies

	B	SE	P	% Var explained
Weight estimated by PRS-CSx				
Cross-Population $PS_{FI} = 0.06 \times PSFI_EA + 0.12 \times PSFI_AA + 0.18 \times PSFI_HA$				
Cross-population PS_{FI}	0.10	0.004	0.10	0.03
Re-weighted using the ratio of proportion of populations in the testing & validation sets				
Cross-Population $PS_{FI} = 0.12 \times PSFI_EA + 0.10 \times PSFI_AA + 0.04 \times PSFI_HA$				
Cross-population PS_{FI}	0.19	0.004	2.23e-308	0.12

Table S4: Description of clustering analyses used to derive partitioned polygenic scores related to insulin resistance (IR)

Trait*	Ancestry population	cluster	Number of genetic variants	Reference
T2D	European	Obesity Lipodystrophy Liver/Lipid ALP* negative Hyper Insulin secretion	N=35 N=54 N=11 N=4 N=32	Set 1 Kim PMID: 36538063
T2D	Multi-ancestry	Obesity Lipodystrophy 1 Lipodystrophy 2 Liver/Lipid ALP* negative Hyper Insulin secretion	N=75 N=47 N=29 N=7 N=6 N=41	Set 2 Smith, Deutsch PMID: 38443691
T2D	Multi-ancestry	Obesity Lipodystrophy Liver/Lipid Metabolic syndrome	N=233 N=45 N=3 N=166	Set 3 Suzuki PMID: 38374256
FI	European	IR mediated by visceral adiposity Adiposity-driven hyperinsulinemia IR-lipodystrophy Hepatic IR	N=25 N=19 N=37 N=4	Set 4 Sevilla-Gonzalez PMID: 40089507

*T2D: type 2 diabetes; FI: fasting insulin; ALP: alkaline phosphatase

Table S5: Description of TOPMed participants with neurological outcomes

	Dementia & Alzheimer's disease	General Cognitive Function	Volumes derived from MRI
N	9,388	19,191	7,674
Age, mean (SD)	74.4 (10.8)	61.3 (10.4)	60.5 (16.2)
Males, N (%)	4,998 (53.2)	8,018 (41.8)	3330 (43.4)
Population group			
N _{EA} (%)	8,360 (89.0)	13,426 (70.0)	4,748 (61.9)
N _{AA} (%)	1,003 (10.7)	4,625 (24.1)	1,591 (20.7)
N _{HA} (%)	20 (0.2)	1,140 (5.9)	1,189 (15.5)
N _{AS} (%)	5 (0.05)	0 (0)	146 (0.2)
N cases (Dementia / Alzheimer's disease)	1,124 / 880	--	--
T2D*, N (%)	2,091 (22.3)	1,844 (9.6)	1,027 (13.4)
APOE- ϵ 4 carriers, N (%)	2,233 (23.8)	4,544 (23.7)	1,677 (21.9)
Hippocampal Volume, mean (SD)	--	--	7.36 (1.27)
Total Brain Volume, mean (SD)	--	--	1097.7 (135.7)
Total Cranial Volume, mean (SD)	--	--	1434.9 (159.8)
Lateral Ventricular Volume, mean (SD)	--	--	24.6 (16.5)

*at the time of neurological traits measurement

Table S6: Association results of the IR-related partitioned polygenic scores (set 1-Kim, PMID: 36538063) with HOMA-IR in the pooled sample of TOPMed studies or by population groups

