NFAT5 and *SLC4A10* Loci Associate with Plasma Osmolality

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ABSTRACT

Disorders of water balance, an excess or deficit of total body water relative to body electrolyte content, are common and ascertained by plasma hypo- or hypernatremia, respectively. We performed a two-stage genome-wide association study meta-analysis on plasma sodium concentration in 45,889 individuals of European descent (stage 1 discovery) and 17,637 additional individuals of European descent (stage 2 replication), and a transethnic meta-analysis of replicated single-nucleotide polymorphisms in 79,506 individuals (63,526 individuals of European descent, 8765 individuals of Asian Indian descent, and 7215 individuals of African descent). In stage 1, we identified eight loci associated with plasma sodium concentration at $P<5.0 \times 10^{-6}$. Of these, rs9980 at *NFAT5* replicated in stage 2 meta-analysis ($P=3.1 \times 10^{-5}$), with combined stages 1 and 2 genome-wide significance of $P=5.6 \times 10^{-10}$. Transethnic meta-analysis further supported the association at rs9980 ($P=5.9 \times 10^{-12}$). Additionally, rs16846053 at *SLC4A10* showed nominally, but not genome-wide, significant association in combined stages 1 and 2 meta-analysis ($P=6.7 \times 10^{-8}$). *NFAT5* encodes a ubiquitously expressed transcription factor that coordinates the intracellular response to hypertonic stress but was not previously implicated in the regulation of systemic water balance. *SLC4A10* encodes a sodium bicarbonate transporter with a brain-restricted expression pattern, and variant rs16846053 affects a putative intronic NFAT5 DNA binding motif. The lead variants for *NFAT5* and *SLC4A10* are *cis* expression quantitative trait loci in tissues of the central nervous system and relevant to transcriptional regulation. Thus, genetic variation in *NFAT5* and *SLC4A10* expression and function in the central nervous system may affect the regulation of systemic water balance.

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Abnormal water balance is an excess or deficit of total body water relative to electrolyte content, and it is determined by measuring the plasma sodium concentration.[1] Hyponatremia (relative water excess) is the most common electrolyte abnormality among hospitalized patients[2]; it is highly prevalent among the acutely ill,[3] patients undergoing surgery,[4] and the elderly.[5,6] Severe acute hyponatremia causes brain edema, seizures, and death.[7] Reversible defects in cognition, coordination, and mood occur with even subtle chronic hyponatremia.[8,9]

Water balance is regulated by thirst and aquaporin-2–dependent water reclamation in the kidney collecting duct. Both phenomena are influenced by arginine vasopressin, the secretion of which is governed by brain regions that continually monitor the osmolality of the extracellular fluid compartment. Activation of arginine vasopressin receptor-2 (encoded by *AVPR2*) by circulating arginine vasopressin mediates the insertion of preformed aquaporin-2 into the luminal membrane of principal cells of the kidney collecting duct and is permissive for water reabsorption. The degree of water reabsorption, in turn, affects the concentration of plasma sodium, the principal extracellular cation and determinant of plasma osmolality or tonicity. Changes in systemic osmolality or tonicity are almost immediately transmitted to the intracellular milieu *via* water movement. Within cells, osmoregulation and thus, water balance are governed by the tonicity-responsive transcription factor tonicity-enhancer binding protein[10], also known as the osmotic response element binding protein[11] and NF of activated T cells 5 (NFAT5).[12,13]

Identification of molecular pathways influencing systemic water balance has implications for both understanding the pathogenesis of primary disorders of water imbalance (such as the syndrome of inappropriate antidiuresis[7]) and the development of novel therapies. Exceedingly rare point mutations in *AQP2* (encoding aquaporin-2) and *AVPR2* cause Mendelian disturbances in water balance[14–19]; however, little is known about the genes influencing the interindividual variability of plasma sodium concentration (*i.e.*, water balance) in the general population. We previously showed heritability of plasma sodium concentration at the population level.[20] Genome-wide association study (GWAS)–based approaches have proven to be instrumental in identifying genetic loci associating with a wide variety of diseases and physiologic traits[21] and thus, novel biologic mechanisms[22,23]; however, the only previous GWAS of plasma sodium had limited power and did not detect any significant associations.[24] Other efforts to determine the genetic architecture of water balance have been limited to candidate gene–based studies.[25] We, therefore, performed a GWAS and replication on the phenotype of plasma sodium concentration in 45,889 and 17,637 individuals of European descent, respectively, with follow-up in 8765 and 7215 individuals of Asian Indian and African descent, respectively, and transethnic meta-analysis of replicated single-nucleotide polymorphisms (SNPs) in all 79,506 individuals.

