NFAT5 and SLC4A10 Loci Associate with Plasma Osmolality

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§ LifeLines Cohort Study

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Supplementary Table 1: Number of individuals excluded due to low eGFRcrea or high glucose.

Study	Sample Size	plasma glucose > 150 mg/dl, n	eGFR < mean eGFRcrea-2 SD of eGFRcrea, n
Stage 1 discovery (European descent)			
Amish studies	1,131	0	18
BLSA	594	0	0
ARIC: Europeans	8,535	0	7
FHS	2,494	0	18
COLAUS	2,816	98	47
MrOS	3,909	0	34
MICROS	1,146	0	6
KORA F3	1,425	138	44
KORA F4	1,671	66	39
GENOA: Europeans	1,064	428	445
InCHIANTI	1,142	48	16
LOLIPOP_EW610	881	0	11
LOLIPOP_EWA	546	0	4
LOLIPOP_EWP	574	0	9
LURIC	2,579	327	84
Ogliastra Genetic Park Talana study	691	18	18
Ogliastra Genetic Park study	382	18	6
SHIP	3,767	201	88
SHIP-TREND	979	1	6
Rotterdam	3,415	0	NA
SARDINIA	6,148	0	118
Stage 2 Replication (European descent)			
DIACORE	1,151	364	25
FINCAVAS	1,761	220	63
LifeLines	12,270	137	148
MESA	2,455	43	53
Indian			
LOLIPOP_IA610	5,654	0	109
LOLIPOP_IA317	1,886	0	34
LOLIPOP_IAOmniEE	802	0	6
LOLIPOP_IAP	423	0	8
African American			
JHS	1,850	0	0
HANDLS	890	0	13
HUFS	981	0	4
GENOA: African-Americans	1,049	465	483
ARIC: African-Americans	2,445	0	18

Supplementary Table 2: Study characteristics of cohorts of African American and Indian ethnicity. Data are given as mean (standard deviation), if not indicated otherwise.

Study	Sample size	Age, years	Sex, % women	eGFRcrea, ml/min/1.73 m^2	Plasma sodium, mEq/l	plasma glucose, mg/dl
African American						
JHS	1,850	49.4(11.7)	61.5	88.78 (17.7)	140.5 (2.2)	91.4 (12.5)
HANDLS	890	48.0 (8.96)	56.1	96.9 (20.5)	139.7 (2.6)	94.8 (13.7)
HUFS	981	46.9 (13.9)	58.6	107.1 (31.2)	137.6 (6.0)	87.2 (14.0)
GENOA: African-Americans	1,049	62.9 (9.4)	70.1	75.5 (19.5)	139.5 (2.1)	99.4 (16.5)
ARIC: African-Americans	2,445	53.1 (5.7)	62.1	103.8 (23.0)	141.5 (2.4)	100.6 (13.2)
Asian Indian						
LOLIPOP_IA610	5,654	55.0 (10.7)	15,9	81.0 (16.5)	139.6 (2.6)	98.0 (16.6)
LOLIPOP_IA317	1,886	47.8 (10.4)	0,0	82.1 (12.6)	139.6 (2.2)	96.0 (14.9)
LOLIPOP_IAOmniEE	802	49.5 (9.8)	50,3	85.5 (18.8)	139.9 (2.2)	94.6 (12.5)
LOLIPOP_IAP	423	50.8 (8.4)	0,0	90.0 (14.0)	139.7 (2.3)	98.5 (15.7)

Supplementary Table 3: Study descriptions

Study name (key references)	Study design	Total genotyped sample size	Study exclusions or disease enrichment	References (Pub-Med ID)	Acknowledgments and funding source
Amish Studies	Population based "founder" cohort	1264	age <20, severe chronic disease, call rate <95%, pHWE<10E-6. No enrichment	[1, 2]	We thank our Amish research volunteers for their long-standing partnership in research, and the research staff at the Amish Research Clinic for their hard work and dedication. We are supported by grants and contracts from the NIH including R01 AG18728 (Amish Longevity Study), R01 HL088119 (Amish Calcification Study), U01 GM074518-04 (PAPI Study), U01 HL072515-06 (HAPI Study), U01 HL084756 and NIH K12RR023250 (University of Maryland MCRDP), the University of Maryland General Clinical Research Center, grant M01 RR 16500, the Baltimore Veterans Administration Medical Center Geriatrics Research and Education Clinical Center and the Paul Beeson Physician Faculty Scholars in Aging Program.
ARIC: Europeans	Prospective, population-based	9713	Of the 9713 genotyped individuals of European ancestry, we excluded 658 individuals based on discrepancies with previous genotypes, disagreement between reported and genotypic sex, one randomly selected member of a pair of first-degree relatives, or outlier based on measures of average DST or >8 SD away on any of the first 10 principal components.	[3] https://www2.cscc.unc.edu/aric/sites/default/files/public/manuals/Clinical_Chemistry_Determinations.1_10.pdf	The ARIC study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C), R01HL087641, R01HL59367 and R01HL086694; National Human Genome Research Institute contract U01HG004402; and National Institutes of Health contract HHSN268200625226C. The authors thank the staff and participants of the ARIC study for their important contributions. Infrastructure was partly supported by Grant Number UL1RR025005, a component of the National Institutes of Health and NIH Roadmap for Medical Research. PS and AK were supported by the Emmy Noether Program of the German Research Foundation (KO 3598/2-1 to AK).
BLSA	Population based cohort	848	call rate <98.5%, sex misspecification	[4]	The BLSA was supported by the Intramural Research Program of the NIH, National Institute on Aging
FHS	Population based cohort	2494	Call rate<95%; pHWE<10E-06	[5]	This research was conducted in part using data and resources from the Framingham Heart Study of the National Heart Lung and Blood Institute of the National Institutes of Health and Boston University School of Medicine. The analyses reflect intellectual input and resource development from the Framingham Heart Study investigators participating in the SNP Health Association Resource (SHARe) project. A portion of this research utilized the Linux Cluster for Genetic Analysis (LinGA-II) funded by the Robert Dawson Evans Endowment of the Department of Medicine at Boston University School of Medicine and Boston Medical Center.

COLAUS	Prospective population-based	5150	none	[6]	The CoLaus authors thank Yolande Barreau, Mathieu Firmann, Vladimir Mayor, Anne-Lise Bastian, Binasa Ramic, Martine Moranville, Martine Baumer, Marcy Sagette, Jeanne Ecoffey and Sylvie Mermoud for data collection. The CoLaus study received financial contributions from GlaxoSmithKline, the Faculty of Biology and Medicine of Lausanne, the Swiss National Science Foundation (33CSCO-122661, 3200BO-111361/2, 3100AO-116323/1,310000-112552), Swiss National Science Foundation project grant 310030_146490 and NCCR Kidney.CH Program. The computations for CoLaus imputation were performed in part at the Vital-IT center for high performance computing of the Swiss Institute of Bioinformatics. MB is supported by the Swiss School of Public Health Plus (SSPH+). We thank Vincent Mooser for his contribution to the CoLaus study. The authors acknowledge support from the Swiss National Science Foundation project grant 310030_146490 and NCCR Kidney.CH Program. Work on this project was supported by the Swiss National Science Foundation project grant 310030_146490 and NCCR Kidney.CH Program
DIACORE	prospective cohort study of patients with diabetes mellitus type 2	1523	1) Missing phenotype 2) Ancestry not European 3) Relatedness 2nd degree or closer 4) Genetic gender discordant with phenotypic gender 5) Gonosomal aberration 6) Excess of Heterocygosity 7) low callrate	[7]	Recruiting and follow-up examinations are supported by the KfH Stiftung Präventivmedizin. Genotyping is supported by the Else Kröner-Fresenius-Stiftung (2012_A147), the KfH Stiftung Präventivmedizin and the University Hospital Regensburg.
GENOA	Community-based, sibships	1532 (blacks)/1509 (whites)	The two GENOA cohorts were originally ascertained (1995-2000) through sibships in which at least 2 siblings had essential hypertension diagnosed prior to age 60 years. All siblings in the sibship were invited to participate, both normotensive and hypertensive.	[8-10]	The Genetic Epidemiology Network of Arteriopathy (GENOA) study was supported by the National Heart, Lung and Blood Institute (HL054464, HL054481, HL071917, and HL87660) and the National Institute of Neurological Disorders and Stroke (NS041558) of the National institute of Health.

MrOS	Population based	4735	Participants had to be ≥ 65 years old, able to walk unassisted, and be without bilateral hip replacements.	[11]	The Osteoporotic Fractures in Men (MrOS) study is supported by National Institutes of Health funding. The following institutes provide support: the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Institute on Aging (NIA), the National Center for Research Resources (NCRR), and NIH Roadmap for Medical Research under the following grant numbers: U01 AR45580, U01 AR45614, U01 AR45632, U01 AR45647, U01 AR45654, U01 AR45583, U01 AG18197, U01-AG027810, and UL1 RR024140. The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) provided funding for the MrOS ancillary study "GWAS in MrOS and SOF" under the grant number RC2ARO58973.
MICROS	cross-sectional population based study	1391	call rate<95%, excess of heterozygosity, outliers by IBS clustering analysis. No enrichment	[12, 13]	We thank the primary care practitioners Raffaela Stocker, Stefan Waldner, Toni Pizzecco, Josef Plangger, Ugo Marcadent and the personnel of the Hospital of Silandro (Department of Laboratory Medicine) for their participation and collaboration in the research project. The MICROS study was supported by the Ministry of Health and Department of Educational Assistance, University and Research of the Autonomous Province of Bolzano and the South Tyrolean Sparkasse Foundation.
KORA F3	Population based	1644	none	[14, 15]	The KORA research platform (KORA, Cooperative Research in the Region of Augsburg) was initiated and financed by the Helmholtz Zentrum München - German Research Center for Environmental Health, which is funded by the German Federal Ministry of Education and Research and by the State of Bavaria. Furthermore, KORA research was supported within the Munich Center of Health Sciences (MC Health), Ludwig-Maximilians-Universität, as part of LMUinnovativ.
KORA F4	Population based	1814	none	[14, 15]	The KORA research platform (KORA, Cooperative Research in the Region of Augsburg) was initiated and financed by the Helmholtz Zentrum München - German Research Center for Environmental Health, which is funded by the German Federal Ministry of Education and Research and by the State of Bavaria. Furthermore, KORA research was supported within the Munich Center of Health Sciences (MC Health), Ludwig-Maximilians-Universität, as part of LMUinnovativ.
InCHIANTI	Population based cohort	1210	call rate <97%, Heterozygosity>0.3, sex misspecification	[16]	The InCHIANTI study baseline (1998-2000) was supported as a "targeted project" (ICS110.1/RF97.71) by the Italian Ministry of Health and in part by the U.S. National Institute on Aging (Contracts: 263 MD 9164 and 263 MD 821336).

LOLIPOP_EW610	Population based cohort	945	Duplicates, gender discrepancy, contaminated samples, relatedness, call rate <95%	[17, 18]	The LOLIPOP study is supported by the National Institute for Health Research (NIHR) Comprehensive Biomedical Research Centre Imperial College Healthcare NHS Trust, the British Heart Foundation (SP/04/002), the Medical Research Council (G0601966,G0700931), the Wellcome Trust (084723/Z/08/Z) the NIHR (RP-PG-0407-10371),European Union FP7 (EpiMigrant, 279143) and Action on Hearing Loss (G51). The work was carried out in part at the NIHR/Wellcome Trust Imperial Clinical Research Facility. We thank the participants and research staff who made the study possible.
LOLIPOP_EWA	Population based cohort	878	Duplicates, contaminated samples, relatedness, samples already in EW610, call rate <95%	[19]	The LOLIPOP study is supported by the National Institute for Health Research (NIHR) Comprehensive Biomedical Research Centre Imperial College Healthcare NHS Trust, the British Heart Foundation (SP/04/002), the Medical Research Council (G0601966,G0700931), the Wellcome Trust (084723/Z/08/Z) the NIHR (RP-PG-0407-10371),European Union FP7 (EpiMigrant, 279143) and Action on Hearing Loss (G51). The work was carried out in part at the NIHR/Wellcome Trust Imperial Clinical Research Facility. We thank the participants and research staff who made the study possible.
LOLIPOP_EWP	Population based cohort with some enrichment	1006	Duplicates, contaminated samples, samples already in EW610, call rate <95%, samples ascertained on Adult Treatment Panel (ATP) III criteria for metabolic syndrome	[20]	The LOLIPOP study is supported by the National Institute for Health Research (NIHR) Comprehensive Biomedical Research Centre Imperial College Healthcare NHS Trust, the British Heart Foundation (SP/04/002), the Medical Research Council (G0601966,G0700931), the Wellcome Trust (084723/Z/08/Z) the NIHR (RP-PG-0407-10371),European Union FP7 (EpiMigrant, 279143) and Action on Hearing Loss (G51). The work was carried out in part at the NIHR/Wellcome Trust Imperial Clinical Research Facility. We thank the participants and research staff who made the study possible.
LURIC	case-control	2984	any acute disease other than acute coronary syndrome, malignancy within the past 5 years	[21]	We extend our appreciation to the participants of the LURIC study; without their collaboration, this article would not have been written. We thank the LURIC study team who were either temporarily or permanently involved in patient recruitment as well as sample and data handling, in addition to the laboratory staff at the Ludwigshafen General Hospital and the Universities of Freiburg, Ulm, and Graz, Germany. LURIC received funding through the 6th Framework Programme (integrated project Bloodomics, grant LSHM-CT-2004-503485) and the 7th Framework Programme (integrated project AtheroRemo, Grant Agreement number 201668 and RiskyCAD, grant agreement number 305739) of the European Union.
Ogliastra Genetic Park Talana study	Population based "founder" cohort	806	age<18, call rate per person <90%, call rate per SNP<90%, MAF<0.01, HWEp<10E-6	[22, 23]	We thank the Ogliastra population and all the individuals who participated in this study. We are very grateful to the municipal administrators for their collaboration to the project and for economic and logistic support. This work was supported by grants from the Italian Ministry of Education, University and Research (MIUR) no.5571/DSPAR/2002 and (FIRB) D. M. no. 718/Ric/2005.