	Lipodystrophy (N=54 SNPs)		Obesity (N=35 SNPs)		Liver/Lipid (N=11 SNPs)		Hyper Insulin Secretion (N=32 SNPs)		ALP negative (N=4 SNPs)	
	B	P	B	P	B	P	B	P	B	P
Pooled N ~ 38.8K	0.006	2.7E-66	0.004	2.4E-14	0.005	1.6E-19	0.002	1.7E-04	0.002	6.7E-07
European N~ 19.4K	0.006	6.4E-39	0.004	5.0E-09	0.005	4.4E-13	0.003	4.1E-04	0.002	0.002
African N~ 8.7K	0.005	2.4E-10	0.004	6.1E-04	0.004	6.2E-03	0.001	0.298	0.002	0.034
Hispanic N~ 8.1K	0.008	2.3E-20	0.005	1.3E-04	0.005	3.2E-05	0.003	0.048	0.003	0.021
Asian N~ 1.6K	0.010	1.1E-05	0.001	0.747	0.007	0.015	0.002	0.647	0.010	9.5E-05

All models except for the obesity partitioned polygenic score were adjusted for BMI

ALP: alkaline phosphatase

Table S7: Association results of the IR-related partitioned polygenic scores (set 2-Smith, Deutsch, PMID: 38443691) with HOMA-IR in the pooled sample of TOPMed studies or by population groups

	Lipodystrophy 1 (N=47 SNPs)		Lipodystrophy 2 (N=29 SNPs)		Obesity (N=75 SNPs)		Liver/Lipid (N=7 SNPs)		Hyper Insulin Secretion (N=41 SNPs)		ALP negative (N=6 SNPs)	
	B	P	B	P	B	P	B	P	B	P	B	P
Pooled	0.006	1.3E-49	0.008	7.9E-37	0.005	1.4E-25	0.005	9.5E-20	0.003	3.0E-07	0.002	7.9E-05
European	0.006	6.2E-30	0.008	3.2E-24	0.004	4.5E-13	0.004	2.9E-13	0.004	3.4E-07	0.002	0.009
African	0.006	4.0E-10	0.006	1.5E-04	0.006	1.3E-06	0.003	0.050	0.0008	0.563	0.002	0.113
Hispanic	0.007	1.0E-11	0.010	3.9E-11	0.008	1.7E-10	0.006	6.5E-07	0.003	0.085	0.002	0.174
Asian	0.007	0.004	0.013	0.001	0.004	0.165	0.007	0.014	0.007	0.074	0.009	5.1E-04

All models except for the obesity partitioned polygenic score were adjusted for BMI

ALP: alkaline phosphatase

Table S8: Association results of the IR-related partitioned polygenic scores (set 3-Suzuki, PMID: 38374256) with HOMA-IR in the pooled sample of TOPMed studies or by population groups

	Lipodystrophy (N=45 SNPs)		Obesity (N=233 SNPs)		Liver/Lipid (N=3 SNPs)		Metabolic Syndrome (N=166 SNPs)	
	B	P	B	P	B	P	B	P
Pooled	0.305	2.3E-67	0.148	3.2E-37	0.051	0.422	0.088	3.2E-19
European	0.308	5.0E-46	0.139	4.5E-22	0.104	0.224	0.090	1.3E-13
African	0.271	3.7E-10	0.142	3.8E-07	-0.054	0.671	0.068	5.1E-03
Hispanic	0.331	2.6E-14	0.195	2.8E-11	0.009	0.955	0.097	9.2E-05
Asian	0.258	0.039	0.241	0.002	0.117	0.768	0.205	0.003

All models except for the obesity partitioned polygenic score were adjusted for BMI

Table S9: Association results of the IR-related partitioned polygenic scores (set 4-Sevilla, PMID: PMID: 40089507) with HOMA-IR in the pooled sample of TOPMed studies or by population groups

	IR Lipodystrophy (N=37 SNPs)		IR mediated by visceral adiposity (N=25 SNPs)		Adiposity driven hyperinsulinemia (N=19 SNPs)		Hepatic IR (N=4 SNPs)	
	B	P	B	P	B	P	B	P
Pooled	0.008	2.4E-61	0.006	3.4E-14	0.002	0.001	0.007	1.3E-27
European	0.008	5.1E-44	0.006	1.7E-10	0.001	0.08	0.007	6.4E-18
African	0.007	1.0E-10	0.006	2.8E-03	0.003	0.03	0.005	0.007
Hispanic	0.008	1.3E-11	0.005	6.4E-03	0.002	0.16	0.009	8.1E-09
Asian	0.003	0.27	0.009	0.06	0.0006	0.88	0.009	0.014