RESULTS

Study Participants

After excluding individuals with high glucose or impaired kidney function (Concise Methods, Supplemental Table 1), 63,526 individuals of European descent from 25 cohorts were included in this analysis: 45,889 individuals from 21 cohorts in stage 1 meta-analysis and 17,637 individuals from four cohorts in stage 2 meta-analysis (Table 1). Furthermore, a total of 7215 individuals from five cohorts of African descent and 8765 individuals from four Asian Indian cohorts were included in the transethnic analyses (Supplemental Table 2). Details of each cohort's study design, genotyping methods, and quality control criteria are shown in Concise Methods and Supplemental Tables 3 and 4. Plasma sodium and glucose concentrations were within expected ranges in all cohorts (Table 1).

Stage 1 Meta-Analysis of European Descent Studies

In stage 1 meta-analysis, there was little evidence of population stratification as evidenced by the quantile-quantile plot (Supplemental Figure 1) and the low genomic inflation factor λ=1.02 with study-specific inflation factors ranging from 0.9 to 1.04. Eight SNPs met the prespecified criteria for follow-up in stage 2 meta-analysis ($P<5 \times 10^{-6}$), with minimum $P=1.9 \times 10^{-7}$. These SNPs, detailed in Table 2, showed no relevant heterogeneity ($I^2 \leq 30\%$) and good imputation quality, except for rs6565990 at the *GALR1* locus (Supplemental Table 5). Figure 1 shows the $-\log10\ P$ value (Manhattan) plot, and Supplemental Tables 6 and 7 list all SNPs associated with plasma sodium concentration with $P<1 \times 10^{-5}$.

Stage 2 Meta-Analysis of European Descent Studies

In stage 2 meta-analysis, the minor G allele (frequency =0.15) of rs9980 in the *NFAT5* locus on chromosome 16 showed a direction-consistent significant association with higher plasma sodium concentration of similar magnitude as in stage 1 meta-analysis (β=0.06, one-sided $P=3.1 \times 10^{-5}$; significance threshold by Bonferroni method: $P<0.01$). In the combined meta-analysis of stages 1 and 2 cohorts, the association of the rs9980 minor G allele (frequency =0.14) with higher plasma sodium concentration values was genome-wide significant (β=0.06 for each copy of the minor G allele, $P=5.6 \times 10^{-10}$) (Supplemental Figure 2A, Table 2).

The minor allele G (frequency =0.10) of rs16846053 in the *SLC4A10* locus on chromosome 2 (Supplemental Figure 2B) was nominally associated with plasma sodium, and the direction of effect was consistent with stage 1 results (one-sided P=0.04). The combined stages 1 and 2 P value was lower than stage 1 results but did not reach strict genome-wide significance ($P=6.7 \times 10^{-8}$) (Table 2). Nonetheless, some have advocated for a more lenient genome-wide significance threshold, especially among more recently founded populations.[26]

The remaining SNPs selected for replication in stage 2 did not replicate (Table 2). However, although the SNP rs6565990

at the *GALR1* locus showed only a near-significant *P* value in stage 2 replication (one-sided $P=0.06$), the stage 2 replication meta-analysis effect estimate was direction consistent with stage 1 meta-analysis, and the *P* value of the stages 1 and 2 combined meta-analysis ($P=3.0 \times 10^{-7}$) was lower than that of the stage 1 meta-analysis ($P=1.5 \times 10^{-6}$). This SNP had poor imputation quality (Supplemental Table 5) and was available in only two studies with a sample size of $n=2912$ in stage 2 replication, thus limiting the power of the analysis.

Transethnic Analyses

In transethnic meta-analysis combining the summary statistics of a total of 79,506 individuals of European, African, and Asian Indian ethnicity, rs9980 at *NFAT5* showed direction-consistent genome-wide significant association with plasma sodium concentration across all ethnicities ($\beta=0.06$ for each copy of the minor G allele, $P=5.9 \times 10^{-12}$), with similar effect sizes in each studied ethnicity (Table 3). Results of our top SNPs ($P<10^{-5}$) for the individual African ancestry and Asian Indian cohorts meta-analyses are shown in Supplemental Tables 8 and 9, respectively.