Ogliastra Genetic Park study	unrelated individuals (males) from 7 villages	406	call rate per person <90%, call rate per SNP<90%, MAF<0.01, HWEp<10E-6		as above
SHIP	population based	4079	none	[24, 25]	SHIP is part of the Community Medicine Research net of the University of Greifswald, Germany, which is funded by the Federal Ministry of Education and Research (grants no. 01ZZ9603, 01ZZ0103, and 01ZZ0403), the Ministry of Cultural Affairs as well as the Social Ministry of the Federal State of Mecklenburg-West Pomerania, and the network 'Greifswald Approach to Individualized Medicine (GANI_MED)' funded by the Federal Ministry of Education and Research (grant 03IS2061A). Genome-wide data have been supported by the Federal Ministry of Education and Research (grant no. 03ZIK012) and a joint grant from Siemens Healthcare, Erlangen, Germany and the Federal State of Mecklenburg- West Pomerania. The University of Greifswald is a member of the 'Center of Knowledge Interchange' program of the Siemens AG and the Caché Campus program of the InterSystems GmbH.
SHIP-TREND	population based	986	none	[25]	SHIP is part of the Community Medicine Research net of the University of Greifswald, Germany, which is funded by the Federal Ministry of Education and Research (grants no. 01ZZ9603, 01ZZ0103, and 01ZZ0403), the Ministry of Cultural Affairs as well as the Social Ministry of the Federal State of Mecklenburg-West Pomerania, and the network 'Greifswald Approach to Individualized Medicine (GANI_MED)' funded by the Federal Ministry of Education and Research (grant 03IS2061A). Whole-body MR imaging was supported by a joint grant from Siemens Healthcare, Erlangen, Germany and the Federal State of Mecklenburg West Pomerania. The University of Greifswald is a member of the 'Center of Knowledge Interchange' program of the Siemens AG and the Caché Campus program of the InterSystems GmbH. The SHIP authors are grateful to Mario Stanke for the opportunity to use his Server Cluster for the SNP imputation as well as to Holger Prokisch and Thomas Meitinger (Helmholtz Zentrum München) for the genotyping of the SHIP-TREND cohort.

The Rotterdam Study	Prospective population based study	5974	Any samples with a call rate below 97.5%, excess autosomal heterozygosity >0.336 (~FDR <0.1%), mismatch between called and phenotypic gender, or if there were outliers identified by the IBS clustering analysis (see below) with >3 standard deviations from population mean or IBS probabilities >97% were excluded from the analysis	[26]	The generation and management of GWAS genotype data for the Rotterdam Study was executed by the Human Genotyping Facility of the Genetic Laboratory of the Department of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands. The GWAS datasets are supported by the Netherlands Organisation of Scientific Research NWO Investments (nr. 175.010.2005.011, 911-03-012), the Genetic Laboratory of the Department of Internal Medicine, Erasmus MC, the Research Institute for Diseases in the Elderly (014-93-015; RIDE2), the Netherlands Genomics Initiative (NGI)/Netherlands Organisation for Scientific Research (NWO) Netherlands Consortium for Healthy Aging (NCHA), project nr. 050-060-810. We thank Pascal Arp, Mila Jhamai, Marijn Verkerk, Lizbeth Herrera and Marjolein Peters, MSc, and Carolina Medina-Gomez, MSc, for their help in creating the GWAS database, and Karol Estrada, PhD, Yurii Aulchenko, PhD, and Carolina Medina-Gomez, MSc, for the creation and analysis of imputed data. The Rotterdam Study is funded by Erasmus Medical Center and Erasmus University, Rotterdam, the Netherlands Organization for the Health Research and Development (ZonMw), the Research Institute for Diseases in the Elderly (RIDE), the Ministry of Education, Culture and Science, the Ministry for Health, Welfare and Sports, the European Commission (DG XII), and the Municipality of Rotterdam. The authors are grateful to the study participants, the staff from the Rotterdam Study and the participating general practitioners and pharmacists. Dr Franco works in ErasmusAGE, a center for aging research across the life course funded by Nestlé Nutrition (Nestec Ltd); Metagenics Inc; and AXA. Abbas Dehghan is supported by NOW grant (veni, 916.12.154) and the EUR Fellowship.
SardiNIA	family-based cohort	6148		[27]	This work was supported by the National Institute on Aging (contract NO1-AG-1-2109). We thank the many individuals who generously participated in this study, Monsignore Piseddu, Bishop of Ogliastra, the mayors and citizens of the Sardinian towns (Lanusei, Ilbono, Arzana, and Elini) for their volunteerism and cooperation;
FINCAVAS	Cross-sectional follow-up study	2544	call rate < 98%, pHWE < 10E-4. Enrichment of coronary heart disease.	[28]	This work was supported by the Competitive Research Funding of the Tampere University Hospital (Grant 9M048 and 9N035), the Finnish Cultural Foundation, the Finnish Foundation for Cardiovascular Research, the Emil Aaltonen Foundation, Finland, and the Tampere Tuberculosis Foundation. The authors thank the staff of the Department of Clinical Physiology for collecting the exercise test data.

LifeLines	Population-based	13.386	none	[29, 30]	The LifeLines Cohort Study, and generation and management of GWAS genotype data for the LifeLines Cohort Study is supported by the Netherlands Organization of Scientific Research NWO (grant 175.010.2007.006), the Economic Structure Enhancing Fund (FES) of the Dutch government, the Ministry of Economic Affairs, the Ministry of Education, Culture and Science, the Ministry for Health, Welfare and Sports, the Northern Netherlands Collaboration of Provinces (SNN), the Province of Groningen, University Medical Center Groningen, the University of Groningen, Dutch Kidney Foundation and Dutch Diabetes Research Foundation. We thank Behrooz Alizadeh, Annemieke Boesjes, Marcel Bruinenberg, Noortje Festen, Pim van der Harst, Ilja Nolte, Lude Franke, Mitra Valimohammadi for their help in creating the GWAS database, and Rob Bieringa, Joost Keers, René Oostergo, Rosalie Visser, Judith Vonk for their work related to data-collection and validation. The authors are grateful to the study participants, the staff from the LifeLines Cohort Study and the contributing research centers delivering data to LifeLines and the participating general practitioners and pharmacists.
MESA	Community-based prospective cohort study	2455	age <45, age>84, Prevalent cardiovascular disease, defined as myocardial infarction, angina, stroke, transient ischemic attack, heart failure, atrial fibrillation, use of nitroglycerin, prior angioplasty, coronary artery bypass graft surgery, valve replacement, pacemaker or defibrillator implant, or any surgery on the heart or arteries, call rate <95%. For this study, only European Americans were analysed.	[31]	MESA and the MESA SHARe project are conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with MESA investigators. Support for MESA is provided by contracts HHSN268201500003I, N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168, N01-HC-95169, UL1-TR-001079, UL1-TR-000040, and DK063491. Serum sodium data were funded by NHLBI grant HL096875.
Asian Indian ancestry					
LOLIPOP_IA610	CHD cases and controls (CHD was used as a covariate)	7032	Duplicates, gender discrepancy, ethnic outliers, contaminated samples, relatedness, call rate <95. Enriched with CHD cases (a case-control study).	[32, 33]	The LOLIPOP study is supported by the National Institute for Health Research (NIHR) Comprehensive Biomedical Research Centre Imperial College Healthcare NHS Trust, the British Heart Foundation (SP/04/002), the Medical Research Council (G0601966,G0700931), the Wellcome Trust (084723/Z/08/Z) the NIHR (RP-PG-0407-10371),European Union FP7 (EpiMigrant, 279143) and Action on Hearing Loss (G51). The work was carried out in part at the NIHR/Wellcome Trust Imperial Clinical Research Facility. We thank the participants and research staff who made the study possible.

LOLIPOP_IA317	Population based cohort with some enrichment	2694	Duplicates, gender discrepancy, ethnic outliers, contaminated samples, relatedness, call rate <95%, samples enriched for insulin resistance and component phenotypes.	[34]	The LOLIPOP study is supported by the National Institute for Health Research (NIHR) Comprehensive Biomedical Research Centre Imperial College Healthcare NHS Trust, the British Heart Foundation (SP/04/002), the Medical Research Council (G0601966,G0700931), the Wellcome Trust (084723/Z/08/Z) the NIHR (RP-PG-0407-10371),European Union FP7 (EpiMigrant, 279143) and Action on Hearing Loss (G51). The work was carried out in part at the NIHR/Wellcome Trust Imperial Clinical Research Facility. We thank the participants and research staff who made the study possible.
LOLIPOP_IAOmniEE	Population based cohort	1248	Duplicates, gender discrepancy, ethnic outliers, contaminated samples, relatedness, call rate <98%, extreme heterozygosity	[35]	The LOLIPOP study is supported by the National Institute for Health Research (NIHR) Comprehensive Biomedical Research Centre Imperial College Healthcare NHS Trust, the British Heart Foundation (SP/04/002), the Medical Research Council (G0601966,G0700931), the Wellcome Trust (084723/Z/08/Z) the NIHR (RP-PG-0407-10371),European Union FP7 (EpiMigrant, 279143) and Action on Hearing Loss (G51). The work was carried out in part at the NIHR/Wellcome Trust Imperial Clinical Research Facility. We thank the participants and research staff who made the study possible.
LOLIPOP_IAP	Population based cohort with some enrichment	1005	Duplicates, contaminated samples, samples already in IA610, call rate <95%, samples ascertained on Adult Treatment Panel (ATP) III criteria for metabolic syndrome	[20]	The LOLIPOP study is supported by the National Institute for Health Research (NIHR) Comprehensive Biomedical Research Centre Imperial College Healthcare NHS Trust, the British Heart Foundation (SP/04/002), the Medical Research Council (G0601966,G0700931), the Wellcome Trust (084723/Z/08/Z) the NIHR (RP-PG-0407-10371),European Union FP7 (EpiMigrant, 279143) and Action on Hearing Loss (G51). The work was carried out in part at the NIHR/Wellcome Trust Imperial Clinical Research Facility. We thank the participants and research staff who made the study possible.
African American					
JHS	Population based	1850	Age between 35 and 84 years for unrelated cohort and age >20 for family cohort	[36]	We thank the Jackson Heart Study (JHS) participants and staff for their contributions to this work. The JHS is supported by contracts HHSN268201300046C, HHSN268201300047C, HHSN268201300048C, HHSN268201300049C, HHSN268201300050C from the National Heart, Lung, and Blood Institute and the National Institute on Minority Health and Health Disparities.
HANDLS	Population based	1024	area probability sample of Baltimore based on the 2000 Census	[37]	This research was supported by the Intramural Research Program of the NIH, National Institute on Aging and the National Center on Minority Health and Health Disparities (project # Z01-AG000513 and human subjects protocol number 09-AG-N248). Data analyses for the HANDLS study utilized the high-performance computational capabilities of the Biowulf Linux cluster at the

					National Institutes of Health, Bethesda, Md. (http://biowulf.nih.gov).
HUFS	Family based	981	age < 20, non T2D, unrelated from 328 pedigrees	[38-40]	The HUFS (Howard University Family Study) was supported by grants S06GM008016-380111 to AA and S06GM008016-320107 to CR, both from the NIGMS/MBRS/SCORE Program. Participant enrollment for the HUFS was carried out at the Howard University General Clinical Research Center (GCRC), which was supported by grant 2M01RR010284 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH). This research was supported in part by the NIH Intramural Research Program in the Center for Research on Genomics and Global Health (CRGGH) with support from the National Human Genome Research Institute, the National Institute of Diabetes and Digestive and Kidney Diseases, the Center for Information Technology, and the Office of the Director at the National Institutes of Health (Z01HG200362). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.
ARIC: African Americans	Prospective, population-based	3207	Of the 3207 genotyped African-American individuals, we excluded 336 individuals based on discrepancies with previous genotypes, disagreement between reported and genotypic sex, one randomly selected member of a pair of first-degree relatives, or outlier based on measures of average DST or >8 SD away on any of the first 10 principal components.	[3] https://www2.cscc.unc.edu/aric/sites/default/files/public/manuals/Clinical_Chemistry_Determinations.1_10.pdf	The ARIC study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C), R01HL087641, R01HL59367 and R01HL086694; National Human Genome Research Institute contract U01HG004402; and National Institutes of Health contract HHSN268200625226C. The authors thank the staff and participants of the ARIC study for their important contributions. Infrastructure was partly supported by Grant Number UL1RR025005, a component of the National Institutes of Health and NIH Roadmap for Medical Research. PS and AK were supported by the Emmy Noether Program of the German Research Foundation (KO 3598/2-1 to AK).
GENOA: African-Americans	Community-based, sibships	1532 (blacks)/1509 (whites)	The two GENOA cohorts were originally ascertained (1995-2000) through sibships in which at least 2 siblings had essential hypertension diagnosed prior to age 60 years. All siblings in the sibship were invited to participate, both normotensive and hypertensive.	[8, 9]	The Genetic Epidemiology Network of Arteriopathy (GENOA) study was supported by the National Heart, Lung and Blood Institute (HL054464, HL054481, HL071917, and HL87660) and the National Institute of Neurological Disorders and Stroke (NS041558) of the National institute of Health.