All models except for the obesity partitioned polygenic score were adjusted for BMI

Table S10: Association results of the metabolic syndrome European GWAS polygenic score [PMID: 35983957] with HOMA-IR in the pooled sample of TOPMed studies or by population groups

	Metabolic Syndrome (N=318 SNPs)	
	B	P
Pooled	0.045	6.7E-04
European	0.050	0.002
African	0.030	0.325
Hispanic	0.030	0.358
Asian	0.005	0.952

Table S11: Association results of the fasting insulin (FI) polygenic scores (PSs) with neurological outcomes in the pooled sample of studies included in the testing set and stratified by population group

	European population			African population			Hispanic/Latino population		
	B	SE	P	B	SE	P	B	SE	P
Dementia									
Cross-population PS _{FI}									
European PS _{FI}	-0.007	0.053	0.890						
African PS _{FI}				0.175	0.120	0.143			
Alzheimer's disease									
Cross-population PS _{FI}									
European PS _{FI}	-0.010	0.060	0.862						
African PS _{FI}				0.152	0.131	0.248			
General Cognitive Function									
Cross-population PS _{FI}									
European PS _{FI}	-0.008	0.010	0.410						
African PS _{FI}				-0.003	0.018	0.874			
Hispanic PS _{FI}							-0.039	0.020	0.047
Hippocampal Volume									
Cross-population PS _{FI}									
European PS _{FI}	-0.005	0.012	0.661						
African PS _{FI}				0.065	0.037	0.079			
Hispanic PS _{FI}							0.043	0.018	0.015

	European population			African population			Hispanic/Latino population		
	B	SE	P	B	SE	P	B	SE	P
Total Brain Volume									
Cross-population PS_{FI}									
European PS_{FI}	-0.385	0.630	0.541						
African PS_{FI}				0.005	1.714	0.998			
Hispanic PS_{FI}							-0.272	1.003	0.786
Lateral Ventricular Volume									
Cross-population PS_{FI}									
European PS_{FI}	0.010	0.008	0.212						
African PS_{FI}				-0.013	0.015	0.389			
Hispanic PS_{FI}							0.006	0.011	0.576
Total Cranial Volume									
Cross-population PS_{FI}									
European PS_{FI}	-12.045	2.189	3.7E-08						
European PS_{FI} model adjusted for height	-12.742	2.150	3.1E-09						
European PS_{FI} model adjusted for height & BMI	-13.337	2.351	1.4E-08						
European PS_{FI} model adjusted for height excluding participants with diabetes at the time of neurological traits measurement	-12.104	2.289	1.3E-07						

	European population			African population			Hispanic/Latino population		
	B	SE	P	B	SE	P	B	SE	P
European PS _{FI} model adjusted for height in <i>APOE-ε4</i> non carriers	-13.112	2.476	<i>1.2E-07</i>						
African PS _{FI}				0.746	4.267	0.861			
Hispanic PS _{FI}							-2.793	2.943	0.343

AD/Dementia: N=9,383 (89 % EA, 11% AA); Cross-Population PS_{FI}: $0.16 \times \text{PS}_{\text{FI_EA}} + 0.05 \times \text{PS}_{\text{FI_AA}}$

General Cognitive Function: N=18,726 (70% EA, 24% AA, 6% HA); Cross-Population PS_{FI}: $0.12 \times \text{PS}_{\text{FI_EA}} + 0.11 \times \text{PS}_{\text{FI_AA}} + 0.03 \times \text{PS}_{\text{FI_HA}}$

Brain MRI Volumes and Total Cranial Volume: N=7,589 (63% EA, 21% AA, 16% HA); Cross-Population PS_{FI}: $0.11 \times \text{PS}_{\text{FI_EA}} + 0.09 \times \text{PS}_{\text{FI_AA}} + 0.08 \times \text{PS}_{\text{FI_HA}}$