Bioinformatic Characterization of Associated Loci

rs9980/NFAT5 Locus

NFAT5 (Supplemental Figure 2A) encodes the ubiquitously expressed tonicity-responsive transcription factor that serves as master regulator of intracellular osmoregulation. The 3′ untranslated region of *NFAT5*, containing the lead variant rs9980 (Supplemental Figure 2A), confers tonicity-dependent regulation *via* miRNA-mediated effects on mRNA stability and protein translation.[27–30] In addition, a SNP in strong linkage disequilibrium (LD) with rs9980, rs7193778 ($r^2=0.90$, $D'=1.0$, within a large LD block), is significantly associated with plasma sodium concentration in stage 1 meta-analysis (minor allele C frequency =13%, $\beta=0.05$, $P=4.5 \times 10^{-6}$,) (Supplemental Figure 2A, Supplemental Table 6) and resides in the midst of a heavily ENCODE-annotated putative superenhancer region for *NFAT5* (Figure 2, Supplemental Figure 3). A superenhancer is a group of closely spaced or even overlapping enhancers exhibiting high levels of transcription factor binding in chromatin immunoprecipitation–based approaches.[31] This 3-kb region approximately 35 kb upstream of the *NFAT5* transcriptional start site (TSS) is spanned by three dense peaks of chromatin modification emblematic of a transcriptional enhancer. Specifically, both H3K27Ac (Figure 2) and H3K4me1 (not shown) histone modifications are heavily enriched in the vicinity of this variant in ENCODE-tested cell lines. The putative superenhancer also encompasses two long DNaseI-hypersensitive regions present in 92 and 118 of 125 ENCODE-tested cell lines (Figure 2B). Moreover, ENCODE transcription factor ChIP-Seq experimental data showed binding of 115 of 161 ENCODE-tested transcription factors over the region (ENCODE data displayed in the UCSC Genome Browser) (Figure 2B). Because enhancers regulate spatiotemporal and tissue-specific gene expression, it is noteworthy that both rs9980 and rs7193778 are *cis* eQTLs for *NFAT5* expression in cerebellum and temporal cortex (HaploReg v4.0[32] citing Zou *et al.*[33]).

Ancillary data support functional relevance of rs7193778 to the CNS and glial/astrocytic cells in particular. *In silico* comparison of putative transcription factor binding sites (JASPAR 2016[34]; http://jaspar.genereg.net) affected by rs7193778 primarily identified motifs for members of the sex-determining region Y-box (*SOX*) family of transcription factors (*SRY* and *SOX2*, *-3*, *-5*, *-6*, and *-17*). Of these, *SOX2*, *-3*, *-5*, and *-6* are enriched in tissue derived from brain and/or glioma (Concise Methods). Furthermore, glial tissue (*i.e.*, astrocytes) have been proposed as the cell type conferring central sensing of extracellular sodium concentration,[35,36] in contrast to the neuronal sensing of systemic osmolality.[37,38] DNaseI-hypersensitive regions (*i.e.*, open chromatin) reported in ENCODE data further support a glial cell–specific effect for this regulatory region. Although most such regions are detected across a large number of cell types, a short DNaseI-hypersensitive region immediately upstream of rs7193778 (indicated by 2 in Figure 2C) was detected in only two tissues—the HA-sp astrocytic (glial) cell line and pancreatic islets (Figure 2C). The Regulatory Elements Database (http://dnase.genome.duke.edu/index.php) identified a DNase site (DHS1020946) physically crossing the variant (Figure 2C, orange bar) and mapping to a cluster (self-organizing map [SOM] Cluster: 977) of similar regions preferentially operative in astrocytes.[39] The SOM designation refers to SOM-based clustering of DNase sites according to their profile of DNaseI hypersensitivity across diverse cell types.[39]

The biology of other genes in this locus (Supplemental Figure 2A) (*NQO1*, *NOB1*, *WWP2*, and *CLEC18A*) is summarized in Supplemental Table 7.