Supplementary Table 4: Genotyping and Imputation Platforms Used by all Participating Studies

Study Name	Array type	Genotype calling	QC filters for genotyped SNPs used for imputation	No of SNPs used for imputation	Imputation - one or two step approach; programs used	Imputation Reference panel (NCBI build)	Filtering of imputed genotypes	Data management and statistical analysis	population stratification or principal components (PCs)
Amish Studies	Affymetrix 500K	BRLMM	MAF < 0.01, non-HapMap,call rate <95%, pHWE<10E-6	338,598	MACH version 1.0.15	phased CEU haplotypes, HapMap release 22 (build 36)	none	Measured genotype accounting for polygenic component	NA
ARIC	Affymetrix 6.0	Birdseed	call rate <95%, MAF<1%, pHWE <10e-5	669,450	MACH v1.0.16	phased CEU haplotypes, HapMap release 22 (build 36)	none	R, ProbABEL, PLINK	Adjusted for any of the first 10 PC associated with phenotype at p<0.05
FINCAVAS	Metabochip	GenomeStudio	MAF < 0.01, call rate <98%, pHWE<10E-4	116,699	SHAPEIT v2 / IMPUTE v2.3.0	1000Genomes Phase I integrated variant set release (v3) in (build 37)	none		NA
BLSA	Illumina 550K	Beadstudio	MAF < 0.01, non-HapMap,call rate <99%, pHWE<10E-4	514,027	MACH version 1.0.15	phased CEU haplotypes, HapMap release 22 (build 36)	none	merlinoffline	Genomic Control
COLAUS	Affymetrix 500K	Affymetrix	call rate <90%, pHWE<10E-7	411,984	MACH	CEU,Hapmap22,build36	none	R/Matlab	10 first PCs
DIACORE	Axiom UK Biobank Array	Axiom GT1 in Genotyping Console 4.0	callrate≥95%, pHWE≥ 10-6	799,756	minimac	Giant 100 Genomes All	none	R	NA
FHS	Affymetrix 500K	BRLMM	Call rate<95%; pHWE<10E-6	503,526	MACH v.1.0.15	Phased CEU haplotypes, HapMap release 22	none	R, lmekin function in Kinship package for continuous traits and	NA

						(build 36)		gee function in GEE package for dichotomous traits	
GENOA: Europeans	Affymetric 6.0 and	Birdseed for Affymtrix	call rate <95%, MAF =0, flag for pHWE, MAF =0, flag for pHWE,	1,434,182	MACH version 1.0.15	Phased CEU haplotypes, HapMap release 22 (build 36)	none	dosage accounting for family relatedness	NA
MrOS	Illumina HumanOmni1_Quad_v1-0 B	BeadStudio	MAF < 0.01, call rate <90%, pHWE<10E-6	740,713	MACH (phasing) and MINIMAC (imputation)	HapMap release 22 (build 36)	RSQ < 0.3 excluded	R	First 4 PCs
MICROS	Illumina 300k (HumHap300 v2)	BeadStudio	MAF>0.01, call rate>98%, pHWE<10E-6	292,917	MACH version 1.0.16	Phased CEU haplotypes, HapMap release 22 (build 36)	none	polygenic linear model	Adjustment for participant relatedness based on genomic kinship matrix
KORA F3	Affymetrix 500K	BRLMM	call rate 93%	490,033	MACH version 1.0.9	phased CEU haplotypes, HapMap release 21 (build 35)	none		NA
KORA F4	Affymetrix 6.0	Birdseed2		651,596	MACH v1.0.15	phased CEU haplotypes, HapMap release 22 (build 36)	none		NA
LOLIPOP_EW610	Illumina Human610	BeadStudio	MAF < 0.01, call rate <95%, pHWE<10E-6	544,620	IMPUTE2 V2.3.0	phased CEU haplotypes, HapMap release 22 (build 36)	none	snptest was used for association with additive effect	First five PCs included
LOLIPOP_EWA	Affymetrix 500K	BRLMN	MAF < 0.01, call rate <95%, pHWE<10E-6	374,773	IMPUTE2 V2.3.0	phased CEU haplotypes, HapMap release 22 (build 36)	none	snptest was used for association with additive effect	First five PCs included
LOLIPOP_EWP	Perlegen custom	Perlegen custom	MAF < 0.01, call rate <95%,	184,469	IMPUTE2 V2.3.0	phased CEU haplotypes,	none	snptest was used for association with	First five PCs

			pHWE<10E-6			HapMap release 22 (build 36)		additive effect	included
InCHIANTI	Illumina 550K	Beadstudio	MAF < 0.01, non-HapMap,call rate <99%, pHWE<10E-6	498,838	MACH version 1.0.15	phased CEU haplotypes, HapMap release 22 (build 36)	none	merlinoffline	Genomic Control
LifeLines	Illumina Cyto SNP12 v2	GenomeStudio	SNPs with Callrate < 95%, pHWE < 0.001, MAF < 0.01, samples with excess heterozygosity or non-caucasian origin	268,407	BEAGLE v3.1.0	Hapmap CEU, rel 24, build 36	none	Analysis in PLINK	PCs 1-10
LURIC	Affymetrix 6.0	Birdseed v2	MAF < 1%, call rate < 98%, pHWE < 10E-4	686,195	MACH version 1.0.15	phased CEU haplotypes, HapMap release 22 (build 36)	none		PCA
OGP_Talana	Affymetrix 500K	BRLMM	MAF < 0.01, call rate <90%, pHWE<10E-6	373,685	MACH version 1.0.15	phased CEU haplotypes, HapMap release 22 (build 36)	none	R, GenABEL; mixed model to account for relatedness	NA
OGP	Affymetrix 500K	BRLMM	MAF < 0.01, call rate <90%, pHWE<10E-6	399,556	MACH version 1.0.15	phased CEU haplotypes, HapMap release 22 (build 36)	none	R, GenABEL	NA
SHIP	Affymetrix SNP 6	Birdseed2	none	869,224	IMPUTE v0.5.0	phased CEU haplotypes, HapMap release 22 (build 36)	none	IntserSystems Caché, InforSense, PLINK	10 PCs
SHIP-TREND	Illumina Omni 2.5	GenCall	pHWE <= 0.0001 , call rate <= 90%, MAF=0	1,782,967	IMPUTE v2.1.2.3	phased CEU haplotypes, HapMap release 22 (build 36)	duplicaters id but different positions	IntserSystems Caché, InforSense, PLINK	10 PCs

The Rotterdam Study-I	Version 3 Illumina Infinium II HumanHap550	BeadStudio	pHWE < 1e-5, call rate<90%, MAF<0.01, Mendelian errors>100, SNPs not in Hapmap or strandedness issues merging with Hapmap	530,683	MACH	HapMap release 22 (build 36)	none	ProbABEL	NA
Sardinia	Affymetrix 500K	BRLMM	MAF < 0.01, non-HapMap,call rate <95%, pHWE<10E-6	NA	1 step / MACH version 1.0.15	phased CEU haplotypes, HapMap release 22 (build 36)	RSQ < 0.3 excluded		genomic control
MESA	Affymetrix 6.0	Birdseed	MAF < 0.01, call rate <95%	934,940	genotyped SNPs only were used for this analysis.	---	---	R	First 10 PCs of Ancestry
African American studies									
JHS	Affymetrix 6.0	Birdseed	MAF < 0.01, call rate <95%	868,969	MACH version 1.0.16	Panel of reference haplotypes using HapMap phase II CEU and YRI data (release 22, build 36)			
HANDLS	Illumina 1M	GenomeStudio	pHWE > 1e-7, missing by haplotype p-values > 1e-7, minor allele frequency > 0.01, and call rate > 95%	907,763	MACH and miniMac (http://www.sph.umich.edu/csg/abecasis/mach/)	combined haplotype data for HapMap Phase 2 YRI and CEU samples that includes monomorphic SNPs in either of the two constituent	Excluded RSQ ≤ 0.3 and MAF ≤ 0.01	PLINK/R – GLM from dosages	10 PCs

						populations (release 22, build 36.3)			
HUFS	Affy 6.0	Birdseed v2	MAF < 0.01, call rate < 0.95, pHWE < 0.01	809,465	MACH version 1.16	CEU and YRI in 1KG (2010-06 releases)	excluded RSQ< 0.3, call rate < 0.9, MAF < 0.01, HWE < 0.01; 5,396,838 SNPs for analysis	Asusming genetic addtive model and association performed in PLINK	Frist two PCs were used
ARIC: African-Americans	Affymetrix 6.0	Birdseed	call rate <95%, MAF<1%, pHWE <10e-5	806,416	Shapeit / Impute v2	1000Genomes Phase 1 v3	none	R, ProbABEL, Plink	Adjusted for any of the first 10 PC associated with phenotype at p<0.05
GENOA: African-Americans	Illumina 1Mi	BeadStudio for Illumina	call rate <95%, MAF =0, flag for pHWE, MAF =0, flag for pHWE,	1,613,471	MACH version 1.0.15	and for Blacks, combined phased CEU and YRI phenotypes, HapMap release 22 (build 36)	none	dosage accounting for family relatedness	NA
Asian Indian studies									
LOLIPOP_IA610	Illumina Human610	BeadStudio	MAF < 0.01, call rate <95%, pHWE<10E-6	544,390	IMPUTE2 V2.3.0	phased CEU+CHB+JPT+YRI haplotypes, HapMap release 22 (build 36)	none	snptest was used for association with additive effect	First five PCs included, also corrected for cohort recruitment time (0/1) and CHD status

LOLIPOP_IA317	Illumina HumanHap300K	BeadStudio	MAF < 0.01, call rate <95%, pHWE<10E-6	245,892	IMPUTE2 V2.3.0	phased CEU+CHB+JPT+YRI haplotypes, HapMap release 22 (build 36)	none	snptest was used for association with additive effect	First five PCs included
LOLIPOP_IAOmniEE	OmniExpressExome BeadChip	zCall	MAF < 0.01, call rate <99%, pHWE<10E-6	692,266	IMPUTE2 V2.3.0	phased CEU+CHB+JPT+YRI haplotypes, HapMap release 22 (build 36)	none	snptest was used for association with additive effect	First five PCs included
LOLIPOP_IAP	Perlegen custom	Perlegen custom	MAF < 0.01, call rate <95%, pHWE<10E-6	170,055	IMPUTE2 V2.3.0	phased CEU+CHB+JPT+YRI haplotypes, HapMap release 22 (build 36)	none	snptest was used for association with additive effect	First five PCs included

Supplementary Table 5: Imputation quality across studies in SNPs analyzed in stage 1 meta-analysis

Study/ SNP	rs16846053	rs753628	rs12677356	rs10774613	rs17074418	rs9980	rs11662617	rs6565990
BLSA	0.98	0.98	0.60	1.00	0.86	0.99	1.00	0.87
ARIC: Europeans	0.99	0.56	1.00	1.00	0.96	0.99	0.82	0.44
Colaus	0.99	0.53	0.80	1.00	0.63	0.98	0.81	0.38
FHS	1.01	0.47	0.80	1.01	0.96	0.98	0.99	0.32
Micros	0.98	0.99	0.57	1.00	0.45	0.92	0.62	0.78
Genoa	0.99	0.64	0.97	0.99	0.94	0.99	0.81	0.49
Amish	0.97	0.64	0.42	0.99	0.62	0.97	0.81	0.39
InCHIANTI	0.98	0.99	0.54	0.99	0.84	0.97	0.99	0.83
KORAF3	0.99	0.48	0.79	0.99	0.38	0.98	0.73	0.34
KORAF4	0.99	0.89	0.99	1.00	0.97	0.97	0.74	0.38
MrOS	0.99	0.98	0.86	0.99	1.00	1.00	0.99	0.92
Rotterdam	0.98	NA	0.62	NA	0.87	NA	0.99	NA
LOLIPOP_EW610	0.96	1.00	0.60	1.00	0.84	0.98	1.00	0.82
LOLIPOP_EWA	0.97	0.41	0.44	0.99	0.55	0.96	0.80	0.21
LOLIPOP_EWP	0.76	0.02	0.45	0.71	0.81	0.98	0.21	0.69
LURIC	0.99	0.96	1.00	1.00	0.99	0.98	0.82	0.43
OGP	0.99	0.40	0.58	NA	0.63	0.95	0.72	0.30
OGPTalana	0.95	0.64	0.32	NA	0.48	0.96	0.84	0.40
SHIP	0.98	0.62	0.84	0.78	0.97	0.99	0.85	0.42
SHIP-TREND	0.96	0.85	0.80	0.82	0.97	0.99	0.98	0.89
Min	**0.76**	**0.02**	**0.32**	**0.71**	**0.38**	**0.92**	**0.21**	**0.21**
Max	**1.01**	**1.00**	**1.00**	**1.01**	**1.00**	**1.00**	**1.00**	**0.92**
Median	**0.98**	**0.64**	**0.70**	**0.99**	**0.85**	**0.98**	**0.82**	**0.43**

Supplementary Table 6: SNPs associated with serum sodium in stage 1 GWAS meta-analysis of subjects with European Ancestry with $p<10^{-5}$