Threshold for significance: $P=0.05/4/7=0.0018$

P-values in bold and italics are significant after multiple-testing correction

Table S12: Association results of the metabolic syndrome van Walree GWAS polygenic score (n=318 genetic variants, PMID: 35983957) with neurological outcomes in TOPMed European population

	Effect estimates in the European population		
	B	SE	P
Dementia	0.143	0.184	0.44
Alzheimer's disease	0.074	0.206	0.72
General Cognitive Function	-0.129	0.035	<i>0.00019</i>
General Cognitive Function excluding participants with diabetes at the time of neurological traits measurement	-0.128	0.036	<i>0.0004</i>
General Cognitive Function in <i>APOE-ε4</i> non carriers	-0.167	0.044	<i>0.00015</i>
Hippocampal Volume	-0.055	0.044	0.21
Total Brain Volume	-3.021	2.244	0.18
Lateral Ventricular Volume	0.086	0.027	<i>0.0018</i>
Lateral Ventricular Volume excluding participants with diabetes at the time of neurological traits measurement	0.072	0.029	0.013
Lateral Ventricular Volume in <i>APOE-ε4</i> non carriers	0.060	0.032	0.06
Total Cranial Volume	2.369	7.694	0.76

Threshold for significance: $P=0.05/11=0.0045$

P-values in bold and italics are significant after multiple-testing correction

Table S13 Overlap of genetic variants included in the partitioned polygenic scores and polygenic scores related to insulin resistance

Metabolic Syndrome	Van Walree N=318
Suzuki N=166	0

Obesity	Smith, Deutsch N=75	Suzuki N=233
Kim N=35	2	0
Smith, Deutsch	--	16

Lipodystrophy	Smith, Deutsch 1 N=47	Smith, Deutsch 2 N=29	Suzuki N=45	Sevilla-Gonzalez N=37
Kim N=54	4	2	2	6
Smith, Deutsch 1	--	13	5	2
Smith, Deutsch 2	13	--	5	2

Table S14 Cluster trait definitions extracted from clustering/GWAS analyses papers

Cluster	Metabolic Syndrome	Obesity	Lipodystrophy
set 1-Kim	na	BMI (+), waist C (+), % body fat (+), CRP (+)	Adiponectin (-), ISI (-), HDL (-)
set 2-Smith, Deutsch	na	BMI male (+), ASAT (+), waist C female (+), Trunk fat % female (+)	<u>Cluster 1</u> GfatAdjBMI (-), vatGfatRatio (+), Adiponectin (-) <u>Cluster 2</u> ALT (+), ISladjAgeSexBMI (-), AST (+), GGT J+I
set 4-Sevilla-Gonzalez	na	na	+ FI + fat distribution in central compartments - circulating & hepatic lipid deposition
set 3-Suzuki	+FG, +FI, +WHR, +VAT, -GFAT, +TG, -HDL, +BP	+BMI, +WHR, +body fat, +BMR, +TG, -HDL	+FI*, +WHR, -body fat, -GFAT*, +TG, -HDL, +BP
van Walree et al	FG, HDL-C, SBP, TG, WC	na	na

*Adjusted for BMI

Table S15 Comparison of Hispanic/Latino populations in TOPMed FI phenotype file for HCHS/SOL (included in the validation set) and MESA (included in the testing set)

HCHS/SOL		
Population Group	N	%
NA	250	4.28%
Central American	413	7.07%
Cuban	1527	26.16%
Dominican	870	14.90%
Mexican	1326	22.71%
Puerto Rican	1449	24.82%
South American	253	4.33%
5838		

MESA		
Population Group	N	%
NA	10	1.16%
Central American	55	6.40%
Cuban	35	4.07%
Dominican	124	14.42%
Mexican	443	51.51%
Puerto Rican	117	13.60%
South American	76	8.84%
860		