rs16846053/SLC4A10 Locus

The lead variant in *SLC4A10*—a gene encoding a brain-specific member of the sodium-bicarbonate transporter family—is intronic; however, the association signal spans the entire *SLC4A10* gene as well as an additional 0.3 Mb 5′ of the gene (Supplemental Figure 2B). Importantly, this SNP, like rs9980 in *NFAT5*, is a *cis* eQTL for *SLC4A10* expression in cerebellum and temporal cortex (Haploreg v4.0[32] citing Zou *et al.*[33]). Transcriptome data in the public domain (*e.g.*, Unigene, BioGPS, and Epigenome Roadmap) support a heavily brain-enriched expression pattern for *SLC4A10*. Of 127 cell lines and tissues represented in the WashU Epigenome Browser implementation of the Roadmap Epigenomics Project data (http://egg2.wustl.edu/roadmap/web_portal/), *SLC4A10* expression is detectable *via* RNA-Seq in only hippocampus, fetal brain, cultured neurospheres derived from cortex and ganglion eminence, and pancreatic islets (data not shown). Although intronic, the vicinity of rs16846053 is annotated as an active TSS or TSS flanking region in T cells and a number of other tissues. It is annotated as weakly transcribed in brain hippocampus and only in this tissue. Therefore, a novel variant of *SLC4A10* may be expressed in the CNS. Moreover, the DNaseI-hypersensitive regions upstream of

Table 1. Study participant characteristics

Study	Sample Size, *n*	Age, yr	Sex, % Women	Plasma Sodium, mEq/L	eGFRcrea, ml/min per 1.73 m^2	Plasma Glucose, mg/dl
Stage 1 discovery						
Amish studies	1131	48.1 (15.0)	49.8	139.2 (2.2)	94.1 (16.3)	91.1 (14.0)
BLSA	594	69.6 (15.1)	42.9	141.3 (3.0)	72.5 (17.5)	90.1 (13.2)
ARIC: Europeans	8535	54.1 (5.7)	53.2	141.0 (2.3)	90.0 (17.3)	99.8 (11.0)
FHS	2494	48.1 (15.0)	49.8	139.2 (2.2)	94.1 (16.3)	91.1 (14.0)
COLAUS	2816	58.3 (10.4)	53.5	142.6 (1.8)	81.1(15.4)	107.2(21.7)
MrOS	3909	73.8 (5.9)	0	141.5 (2.6)	77.1 (16.4)	100.9 (12.5)
MICROS	1146	45.2 (16.0)	56.5	139.0 (1.9)	91.2 (16.9)	84.1 (11.7)
KORA F3	1425	62.2 (10.1)	51.7	142.9 (4.4)	80.2 (14.4)	102.4 (16.1)
KORA F4	1671	60.7 (8.8)	52.4	139.1 (2.6)	81.6 (14.5)	98.1 (12.6)
GENOA: Europeans	1064	59.0 (10.2)	43.8	138.2 (2.1)	64.4(13.6)	100.4 (14.0)
InCHIANTI	1142	67.9 (15.6)	55.7	141.8 (2.5)	79.1 (17.9)	90.2 (14.6)
LOLIPOP_EW610	881	55.8 (9.8)	27.2	140.4 (2.1)	74.4 (12.5)	94.1 (11.9)
LOLIPOP_EWA	546	54.1 (10.4)	13.3	140.5 (2.7)	82.9 (19.5)	94.6 (13.6)
LOLIPOP_EWP	574	55.4 (9.3)	0	140.5 (2.5)	81.6 (13.0)	96.7 (13.9)
LURIC	2579	62.2 (10.8)	29.7	141.4 (2.8)	83.4 (17.1)	103.5 (15.3)
Ogliastra genetic park Talana study	691	50.2 (19.1)	58.5	139.1 (2.4)	72.6 (13.6)	90.6 (12.1)
Ogliastra genetic park study	382	54.1 (13.5)	0	137.2 (3.0)	75.2 (13.1)	99.6 (14.6)
SHIP	3767	48.8 (16.1)	51.7	138.8 (2.8)	80.5 (14.1)	96.3 (14.5)
SHIP-TREND	979	50.0 (13.6)	56.2	139.3 (2.2)	91.8 (20.1)	96.8 (11.3)
The Rotterdam study	3415	69.2 (8.7)	63	140.2 (3.3)	78.0 (16.3)	109.8 (17.9)
SARDINIA	6148	46.1 (17.7)	57.4	141.7(2.6)	100.5 (26.12)	88.8 (12.5)
Stage 2 replication						
DIACORE	1151	65.8 (8.6)	42.3	139.5 (2.8)	78.5 (23.5)	111.3 (21.0)
FINCAVAS	1761	60.2 (12.1)	37.5	139.8 (2.6)	88.7 (20.7)	105.9 (15.3)
LifeLines Cohort Study	12,270	48.8 (11.4)	58.2	141.7 (1.9)	90.3 (16.3)	91.6 (15.7)
MESA	2455	62.6 (10.3)	47.4	147.2 (3.8)	74.2 (14.3)	91.1 (21.4)

Data are given as mean (SD) or percentage.