SNP ID	Chromo-some	Position	Allele1/ Allele2	frequency of Allele 1	Effect of Allele 1	SE	Direction of effect per study	P-value	I2 (%)	Het p val	Sample Size
rs16845742	2	161,835,280	t/g	0.92	-0.06	0.01	-------++-----+---+++	2.56E-06	48	0.01	45,887
rs2194732	2	161,997,402	a/g	0.10	0.06	0.01	++++++++--++++-+++-+-	2.48E-07	26.6	0.13	45,887
rs16845851	2	162,003,869	a/c	0.90	-0.06	0.01	--------++-----+---+-+	2.41E-07	25.1	0.14	45,887
rs12469052	2	162,027,599	t/c	0.90	-0.06	0.01	--------++-----+---+-+	3.05E-07	24.7	0.15	45,887
rs12467662	2	162,095,030	a/g	0.10	0.06	0.01	++++++++--++++-+++-+-	3.66E-07	23.5	0.16	45,887
rs2020027	2	162,134,124	a/g	0.10	0.06	0.01	++++++++--++++-+++-+-	3.17E-07	21.6	0.18	45,850
rs12469302	2	162,142,077	t/g	0.10	0.06	0.01	++++++++--++++-+++-+-	4.09E-07	21.6	0.18	45,887
rs1515182	2	162,145,180	a/g	0.90	-0.06	0.01	--------++?---+---+-+	2.57E-06	23.2	0.17	41,978
rs12464282	2	162,157,101	t/c	0.10	0.06	0.01	++++++++--++++-+++-+-	6.65E-07	16.6	0.24	45,887
rs2175142	2	162,158,370	t/c	0.90	-0.06	0.01	--------++-----+---+-+	7.14E-07	16.2	0.25	45,887
rs2389549	2	162,170,455	t/c	0.90	-0.06	0.01	--------++-----+---+-+	4.58E-07	4.4	0.40	45,837
rs1567420	2	162,183,847	t/c	0.90	-0.06	0.01	--------++-----+---+-+	1.01E-06	17.2	0.24	45,883
rs1567421	2	162,183,863	t/g	0.10	0.06	0.01	++++++++--++++-+++-+-	1.43E-06	24.2	0.15	45,881
rs16845945	2	162,188,930	t/c	0.10	0.06	0.01	++++++++--++++-+++-+-	9.06E-07	17.4	0.23	45,887
rs12473088	2	162,193,319	a/g	0.90	-0.06	0.01	--------++-----+---+-+	7.58E-07	16.7	0.24	45,887
rs16845997	2	162,229,292	a/c	0.10	0.06	0.01	++++++++--++++-+++-+-	5.27E-07	7.3	0.36	45,887
rs12467042	2	162,235,217	a/g	0.10	0.06	0.01	++++++++--++++-+++-+-	4.73E-07	3.9	0.41	45,887
rs16846026	2	162,245,937	t/c	0.90	-0.06	0.01	--------++-----+---+-+	4.06E-07	3.1	0.42	45,887
rs12467279	2	162,252,990	a/g	0.90	-0.06	0.01	--------++-----+---+-+	3.66E-07	1	0.44	45,887
rs1399650	2	162,259,964	a/g	0.84	-0.04	0.01	---++---+0--------+--	6.78E-06	12	0.30	45,887
rs1515186	2	162,264,606	a/g	0.84	-0.04	0.01	---++---++--------+--	4.82E-06	10.8	0.32	45,887
rs1515185	2	162,267,672	t/c	0.16	0.05	0.01	+++-++++-+++++-+++-++	2.92E-06	4.9	0.39	45,887
rs13417851	2	162,268,165	t/g	0.90	-0.06	0.01	--------++?---+---+-+	1.71E-06	1.1	0.44	41,978
rs16846047	2	162,270,192	t/c	0.90	-0.06	0.01	--------++-----+---+-+	2.21E-07	0	0.58	45,861
rs13014399	2	162,271,397	c/g	0.16	0.05	0.01	+++-++++-+++++-+++-++	2.96E-06	5.2	0.39	45,887
rs16846050	2	162,271,799	a/g	0.10	0.06	0.01	++++++++--++++-+++-+-	2.44E-07	0	0.49	45,887
rs16846053	2	162,274,291	t/g	0.90	-0.06	0.01	--------++-----+---+--	1.86E-07	2.7	0.42	45,887
rs12476631	2	162,275,182	t/c	0.90	-0.06	0.01	--------++-----+---+-+	3.17E-07	0	0.48	45,884

rs16846064	2	162,277,187	c/g	0.10	0.06	0.01	++++++++--++++-+++-+-	2.59E-07	0	0.50	45,887
rs6752007	2	162,277,219	t/c	0.83	-0.05	0.01	-------++--?--+---+--	8.03E-06	12.8	0.30	42,472
rs12474713	2	162,277,587	a/c	0.10	0.06	0.01	++++++++--++++-+++-+-	2.58E-07	0	0.52	45,887
rs7591103	2	162,286,970	a/g	0.16	0.05	0.01	+++-++++-++?++-+++-++	4.52E-06	9.3	0.34	42,472
rs3903713	2	162,288,630	a/c	0.84	-0.05	0.01	---+----+-----+---+--	1.40E-06	5.1	0.39	45,887
rs2322649	2	162,289,182	a/g	0.84	-0.05	0.01	---+----+-----+---+--	1.51E-06	4.5	0.40	45,887
rs3849341	2	162,289,276	t/c	0.16	0.05	0.01	+++-++++-+++++-+++-++	1.53E-06	4.2	0.40	45,887
rs4664048	2	162,290,500	a/t	0.16	0.05	0.01	+++-++++-+++++-+++-++	1.55E-06	3.7	0.41	45,887
rs16846073	2	162,294,794	c/g	0.89	-0.05	0.01	--------++----+---+--	4.94E-06	0	0.55	45,886
rs1006427	2	162,300,574	t/c	0.89	-0.05	0.01	--------++-?--+---+--	9.59E-06	0	0.50	42,472
rs12470743	2	162,319,448	a/g	0.11	0.05	0.01	++++++++--++++-+++-++	1.60E-06	0	0.50	45,887
rs1449641	2	162,327,813	t/c	0.89	-0.05	0.01	--------++----+---+--	1.85E-06	0	0.50	45,887
rs753628	3	196,040,762	a/g	0.37	0.04	0.01	+++++++++-+?++--+++++	1.75E-06	0	0.84	42,472
rs1038078	5	122,309,550	t/c	0.11	0.05	0.01	-+++++--++-?+-+++-++-	9.24E-06	4.2	0.40	42,391
rs4731700	7	130,047,082	a/g	0.94	-0.07	0.02	----+-+---?-----++---	9.81E-06	24	0.16	41,978
rs3857859	7	130,051,846	a/g	0.06	0.07	0.01	++++-+-+++++++++--+++	9.47E-06	14.7	0.27	45,884
rs12677356	8	23,696,389	t/g	0.05	0.09	0.02	++++-+-++++++++++++++	1.41E-06	0	0.60	45,887
rs7968960	12	109,910,998	a/c	0.64	0.04	0.01	+++-++++-++?+++++-++-	9.42E-06	26.8	0.13	42,472
rs10774613	12	110,030,548	t/c	0.57	0.03	0.01	+++-++++--+?+++++-++-	3.77E-06	26.8	0.13	42,459
rs1023104	13	29,675,301	t/c	0.08	-0.07	0.01	+-------+--?--+---+--	5.44E-06	0	0.48	42,472
rs17074418	13	29,675,855	t/c	0.92	0.07	0.01	-++-++++-+++++-+++-++	1.77E-06	0	0.52	45,887
rs17074420	13	29,678,602	t/c	0.07	-0.07	0.02	+--+----+-----+---+--	4.20E-06	0	0.60	45,887
rs9514320	13	104,265,624	a/g	0.25	-0.04	0.01	+------++--?--------+	6.27E-06	0	0.81	42,442
rs4525351	13	104,268,246	a/c	0.75	0.04	0.01	-++++++--++++++++++-	7.82E-06	0	0.90	45,887
rs3751544	15	35,175,263	t/c	0.50	0.04	0.01	+++++++-++++?++++-+-+	7.23E-06	0	0.67	39,739
rs7200764	16	68,106,289	t/c	0.13	0.05	0.01	+++++++-+-+?+-+++++++	8.31E-06	8.5	0.35	42,472
rs4783720	16	68,117,197	t/c	0.87	-0.05	0.01	--+----+-+---+----+--	9.00E-06	21.3	0.19	45,882
rs7193778	16	68,121,391	t/c	0.87	-0.05	0.01	--+----+-+-?-+----+--	4.49E-06	22.2	0.18	42,451
rs1549287	16	68,147,867	a/g	0.14	0.05	0.01	+++++++-+-+++-+++++++	8.12E-06	30	0.10	45,887
rs244422	16	68,175,014	c/g	0.13	0.05	0.01	+++++++-+-+++-+++++++	5.61E-06	27.6	0.12	45,887
rs39999	16	68,211,197	c/g	0.14	0.05	0.01	+++++++-+-+++-+++++++	7.83E-06	31.5	0.08	45,881
rs9980	16	68,294,969	c/g	0.86	-0.05	0.01	-------+-+-?-+-------	2.40E-06	30	0.10	42,472
rs17299478	16	68,333,001	t/c	0.15	0.05	0.01	++++++--+-+-+-+++++++	5.23E-06	43.6	0.02	45,883

rs29062	18	9,955,338	a/g	0.58	-0.03	0.01	----+---+--+?-++-----	8.85E-06	0	0.70	39,738
rs29061	18	9,955,431	t/c	0.58	-0.03	0.01	----+---+--+?-++-----	8.42E-06	0	0.70	39,738
rs11662617	18	13,243,598	a/g	0.48	-0.04	0.01	+-+----+----?--+--+--	2.02E-06	27.8	0.12	39,739
rs7505177	18	73,349,880	t/g	0.40	0.04	0.01	+++++++++-+??++---+++	8.90E-06	0	0.68	36,324
rs6565990	18	73,350,561	t/g	0.49	0.05	0.01	++-+++-+-++??++-++-++	1.51E-06	0	0.65	36,324

The effect directions in the column “direction” correspond sequentially to these studies: BLSA, ARIC:Europeans, COLAUS, FHS, MICROS, GENOA:Europeans, Amish studies, InCHIANTI, KORA F3, KORA F4, MrOS, Rotterdam, SARDINIA, LOLIPOP_EW610, LOLIPOP_EWA, LOLIPOP_EWP, LURIC, Ogliastra Genetic Park study, Ogliastra Genetic Park Talana study, SHIP and SHIP-TREND.

Supplementary Table 7: Known Gene Biology of Genes located in replicated loci

Gene symbol	Gene name	Gene Biology
NOB1	NIN1/RPN12 binding protein 1 homolog	*NOB1* is a nuclease involved in pre-rRNA processing [41]; *NOB1* is an oncogene for development of glioma [42]. No known function in sodium or water balance
NQO1	NAD(P)H dehydrogenase, quinone 1	NQO1 encodes a cytoplasmic 2-electron reductase. Polymorphisms in this gene have been associated with bladder cancer [43, 44]. No known function in sodium or water balance.
WWP2	WW domain containing E3 ubiquitin protein ligase 2	WWP2 encodes a member of the Nedd4 family of E3 ligases, relevant in protein ubiquination and cell cycle regulation. Gene knockout experiments suggest a role in chondrogenesis [45]. No known function in sodium or water balance.
CLEC18A	C-type lectin domain family 18 member A	The gene product is a secreted protein that binds to carbohydrates in the presence of calcium and may be involved in cell adhesion and immune responses (NCBI). No known function in sodium or water balance.
PSMD14	proteasome 26S subunit, non-ATPase 14	PSDM14 encodes a proteasome which is part of a multiprotein complex catalyzing the degradatation of ubiquinated intracellular proteins; knockdown induces cell cycle arrest and senescence [46]. No known function in sodium or water balance.
TBR1	T-box, brain 1	T-box genes encode transcription factors involved in the regulation of developmental processes. Mutations in this gene have been related to sporadic autism [47]. No known function in sodium or water balance.
DPP4	dipeptidyl-peptidase 4	The gene product is a serine exopeptidase that cleaves X-proline dipeptides from the N-terminus of polypeptides, and is a drug target in the treatment of hyperglycemia of type 2 diabetes. DPP4 circulates in plasma and is expressed in the kidney's proximal tubule, the podocyte, endothelium and the mesangium. The circulating form degrades the incretin hormone glucagon-like receptor 1 (GLP-1) which lowers blood glucose by enhancing insulin secretion in response to a meal. DPP4 inhibitors induce natriuresis [48, 49]

Supplementary Table 8: SNPs associated with serum sodium in stage 1 GWAS meta-analysis of subjects with African Ancestry with $p<10^{-5}$

SNP ID	Chromo-some	Position	Allele1/ Allel2	frequency of Allele 1	Effect of Allele 1	SE	Direction	P-value	I2 (%)	Het p val	Total Sample Size
rs7580868	2	43,966,807	a/g	0.11	0.15	0.034	?++++	1.14E-05	0	0.52	6,234
rs6715448	2	81,948,077	t/c	0.29	-0.10	0.020	-----	3.04E-06	0	0.99	7,200
rs16865212	3	176,062,514	a/g	0.32	0.09	0.019	-++++	8.34E-06	0	0.65	7,208
rs10513723	3	176,062,702	a/g	0.32	0.09	0.019	-++++	7.86E-06	0	0.71	7,213
rs16865252	3	176,065,417	a/g	0.28	0.09	0.020	+++++	6.76E-06	0	0.99	7,208
rs16865319	3	176,070,161	a/g	0.28	0.09	0.020	?++++	1.00E-05	0	0.92	6,234
rs7640081	3	197,389,507	t/c	0.11	-0.15	0.033	?----	4.14E-06	0	0.48	6,234
rs6941732	6	51,648,081	t/c	0.75	0.10	0.022	+++++	5.26E-06	0	0.72	7,215
rs10732902	10	126,687,810	t/c	0.90	-0.15	0.033	-----	5.72E-06	0	0.52	7,170
rs933922	11	12,534,867	a/g	0.82	-0.11	0.025	+----	6.96E-06	0	0.51	7,177
rs4622362	13	22,045,448	a/g	0.04	-0.28	0.057	?-?--	9.64E-07	34	0.22	4,384
rs12428841	13	57,289,492	t/c	0.91	0.15	0.033	+++++	9.77E-06	0	0.80	7,171
rs2039659	13	85,136,351	a/g	0.54	0.08	0.018	+++++	8.31E-06	32	0.21	7,205
rs2039658	13	85,136,382	t/c	0.46	-0.08	0.018	-----	8.38E-06	32	0.21	7,205
rs1538064	13	85,138,490	a/c	0.54	-0.08	0.019	-----	1.07E-05	18	0.30	7,205
rs1538063	13	85,138,591	a/g	0.46	-0.08	0.018	-----	9.10E-06	31	0.22	7,205
rs1538061	13	85,138,704	a/c	0.54	-0.08	0.019	-----	1.16E-05	18	0.30	7,205
rs9547306	13	85,145,100	t/c	0.54	-0.08	0.019	-----	1.22E-05	20	0.29	7,145
rs8033133	15	22,901,567	a/g	0.34	0.09	0.019	+++++	8.93E-06	0	0.78	7,148

The effect directions in the column “direction” correspond sequentially to these studies: HUFS, ARIC JHS, GENOA and HANDLS.

Supplementary Table 9: SNPs associated with serum sodium in stage 1 GWAS meta-analysis of subjects with Asian Ancestry with $p<10^{-5}$

MarkerName	Chromo-some	Position	Allele1/ Allele2	frequency of Allele 1	Effect of Allele 1	SE	Direction	P-value	I2 (%)	Het p val	Total Sample Size
rs6739015	2	85,608,868	a/g	0.62	-0.07	0.0158	---+	3.46E-06	60	0.06	8,760
rs2044474	2	85,612,301	a/g	0.38	0.07	0.0158	+++-	3.35E-06	60	0.06	8,760
rs17026396	2	85,612,638	t/c	0.62	-0.07	0.0158	---+	3.34E-06	60	0.06	8,760
rs10198569	2	85,647,926	a/g	0.62	-0.07	0.0158	---+	3.87E-06	59	0.06	8,760
rs3770098	2	85,658,878	a/c	0.39	0.07	0.0157	+++-	4.48E-06	54	0.09	8,760
rs1009	2	85,662,248	a/g	0.61	-0.07	0.0158	---+	4.48E-06	57	0.07	8,760
rs1058588	2	85,662,382	t/c	0.38	0.07	0.0158	+++-	5.18E-06	52	0.10	8,760
rs1010	2	85,662,493	t/c	0.61	-0.07	0.0158	---+	4.60E-06	56	0.08	8,760
rs2970963	2	215,680,305	t/g	0.97	0.32	0.0719	+++-	6.44E-06	43	0.16	8,760
rs13126694	4	159,318,234	a/g	0.63	0.08	0.0170	++++	9.49E-06	0	0.73	8,759
rs12518453	5	163,580,929	a/c	0.97	0.39	0.0765	++++	4.25E-07	0	0.44	8,760
rs215970	6	84,770,855	a/c	0.97	0.36	0.0759	+++-	2.22E-06	29	0.24	8,760
rs6930752	6	101,946,584	a/c	0.64	0.08	0.0170	++++	8.97E-06	0	0.80	8,759
rs12663042	6	135,931,498	a/g	0.02	-0.45	0.0995	----	7.24E-06	8	0.35	8,760
rs3923547	7	52,952,901	a/t	0.06	0.20	0.0455	++++	8.69E-06	16	0.31	8,760
rs744359	8	144,539,581	t/c	0.83	-0.14	0.0306	----	4.80E-06	0	0.85	8,759
rs12261068	10	80,289,142	a/g	0.98	0.88	0.1792	++-+	9.16E-07	51	0.10	8,760
rs1468069	10	98,978,749	a/c	0.46	0.08	0.0153	++++	6.30E-07	0	0.55	8,760
rs2297987	10	98,979,444	a/g	0.46	0.08	0.0153	++++	5.58E-07	0	0.56	8,760
rs10882884	10	99,015,601	a/t	0.53	-0.07	0.0154	----	1.22E-06	0	0.59	8,760
rs10882889	10	99,035,880	a/g	0.45	0.08	0.0154	++++	5.22E-07	0	0.47	8,760
rs16937173	11	19,731,568	t/g	0.02	-0.67	0.1486	----	5.82E-06	16	0.31	8,760
rs7306977	12	8,379,556	a/g	0.80	0.14	0.0296	++-+	1.39E-06	0	0.65	8,760
rs4237947	12	14,281,899	a/g	0.97	0.38	0.0790	++++	1.37E-06	53	0.09	8,760
rs1484224	15	78,886,028	t/g	0.01	-0.66	0.1447	--+-	5.06E-06	0	0.62	8,760
rs7187566	16	79,706,943	a/g	0.99	1.17	0.2526	+-++	3.76E-06	31	0.23	8,760
rs2715824	17	65,023,464	a/t	0.49	0.07	0.0157	++++	8.97E-06	0	0.81	8,759
rs11663316	18	9,017,914	a/t	0.19	0.11	0.0253	++++	5.54E-06	0	0.70	8,759
rs6506633	18	9,019,580	a/g	0.76	-0.11	0.0234	----	7.31E-06	0	0.63	8,759

rs11152056	18	53,861,176	c/g	0.03	-0.65	0.1412	----	3.80E-06	15	0.32	8,759
rs1119598	19	33,540,622	t/c	0.97	0.24	0.0553	+++-	9.41E-06	20	0.29	8,760
rs7286683	22	42,076,650	t/c	0.01	1.18	0.2480	+-++	1.92E-06	50	0.11	8,760

The effect directions in the column “direction” correspond sequentially to these studies: LOLIPOP_IA317, LOLIPOP_IA610, LOLIPOP_IAP and LOLIPOP_OmniEE

References for Supplementary Tables

1. Mitchell, BD, McArdle, PF, Shen, H, Rampersaud, E, Pollin, TI, Bielak, LF, Jaquish, C, Douglas, JA, Roy-Gagnon, MH, Sack, P, Naglieri, R, Hines, S, Horenstein, RB, Chang, YP, Post, W, Ryan, KA, Brereton, NH, Pakyz, RE, Sorkin, J, Damcott, CM, O'Connell, JR, Mangano, C, Corretti, M, Vogel, R, Herzog, W, Weir, MR, Peyser, PA, Shuldiner, AR: The genetic response to short-term interventions affecting cardiovascular function: rationale and design of the Heredity and Phenotype Intervention (HAPI) Heart Study. *Am Heart J,* 155**:** 823-828, 2008.
2. Rampersaud, E, Bielak, LF, Parsa, A, Shen, H, Post, W, Ryan, KA, Donnelly, P, Rumberger, JA, Sheedy, PF, 2nd, Peyser, PA, Shuldiner, AR, Mitchell, BD: The association of coronary artery calcification and carotid artery intima-media thickness with distinct, traditional coronary artery disease risk factors in asymptomatic adults. *Am J Epidemiol,* 168**:** 1016-1023, 2008.
3. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. *Am J Epidemiol,* 129**:** 687-702, 1989.
4. Lindeman, RD, Tobin, JD, Shock, NW: Association between blood pressure and the rate of decline in renal function with age. *Kidney Int,* 26**:** 861-868, 1984.
5. Meyer, TE, Verwoert, GC, Hwang, SJ, Glazer, NL, Smith, AV, van Rooij, FJ, Ehret, GB, Boerwinkle, E, Felix, JF, Leak, TS, Harris, TB, Yang, Q, Dehghan, A, Aspelund, T, Katz, R, Homuth, G, Kocher, T, Rettig, R, Ried, JS, Gieger, C, Prucha, H, Pfeufer, A, Meitinger, T, Coresh, J, Hofman, A, Sarnak, MJ, Chen, YD, Uitterlinden, AG, Chakravarti, A, Psaty, BM, van Duijn, CM, Kao, WH, Witteman, JC, Gudnason, V, Siscovick, DS, Fox, CS, Kottgen, A, Genetic Factors for Osteoporosis, C, Meta Analysis of, G, Insulin Related Traits, C: Genome-wide association studies of serum magnesium, potassium, and sodium concentrations identify six Loci influencing serum magnesium levels. *PLoS Genet,* 6, 2010.
6. Firmann, M, Mayor, V, Vidal, PM, Bochud, M, Pecoud, A, Hayoz, D, Paccaud, F, Preisig, M, Song, KS, Yuan, X, Danoff, TM, Stirnadel, HA, Waterworth, D, Mooser, V, Waeber, G, Vollenweider, P: The CoLaus study: a population-based study to investigate the epidemiology and genetic determinants of cardiovascular risk factors and metabolic syndrome. *BMC Cardiovasc Disord,* 8**:** 6, 2008.
7. Dorhofer, L, Lammert, A, Krane, V, Gorski, M, Banas, B, Wanner, C, Kramer, BK, Heid, IM, Boger, CA, Group, DS: Study design of DIACORE (DIAbetes COhoRtE) - a cohort study of patients with diabetes mellitus type 2. *BMC Med Genet,* 14**:** 25, 2013.
8. Turner, ST, Kardia, SL, Mosley, TH, Rule, AD, Boerwinkle, E, de Andrade, M: Influence of genomic loci on measures of chronic kidney disease in hypertensive sibships. *J Am Soc Nephrol,* 17**:** 2048-2055, 2006.
9. Rule, AD, Jacobsen, SJ, Schwartz, GL, Mosley, TH, Scott, CG, Kardia, SL, Boerwinkle, E, Turner, ST: A comparison of serum creatinine-based methods for identifying chronic kidney disease in hypertensive individuals and their siblings. *Am J Hypertens,* 19**:** 608-614, 2006.
10. Daniels, PR, Kardia, SL, Hanis, CL, Brown, CA, Hutchinson, R, Boerwinkle, E, Turner, ST, Genetic Epidemiology Network of Arteriopathy, s: Familial aggregation of hypertension treatment and control in the Genetic Epidemiology Network of Arteriopathy (GENOA) study. *Am J Med,* 116**:** 676-681, 2004.
11. Orwoll, E, Blank, JB, Barrett-Connor, E, Cauley, J, Cummings, S, Ensrud, K, Lewis, C, Cawthon, PM, Marcus, R, Marshall, LM, McGowan, J, Phipps, K, Sherman, S, Stefanick, ML, Stone, K: Design and baseline characteristics of the osteoporotic fractures in men (MrOS) study--a large observational study of the determinants of fracture in older men. *Contemp Clin Trials,* 26**:** 569-585, 2005.
12. Pattaro, C, Marroni, F, Riegler, A, Mascalzoni, D, Pichler, I, Volpato, CB, Dal Cero, U, De Grandi, A, Egger, C, Eisendle, A, Fuchsberger, C, Gogele, M, Pedrotti, S, Pinggera, GK, Stefanov, SA, Vogl, FD, Wiedermann, CJ, Meitinger, T, Pramstaller, PP: The genetic study of three population microisolates in South Tyrol (MICROS): study design and epidemiological perspectives. *BMC Med Genet,* 8**:** 29, 2007.

13. Marroni, F, Grazio, D, Pattaro, C, Devoto, M, Pramstaller, P: Estimates of genetic and environmental contribution to 43 quantitative traits support sharing of a homogeneous environment in an isolated population from South Tyrol, Italy. *Hum Hered,* 65**:** 175-182, 2008.
14. Holle, R, Happich, M, Lowel, H, Wichmann, HE, Group, MKS: KORA--a research platform for population based health research. *Gesundheitswesen,* 67 Suppl 1**:** S19-25, 2005.
15. Wichmann, HE, Gieger, C, Illig, T, Group, MKS: KORA-gen--resource for population genetics, controls and a broad spectrum of disease phenotypes. *Gesundheitswesen,* 67 Suppl 1**:** S26-30, 2005.
16. Ferrucci, L, Bandinelli, S, Benvenuti, E, Di Iorio, A, Macchi, C, Harris, TB, Guralnik, JM: Subsystems contributing to the decline in ability to walk: bridging the gap between epidemiology and geriatric practice in the InCHIANTI study. *J Am Geriatr Soc,* 48**:** 1618-1625, 2000.
17. Wain, LV, Verwoert, GC, O'Reilly, PF, Shi, G, Johnson, T, Johnson, AD, Bochud, M, Rice, KM, Henneman, P, Smith, AV, Ehret, GB, Amin, N, Larson, MG, Mooser, V, Hadley, D, Dorr, M, Bis, JC, Aspelund, T, Esko, T, Janssens, AC, Zhao, JH, Heath, S, Laan, M, Fu, J, Pistis, G, Luan, J, Arora, P, Lucas, G, Pirastu, N, Pichler, I, Jackson, AU, Webster, RJ, Zhang, F, Peden, JF, Schmidt, H, Tanaka, T, Campbell, H, Igl, W, Milaneschi, Y, Hottenga, JJ, Vitart, V, Chasman, DI, Trompet, S, Bragg-Gresham, JL, Alizadeh, BZ, Chambers, JC, Guo, X, Lehtimaki, T, Kuhnel, B, Lopez, LM, Polasek, O, Boban, M, Nelson, CP, Morrison, AC, Pihur, V, Ganesh, SK, Hofman, A, Kundu, S, Mattace-Raso, FU, Rivadeneira, F, Sijbrands, EJ, Uitterlinden, AG, Hwang, SJ, Vasan, RS, Wang, TJ, Bergmann, S, Vollenweider, P, Waeber, G, Laitinen, J, Pouta, A, Zitting, P, McArdle, WL, Kroemer, HK, Volker, U, Volzke, H, Glazer, NL, Taylor, KD, Harris, TB, Alavere, H, Haller, T, Keis, A, Tammesoo, ML, Aulchenko, Y, Barroso, I, Khaw, KT, Galan, P, Hercberg, S, Lathrop, M, Eyheramendy, S, Org, E, Sober, S, Lu, X, Nolte, IM, Penninx, BW, Corre, T, Masciullo, C, Sala, C, Groop, L, Voight, BF, Melander, O, O'Donnell, CJ, Salomaa, V, d'Adamo, AP, Fabretto, A, Faletra, F, Ulivi, S, Del Greco, F, Facheris, M, Collins, FS, Bergman, RN, Beilby, JP, Hung, J, Musk, AW, Mangino, M, Shin, SY, Soranzo, N, Watkins, H, Goel, A, Hamsten, A, Gider, P, Loitfelder, M, Zeginigg, M, Hernandez, D, Najjar, SS, Navarro, P, Wild, SH, Corsi, AM, Singleton, A, de Geus, EJ, Willemsen, G, Parker, AN, Rose, LM, Buckley, B, Stott, D, Orru, M, Uda, M, LifeLines Cohort, S, van der Klauw, MM, Zhang, W, Li, X, Scott, J, Chen, YD, Burke, GL, Kahonen, M, Viikari, J, Doring, A, Meitinger, T, Davies, G, Starr, JM, Emilsson, V, Plump, A, Lindeman, JH, Hoen, PA, Konig, IR, EchoGen, c, Felix, JF, Clarke, R, Hopewell, JC, Ongen, H, Breteler, M, Debette, S, Destefano, AL, Fornage, M, AortaGen, C, Mitchell, GF, Group, CCHFW, Smith, NL, KidneyGen, c, Holm, H, Stefansson, K, Thorleifsson, G, Thorsteinsdottir, U, consortium, CK, Cardiogenics, c, CardioGram, Samani, NJ, Preuss, M, Rudan, I, Hayward, C, Deary, IJ, Wichmann, HE, Raitakari, OT, Palmas, W, Kooner, JS, Stolk, RP, Jukema, JW, Wright, AF, Boomsma, DI, Bandinelli, S, Gyllensten, UB, Wilson, JF, Ferrucci, L, Schmidt, R, Farrall, M, Spector, TD, Palmer, LJ, Tuomilehto, J, Pfeufer, A, Gasparini, P, Siscovick, D, Altshuler, D, Loos, RJ, Toniolo, D, Snieder, H, Gieger, C, Meneton, P, Wareham, NJ, Oostra, BA, Metspalu, A, Launer, L, Rettig, R, Strachan, DP, Beckmann, JS, Witteman, JC, Erdmann, J, van Dijk, KW, Boerwinkle, E, Boehnke, M, Ridker, PM, Jarvelin, MR, Chakravarti, A, Abecasis, GR, Gudnason, V, Newton-Cheh, C, Levy, D, Munroe, PB, Psaty, BM, Caulfield, MJ, Rao, DC, Tobin, MD, Elliott, P, van Duijn, CM: Genome-wide association study identifies six new loci influencing pulse pressure and mean arterial pressure. *Nat Genet,* 43**:** 1005-1011, 2011.
18. International Consortium for Blood Pressure Genome-Wide Association, S, Ehret, GB, Munroe, PB, Rice, KM, Bochud, M, Johnson, AD, Chasman, DI, Smith, AV, Tobin, MD, Verwoert, GC, Hwang, SJ, Pihur, V, Vollenweider, P, O'Reilly, PF, Amin, N, Bragg-Gresham, JL, Teumer, A, Glazer, NL, Launer, L, Zhao, JH, Aulchenko, Y, Heath, S, Sober, S, Parsa, A, Luan, J, Arora, P, Dehghan, A, Zhang, F, Lucas, G, Hicks, AA, Jackson, AU, Peden, JF, Tanaka, T, Wild, SH, Rudan, I, Igl, W, Milaneschi, Y, Parker, AN, Fava, C, Chambers, JC, Fox, ER, Kumari, M, Go, MJ, van der Harst, P, Kao, WH, Sjogren, M, Vinay, DG, Alexander, M, Tabara, Y, Shaw-Hawkins, S, Whincup, PH, Liu, Y, Shi, G, Kuusisto, J, Tayo, B, Seielstad, M, Sim, X, Nguyen, KD, Lehtimaki,

T, Matullo, G, Wu, Y, Gaunt, TR, Onland-Moret, NC, Cooper, MN, Platou, CG, Org, E, Hardy, R, Dahgam, S, Palmen, J, Vitart, V, Braund, PS, Kuznetsova, T, Uiterwaal, CS, Adeyemo, A, Palmas, W, Campbell, H, Ludwig, B, Tomaszewski, M, Tzoulaki, I, Palmer, ND, consortium, CA, Consortium, CK, KidneyGen, C, EchoGen, c, consortium, C-H, Aspelund, T, Garcia, M, Chang, YP, O'Connell, JR, Steinle, NI, Grobbee, DE, Arking, DE, Kardia, SL, Morrison, AC, Hernandez, D, Najjar, S, McArdle, WL, Hadley, D, Brown, MJ, Connell, JM, Hingorani, AD, Day, IN, Lawlor, DA, Beilby, JP, Lawrence, RW, Clarke, R, Hopewell, JC, Ongen, H, Dreisbach, AW, Li, Y, Young, JH, Bis, JC, Kahonen, M, Viikari, J, Adair, LS, Lee, NR, Chen, MH, Olden, M, Pattaro, C, Bolton, JA, Kottgen, A, Bergmann, S, Mooser, V, Chaturvedi, N, Frayling, TM, Islam, M, Jafar, TH, Erdmann, J, Kulkarni, SR, Bornstein, SR, Grassler, J, Groop, L, Voight, BF, Kettunen, J, Howard, P, Taylor, A, Guarrera, S, Ricceri, F, Emilsson, V, Plump, A, Barroso, I, Khaw, KT, Weder, AB, Hunt, SC, Sun, YV, Bergman, RN, Collins, FS, Bonnycastle, LL, Scott, LJ, Stringham, HM, Peltonen, L, Perola, M, Vartiainen, E, Brand, SM, Staessen, JA, Wang, TJ, Burton, PR, Soler Artigas, M, Dong, Y, Snieder, H, Wang, X, Zhu, H, Lohman, KK, Rudock, ME, Heckbert, SR, Smith, NL, Wiggins, KL, Doumatey, A, Shriner, D, Veldre, G, Viigimaa, M, Kinra, S, Prabhakaran, D, Tripathy, V, Langefeld, CD, Rosengren, A, Thelle, DS, Corsi, AM, Singleton, A, Forrester, T, Hilton, G, McKenzie, CA, Salako, T, Iwai, N, Kita, Y, Ogihara, T, Ohkubo, T, Okamura, T, Ueshima, H, Umemura, S, Eyheramendy, S, Meitinger, T, Wichmann, HE, Cho, YS, Kim, HL, Lee, JY, Scott, J, Sehmi, JS, Zhang, W, Hedblad, B, Nilsson, P, Smith, GD, Wong, A, Narisu, N, Stancakova, A, Raffel, LJ, Yao, J, Kathiresan, S, O'Donnell, CJ, Schwartz, SM, Ikram, MA, Longstreth, WT, Jr., Mosley, TH, Seshadri, S, Shrine, NR, Wain, LV, Morken, MA, Swift, AJ, Laitinen, J, Prokopenko, I, Zitting, P, Cooper, JA, Humphries, SE, Danesh, J, Rasheed, A, Goel, A, Hamsten, A, Watkins, H, Bakker, SJ, van Gilst, WH, Janipalli, CS, Mani, KR, Yajnik, CS, Hofman, A, Mattace-Raso, FU, Oostra, BA, Demirkan, A, Isaacs, A, Rivadeneira, F, Lakatta, EG, Orru, M, Scuteri, A, Ala-Korpela, M, Kangas, AJ, Lyytikainen, LP, Soininen, P, Tukiainen, T, Wurtz, P, Ong, RT, Dorr, M, Kroemer, HK, Volker, U, Volzke, H, Galan, P, Hercberg, S, Lathrop, M, Zelenika, D, Deloukas, P, Mangino, M, Spector, TD, Zhai, G, Meschia, JF, Nalls, MA, Sharma, P, Terzic, J, Kumar, MV, Denniff, M, Zukowska-Szczechowska, E, Wagenknecht, LE, Fowkes, FG, Charchar, FJ, Schwarz, PE, Hayward, C, Guo, X, Rotimi, C, Bots, ML, Brand, E, Samani, NJ, Polasek, O, Talmud, PJ, Nyberg, F, Kuh, D, Laan, M, Hveem, K, Palmer, LJ, van der Schouw, YT, Casas, JP, Mohlke, KL, Vineis, P, Raitakari, O, Ganesh, SK, Wong, TY, Tai, ES, Cooper, RS, Laakso, M, Rao, DC, Harris, TB, Morris, RW, Dominiczak, AF, Kivimaki, M, Marmot, MG, Miki, T, Saleheen, D, Chandak, GR, Coresh, J, Navis, G, Salomaa, V, Han, BG, Zhu, X, Kooner, JS, Melander, O, Ridker, PM, Bandinelli, S, Gyllensten, UB, Wright, AF, Wilson, JF, Ferrucci, L, Farrall, M, Tuomilehto, J, Pramstaller, PP, Elosua, R, Soranzo, N, Sijbrands, EJ, Altshuler, D, Loos, RJ, Shuldiner, AR, Gieger, C, Meneton, P, Uitterlinden, AG, Wareham, NJ, Gudnason, V, Rotter, JI, Rettig, R, Uda, M, Strachan, DP, Witteman, JC, Hartikainen, AL, Beckmann, JS, Boerwinkle, E, Vasan, RS, Boehnke, M, Larson, MG, Jarvelin, MR, Psaty, BM, Abecasis, GR, Chakravarti, A, Elliott, P, van Duijn, CM, Newton-Cheh, C, Levy, D, Caulfield, MJ, Johnson, T: Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. *Nature,* 478**:** 103-109, 2011.

19. Yuan, X, Waterworth, D, Perry, JR, Lim, N, Song, K, Chambers, JC, Zhang, W, Vollenweider, P, Stirnadel, H, Johnson, T, Bergmann, S, Beckmann, ND, Li, Y, Ferrucci, L, Melzer, D, Hernandez, D, Singleton, A, Scott, J, Elliott, P, Waeber, G, Cardon, L, Frayling, TM, Kooner, JS, Mooser, V: Population-based genome-wide association studies reveal six loci influencing plasma levels of liver enzymes. *Am J Hum Genet,* 83**:** 520-528, 2008.
20. Kooner, JS, Chambers, JC, Aguilar-Salinas, CA, Hinds, DA, Hyde, CL, Warnes, GR, Gomez Perez, FJ, Frazer, KA, Elliott, P, Scott, J, Milos, PM, Cox, DR, Thompson, JF: Genome-wide scan identifies variation in MLXIPL associated with plasma triglycerides. *Nat Genet,* 40**:** 149-151, 2008.
21. Winkelmann, BR, Marz, W, Boehm, BO, Zotz, R, Hager, J, Hellstern, P, Senges, J, Group, LS: Rationale and design of the LURIC study--a resource for functional genomics,

pharmacogenomics and long-term prognosis of cardiovascular disease. *Pharmacogenomics,* 2**:** S1-73, 2001.

22. Pistis, G, Piras, I, Pirastu, N, Persico, I, Sassu, A, Picciau, A, Prodi, D, Fraumene, C, Mocci, E, Manias, MT, Atzeni, R, Cosso, M, Pirastu, M, Angius, A: High differentiation among eight villages in a secluded area of Sardinia revealed by genome-wide high density SNPs analysis. *PLoS One,* 4**:** e4654, 2009.
23. Biino, G, Parati, G, Concas, MP, Adamo, M, Angius, A, Vaccargiu, S, Pirastu, M: Environmental and genetic contribution to hypertension prevalence: data from an epidemiological survey on Sardinian genetic isolates. *PLoS One,* 8**:** e59612, 2013.
24. John, U, Greiner, B, Hensel, E, Ludemann, J, Piek, M, Sauer, S, Adam, C, Born, G, Alte, D, Greiser, E, Haertel, U, Hense, HW, Haerting, J, Willich, S, Kessler, C: Study of Health In Pomerania (SHIP): a health examination survey in an east German region: objectives and design. *Soz Praventivmed,* 46**:** 186-194, 2001.
25. Volzke, H, Alte, D, Schmidt, CO, Radke, D, Lorbeer, R, Friedrich, N, Aumann, N, Lau, K, Piontek, M, Born, G, Havemann, C, Ittermann, T, Schipf, S, Haring, R, Baumeister, SE, Wallaschofski, H, Nauck, M, Frick, S, Arnold, A, Junger, M, Mayerle, J, Kraft, M, Lerch, MM, Dorr, M, Reffelmann, T, Empen, K, Felix, SB, Obst, A, Koch, B, Glaser, S, Ewert, R, Fietze, I, Penzel, T, Doren, M, Rathmann, W, Haerting, J, Hannemann, M, Ropcke, J, Schminke, U, Jurgens, C, Tost, F, Rettig, R, Kors, JA, Ungerer, S, Hegenscheid, K, Kuhn, JP, Kuhn, J, Hosten, N, Puls, R, Henke, J, Gloger, O, Teumer, A, Homuth, G, Volker, U, Schwahn, C, Holtfreter, B, Polzer, I, Kohlmann, T, Grabe, HJ, Rosskopf, D, Kroemer, HK, Kocher, T, Biffar, R, John, U, Hoffmann, W: Cohort profile: the study of health in Pomerania. *Int J Epidemiol,* 40**:** 294-307, 2011.
26. Hofman, A, Brusselle, GG, Darwish Murad, S, van Duijn, CM, Franco, OH, Goedegebure, A, Ikram, MA, Klaver, CC, Nijsten, TE, Peeters, RP, Stricker, BH, Tiemeier, HW, Uitterlinden, AG, Vernooij, MW: The Rotterdam Study: 2016 objectives and design update. *Eur J Epidemiol,* 30**:** 661-708, 2015.
27. Pilia, G, Chen, WM, Scuteri, A, Orru, M, Albai, G, Dei, M, Lai, S, Usala, G, Lai, M, Loi, P, Mameli, C, Vacca, L, Deiana, M, Olla, N, Masala, M, Cao, A, Najjar, SS, Terracciano, A, Nedorezov, T, Sharov, A, Zonderman, AB, Abecasis, GR, Costa, P, Lakatta, E, Schlessinger, D: Heritability of cardiovascular and personality traits in 6,148 Sardinians. *PLoS Genet,* 2**:** e132, 2006.
28. Nieminen, T, Lehtinen, R, Viik, J, Lehtimaki, T, Niemela, K, Nikus, K, Niemi, M, Kallio, J, Koobi, T, Turjanmaa, V, Kahonen, M: The Finnish Cardiovascular Study (FINCAVAS): characterising patients with high risk of cardiovascular morbidity and mortality. *BMC Cardiovasc Disord,* 6**:** 9, 2006.
29. Stolk, RP, Rosmalen, JG, Postma, DS, de Boer, RA, Navis, G, Slaets, JP, Ormel, J, Wolffenbuttel, BH: Universal risk factors for multifactorial diseases: LifeLines: a three-generation population-based study. *Eur J Epidemiol,* 23**:** 67-74, 2008.
30. Klijs, B, Scholtens, S, Mandemakers, JJ, Snieder, H, Stolk, RP, Smidt, N: Representativeness of the LifeLines Cohort Study. *PLoS One,* 10**:** e0137203, 2015.
31. Bild, DE, Bluemke, DA, Burke, GL, Detrano, R, Diez Roux, AV, Folsom, AR, Greenland, P, Jacob, DR, Jr., Kronmal, R, Liu, K, Nelson, JC, O'Leary, D, Saad, MF, Shea, S, Szklo, M, Tracy, RP: Multi-Ethnic Study of Atherosclerosis: objectives and design. *Am J Epidemiol,* 156**:** 871-881, 2002.
32. Chambers, JC, Zhang, W, Li, Y, Sehmi, J, Wass, MN, Zabaneh, D, Hoggart, C, Bayele, H, McCarthy, MI, Peltonen, L, Freimer, NB, Srai, SK, Maxwell, PH, Sternberg, MJ, Ruokonen, A, Abecasis, G, Jarvelin, MR, Scott, J, Elliott, P, Kooner, JS: Genome-wide association study identifies variants in TMPRSS6 associated with hemoglobin levels. *Nat Genet,* 41**:** 1170-1172, 2009.
33. Chambers, JC, Zhang, W, Zabaneh, D, Sehmi, J, Jain, P, McCarthy, MI, Froguel, P, Ruokonen, A, Balding, D, Jarvelin, MR, Scott, J, Elliott, P, Kooner, JS: Common genetic variation near melatonin receptor MTNR1B contributes to raised plasma glucose and increased risk of type 2 diabetes among Indian Asians and European Caucasians. *Diabetes,* 58**:** 2703-2708, 2009.

34. Chambers, JC, Elliott, P, Zabaneh, D, Zhang, W, Li, Y, Froguel, P, Balding, D, Scott, J, Kooner, JS: Common genetic variation near MC4R is associated with waist circumference and insulin resistance. *Nat Genet,* 40**:** 716-718, 2008.
35. van der Harst, P, Zhang, W, Mateo Leach, I, Rendon, A, Verweij, N, Sehmi, J, Paul, DS, Elling, U, Allayee, H, Li, X, Radhakrishnan, A, Tan, ST, Voss, K, Weichenberger, CX, Albers, CA, Al-Hussani, A, Asselbergs, FW, Ciullo, M, Danjou, F, Dina, C, Esko, T, Evans, DM, Franke, L, Gogele, M, Hartiala, J, Hersch, M, Holm, H, Hottenga, JJ, Kanoni, S, Kleber, ME, Lagou, V, Langenberg, C, Lopez, LM, Lyytikainen, LP, Melander, O, Murgia, F, Nolte, IM, O'Reilly, PF, Padmanabhan, S, Parsa, A, Pirastu, N, Porcu, E, Portas, L, Prokopenko, I, Ried, JS, Shin, SY, Tang, CS, Teumer, A, Traglia, M, Ulivi, S, Westra, HJ, Yang, J, Zhao, JH, Anni, F, Abdellaoui, A, Attwood, A, Balkau, B, Bandinelli, S, Bastardot, F, Benyamin, B, Boehm, BO, Cookson, WO, Das, D, de Bakker, PI, de Boer, RA, de Geus, EJ, de Moor, MH, Dimitriou, M, Domingues, FS, Doring, A, Engstrom, G, Eyjolfsson, GI, Ferrucci, L, Fischer, K, Galanello, R, Garner, SF, Genser, B, Gibson, QD, Girotto, G, Gudbjartsson, DF, Harris, SE, Hartikainen, AL, Hastie, CE, Hedblad, B, Illig, T, Jolley, J, Kahonen, M, Kema, IP, Kemp, JP, Liang, L, Lloyd-Jones, H, Loos, RJ, Meacham, S, Medland, SE, Meisinger, C, Memari, Y, Mihailov, E, Miller, K, Moffatt, MF, Nauck, M, Novatchkova, M, Nutile, T, Olafsson, I, Onundarson, PT, Parracciani, D, Penninx, BW, Perseu, L, Piga, A, Pistis, G, Pouta, A, Puc, U, Raitakari, O, Ring, SM, Robino, A, Ruggiero, D, Ruokonen, A, Saint-Pierre, A, Sala, C, Salumets, A, Sambrook, J, Schepers, H, Schmidt, CO, Sillje, HH, Sladek, R, Smit, JH, Starr, JM, Stephens, J, Sulem, P, Tanaka, T, Thorsteinsdottir, U, Tragante, V, van Gilst, WH, van Pelt, LJ, van Veldhuisen, DJ, Volker, U, Whitfield, JB, Willemsen, G, Winkelmann, BR, Wirnsberger, G, Algra, A, Cucca, F, d'Adamo, AP, Danesh, J, Deary, IJ, Dominiczak, AF, Elliott, P, Fortina, P, Froguel, P, Gasparini, P, Greinacher, A, Hazen, SL, Jarvelin, MR, Khaw, KT, Lehtimaki, T, Maerz, W, Martin, NG, Metspalu, A, Mitchell, BD, Montgomery, GW, Moore, C, Navis, G, Pirastu, M, Pramstaller, PP, Ramirez-Solis, R, Schadt, E, Scott, J, Shuldiner, AR, Smith, GD, Smith, JG, Snieder, H, Sorice, R, Spector, TD, Stefansson, K, Stumvoll, M, Tang, WH, Toniolo, D, Tonjes, A, Visscher, PM, Vollenweider, P, Wareham, NJ, Wolffenbuttel, BH, Boomsma, DI, Beckmann, JS, Dedoussis, GV, Deloukas, P, Ferreira, MA, Sanna, S, Uda, M, Hicks, AA, Penninger, JM, Gieger, C, Kooner, JS, Ouwehand, WH, Soranzo, N, Chambers, JC: Seventy-five genetic loci influencing the human red blood cell. *Nature,* 492**:** 369-375, 2012.
36. Lettre, G, Palmer, CD, Young, T, Ejebe, KG, Allayee, H, Benjamin, EJ, Bennett, F, Bowden, DW, Chakravarti, A, Dreisbach, A, Farlow, DN, Folsom, AR, Fornage, M, Forrester, T, Fox, E, Haiman, CA, Hartiala, J, Harris, TB, Hazen, SL, Heckbert, SR, Henderson, BE, Hirschhorn, JN, Keating, BJ, Kritchevsky, SB, Larkin, E, Li, M, Rudock, ME, McKenzie, CA, Meigs, JB, Meng, YA, Mosley, TH, Newman, AB, Newton-Cheh, CH, Paltoo, DN, Papanicolaou, GJ, Patterson, N, Post, WS, Psaty, BM, Qasim, AN, Qu, L, Rader, DJ, Redline, S, Reilly, MP, Reiner, AP, Rich, SS, Rotter, JI, Liu, Y, Shrader, P, Siscovick, DS, Tang, WH, Taylor, HA, Tracy, RP, Vasan, RS, Waters, KM, Wilks, R, Wilson, JG, Fabsitz, RR, Gabriel, SB, Kathiresan, S, Boerwinkle, E: Genome-wide association study of coronary heart disease and its risk factors in 8,090 African Americans: the NHLBI CARe Project. *PLoS Genet,* 7**:** e1001300, 2011.
37. Evans, MK, Lepkowski, JM, Powe, NR, LaVeist, T, Kuczmarski, MF, Zonderman, AB: Healthy aging in neighborhoods of diversity across the life span (HANDLS): overcoming barriers to implementing a longitudinal, epidemiologic, urban study of health, race, and socioeconomic status. *Ethn Dis,* 20**:** 267-275, 2010.
38. Adeyemo, A, Gerry, N, Chen, G, Herbert, A, Doumatey, A, Huang, H, Zhou, J, Lashley, K, Chen, Y, Christman, M, Rotimi, C: A genome-wide association study of hypertension and blood pressure in African Americans. *PLoS Genet,* 5**:** e1000564, 2009.
39. Chen, G, Bentley, A, Adeyemo, A, Shriner, D, Zhou, J, Doumatey, A, Huang, H, Ramos, E, Erdos, M, Gerry, N, Herbert, A, Christman, M, Rotimi, C: Genome-wide association study identifies novel loci association with fasting insulin and insulin resistance in African Americans. *Hum Mol Genet,* 21**:** 4530-4536, 2012.

40. Ramos, E, Chen, G, Shriner, D, Doumatey, A, Gerry, NP, Herbert, A, Huang, H, Zhou, J, Christman, MF, Adeyemo, A, Rotimi, C: Replication of genome-wide association studies (GWAS) loci for fasting plasma glucose in African-Americans. *Diabetologia,* 54**:** 783-788, 2011.
41. Lamanna, AC, Karbstein, K: Nob1 binds the single-stranded cleavage site D at the 3'-end of 18S rRNA with its PIN domain. *Proc Natl Acad Sci U S A,* 106**:** 14259-14264, 2009.
42. Zhou, J, Xu, T, Yan, Y, Qin, R, Wang, H, Zhang, X, Huang, Y, Wang, Y, Lu, Y, Fu, D, Chen, J: MicroRNA-326 functions as a tumor suppressor in glioma by targeting the Nin one binding protein (NOB1). *PLoS One,* 8**:** e68469, 2013.
43. Yang, S, Jin, T, Su, HX, Zhu, JH, Wang, DW, Zhu, SJ, Li, S, He, J, Chen, YH: The association between NQO1 Pro187Ser polymorphism and bladder cancer susceptibility: a meta-analysis of 15 studies. *PLoS One,* 10**:** e0116500, 2015.
44. Zhang, Y, Yang, D, Zhu, JH, Chen, MB, Shen, WX, He, J: The association between NQO1 Pro187Ser polymorphism and urinary system cancer susceptibility: a meta-analysis of 22 studies. *Cancer Invest,* 33**:** 39-40, 2015.
45. Chantry, A: WWP2 ubiquitin ligase and its isoforms: new biological insight and promising disease targets. *Cell Cycle,* 10**:** 2437-2439, 2011.
46. Byrne, A, McLaren, RP, Mason, P, Chai, L, Dufault, MR, Huang, Y, Liang, B, Gans, JD, Zhang, M, Carter, K, Gladysheva, TB, Teicher, BA, Biemann, HP, Booker, M, Goldberg, MA, Klinger, KW, Lillie, J, Madden, SL, Jiang, Y: Knockdown of human deubiquitinase PSMD14 induces cell cycle arrest and senescence. *Exp Cell Res,* 316**:** 258-271, 2010.
47. Deriziotis, P, O'Roak, BJ, Graham, SA, Estruch, SB, Dimitropoulou, D, Bernier, RA, Gerdts, J, Shendure, J, Eichler, EE, Fisher, SE: De novo TBR1 mutations in sporadic autism disrupt protein functions. *Nature communications,* 5**:** 4954, 2014.
48. Vallon, V, Docherty, NG: Intestinal regulation of urinary sodium excretion and the pathophysiology of diabetic kidney disease: a focus on glucagon-like peptide 1 and dipeptidyl peptidase 4. *Exp Physiol,* 99**:** 1140-1145, 2014.
49. von Websky, K, Reichetzeder, C, Hocher, B: Physiology and pathophysiology of incretins in the kidney. *Curr Opin Nephrol Hypertens,* 23**:** 54-60, 2014.

SUPPLEMENTARY FIGURE LEGENDS

Supplementary Figure 1: Stage 1 genome-wide association quantile-quantile (QQ) plot, with the minimum, maximum and median genomic inflation factor lambda of contributing studies.

Supplementary Figure 2: Stage 1 meta-analysis regional association plots of replicated loci. The red dotted line indicates the genome-wide significance threshold ($p<5x10^{-8}$).

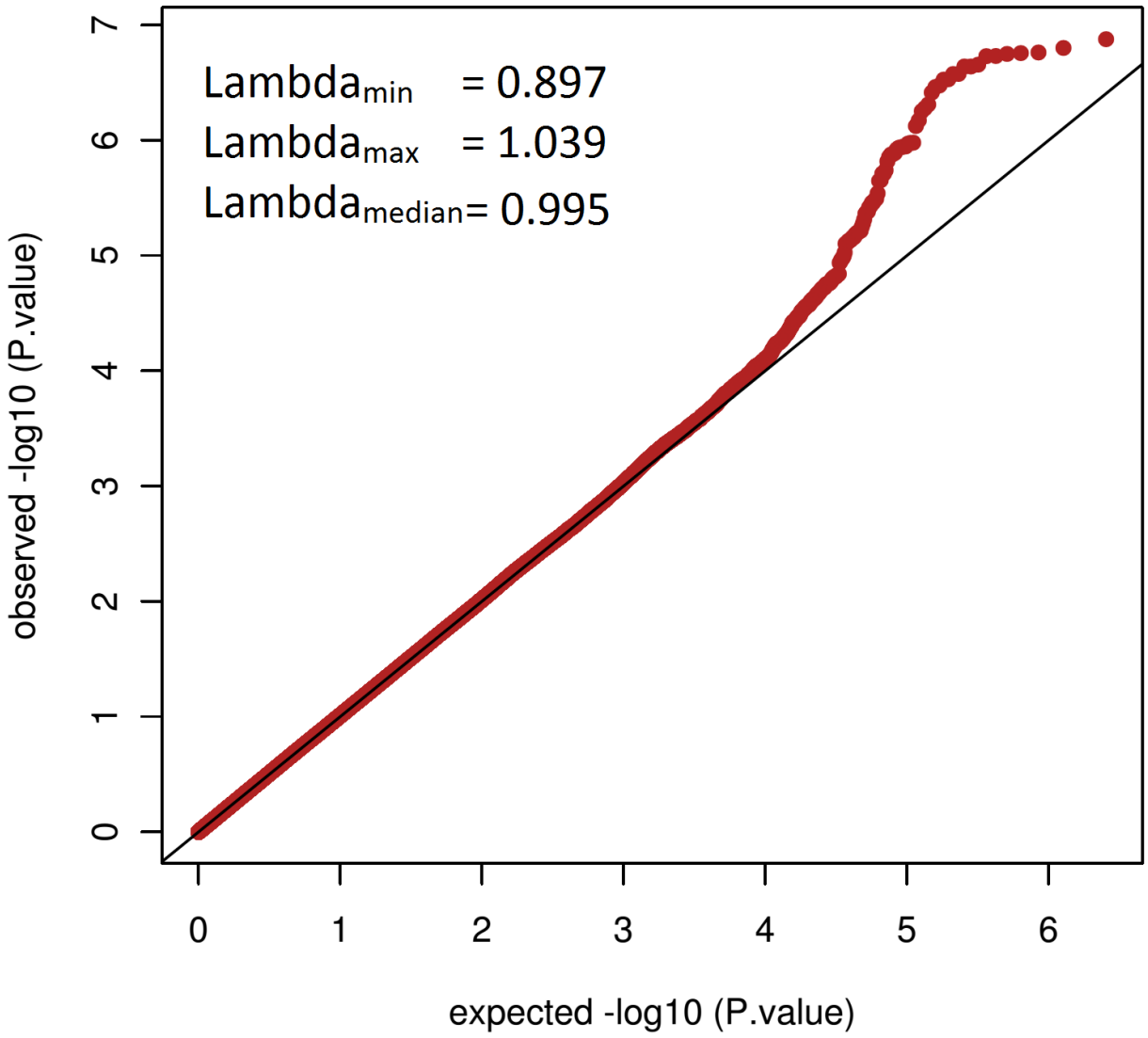
Supplementary Figure 2a: *NFAT5* locus in individuals of European descent (stage 1 GWAS meta-analysis results). The SNP rs7193778 is the SNP implicated by functional genomic annotation that is in near- perfect linkage disequilibrium with rs9980.

Supplementary Figure 2b: SLC4A10 locus in individuals of European descent (stage 1 GWAS meta-analysis results).

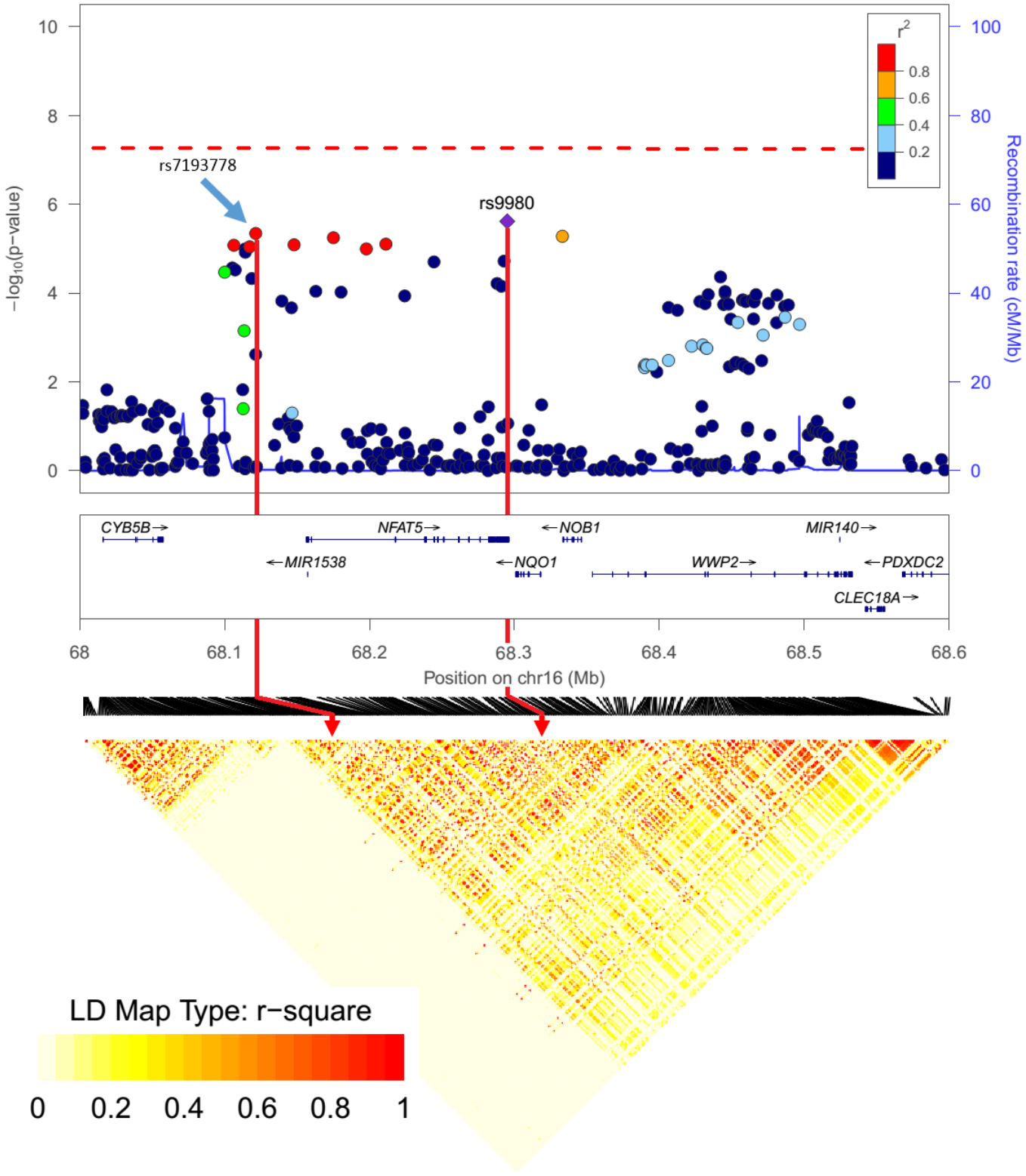
Supplementary Figure 3: Relation of the *NFAT5* SNP rs7193778 to H3K27ac histone acetylation in 107 tissues and cell lines in the Roadmap Epigenome Project.
Tissues exhibiting the most closely related H3K27ac histone acetylation pattern over the depicted genomic interval in the vicinity of rs7193778 upstream of the NFAT5 gene are shown toward the bottom of the figure in this clustered analysis from the ROADMAP EPIGENOME BROWSER v1.19 and the WashU Epigenome Browser v40.0.0 (http://epigenomegateway.wustl.edu/browser/roadmap/). The *NFAT5* super-enhancer region is depicted by clusters of H3K27ac markings (shown as darker blue bands) in the center of the genomic window. Approximately 10,000 bp of genomic sequence are shown. The SNP rs7193778 is located at the genomic position indicated by the red line.

Supplementary Figure 4: Predicted *NFAT5* consensus motif spanning the lead variant rs16846053 in *SLC4A10*. The JASPAR 2016 (http://jaspar.genereg.net/) resource was used to identify in unbiased fashion transcription factor binding sites in the vicinity of the lead variant, rs16846053. *Upper panel*,

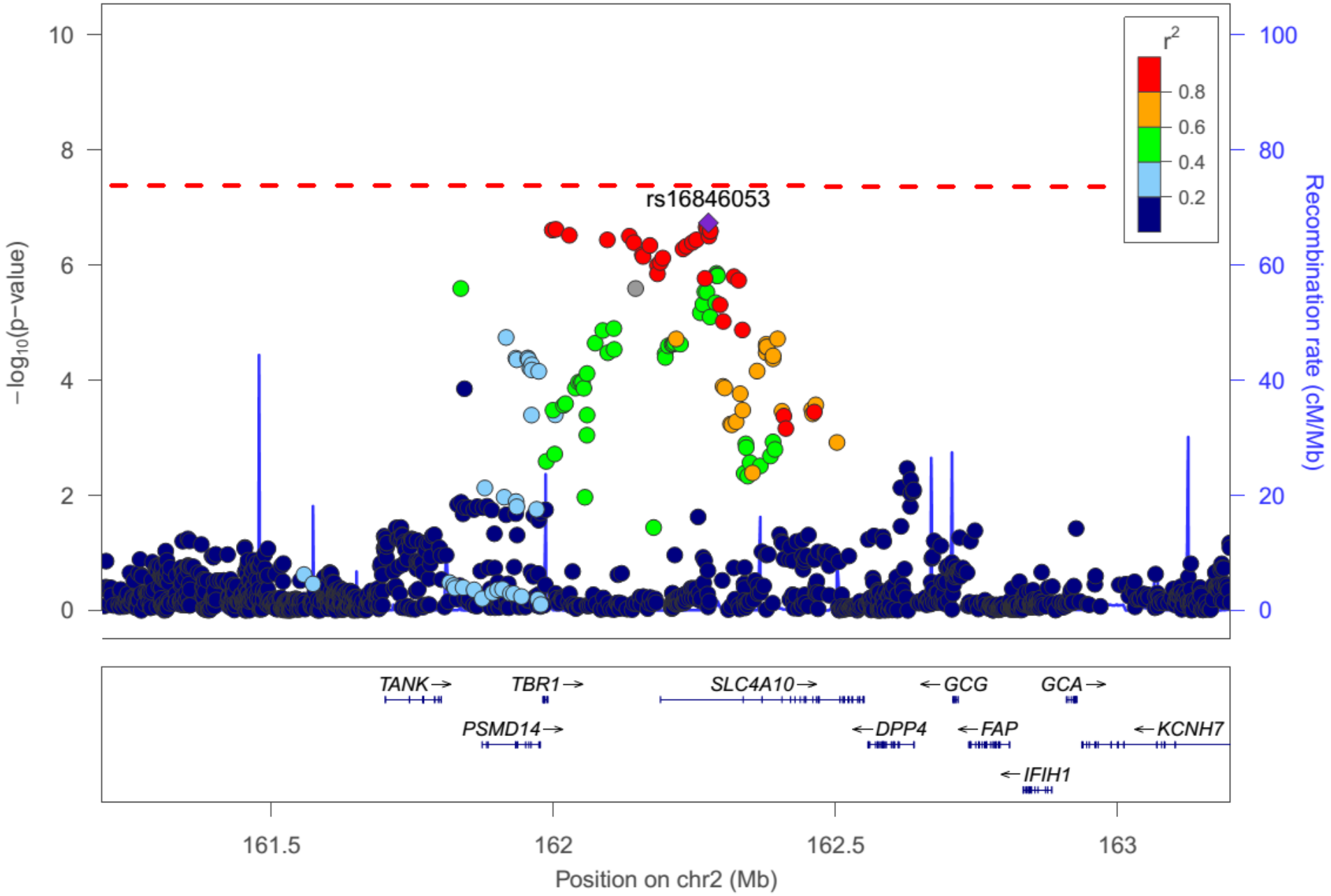
graphical representation of the position-weight matrix for *NFAT5* in JASPAR 2016. Remarkably, the variant was found to affect an *NFAT5* consensus motif. Presence of the minor allele (lower case “g”) reduces the JASPAR score, relative to the major allele (lower case “t”), for the motif (*Lower panel*).



Supplementary Figure 1

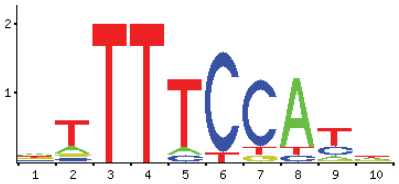


Supplementary Figure 2a



Supplementary Figure 2b

Supplementary Figure 3



Model ID	Model name	Score	Start	End	predicted site sequence	
MA0606.1	NFAT5	8.942	140	149	GtTTTTCACA	**Major**
MA0606.1	NFAT5	6.166	140	149	GgTTTTCACA	**Minor**

Supplementary Figure 4