the gene disproportionately map to cell lines of CNS origin (*e.g.*, SK-N-MC neuroblastoma cells and HA-h, HA-sp, and HAc astrocytic cells). Intriguingly, the lead variant at this locus affects a canonical NFAT5 DNA binding motif as determined *via* unbiased position-weight matrix scanning of the genomic context; moreover, the minor allele reduces the fidelity score for this predicted NFAT5 binding site (Supplemental Figure 4). An additional variant at this locus, rs16845945, maps to the *SLC4A10* proximal promoter approximately 200 bp upstream of the *SLC4A10* TSS. Consistent with this role, promoter-associated H3K4me3 histone modification pattern is observed in brain and pancreatic tissue (data not shown).

The known biology of additional genes in this locus (Supplemental Figure 2B) is summarized in Supplemental Table 7.

DISCUSSION

In this GWAS meta-analysis of systemic water balance, we have identified common variants in *NFAT5* associating with plasma sodium concentration in individuals of European descent, which are further supported by tentative validation in transethnic meta-analysis. Genomic functional annotation data implicate a role for genetic variation at *NFAT5* and *SLC4A10*, the latter a locus with nominally significant association, in regulating systemic water balance through expression-level effects in glial tissue of the central nervous system. These data are the first to implicate these genes in the regulation of systemic water balance.

The NFAT5 transcription factor coordinates the response to osmotic stress at the cellular level. It transactivates genes coding for aquaporins that are permissive for water movement, and for proteins that import or synthesize osmotically protective intracellular solutes.[40] NFAT5 also increases expression of heat shock proteins,[41] molecular chaperones that stabilize protein conformation against the denaturing effect of increased intracellular ionic concentration.[42] In addition, NFAT5 participates in the immune cell response to the varying sodium content within the skin and subcutaneous tissues.[43] The novel role for genetic variation in *NFAT5* in systemic osmoregulation (*i.e.*, water balance) is likely mediated at the level of gene expression.[40] The lead variant, rs9980, functions as a *cis* eQTL for *NFAT5*, such as has been observed for other disease-associated SNPs.[44–47] This variant resides within the 3′ untranslated region, a known site of *NFAT5* regulation by osmotic stress.[27–30] *NFAT5* function is also transcriptionally regulated by changes in tonicity.[11,27,48] Importantly, the lead variant is in LD with variant rs7193778, which resides within a superenhancer region upstream of the TSS. This gene region exhibits

Table 2. Genetic association analysis results in cohorts of European descent

SNP Identification	Chromosome	Position (Build 36)	Locus	Effect/ Other Allele	Stage 1 Discovery (*n*=45,889)			Stage 2 Replication (*n*=17,637)			Stages 1 and 2 Combined (*n*=63,526)			
					Effect Allele Frequency	*β*	*P* Value	Effect Allele Frequency	*β*	One-Sided *P* Value	Effect Allele Frequency	*β*	*P* Value	*N*
rs16846053	2	162274291	*SLC4A10*,[a] *DPP4*	G/T	0.10	0.06	1.86×10^{-7}	0.10	0.03	0.04	0.10	0.05	6.74×10^{-8}	63,524
rs753628	3	196040762	*XXYLT1, LSG1, TMEM44*	A/G	0.37	0.04	1.75×10^{-6}	0.38	0.01	0.24	0.37	0.04	2.87×10^{-6}	60,091
rs12677356	8	23696389	*STC1, SLC25A37*	T/G	0.05	0.09	1.41×10^{-6}	0.05	−0.01	0.58	0.05	0.08	4.64×10^{-6}	51,254
rs10774613	12	110030548	*CUX2*,[a] *CCDC63, ATXN2*	T/C	0.57	0.03	3.77×10^{-6}	0.52	0.02	0.13	0.56	0.03	2.40×10^{-6}	60,095
rs17074418	13	29675855	*KATNAL1*,[a] *HMGB1, UBL3, SLC7A1*	T/C	0.92	0.07	1.77×10^{-6}	0.94	0.02	0.21	0.93	0.05	4.97×10^{-6}	63,523
rs9980	16	68294969	*NFAT5*,[a] *NQO1, NOB1, CYB5B*	G/C	0.14	0.05	2.40×10^{-6}	0.15	0.06	3.05×10^{-5}	0.14	0.06	5.55×10^{-10}	60,108
rs11662617	18	13243598	*LDLRAD4*,[a] *CEP192, RNMT*	A/G	0.48	−0.04	2.02×10^{-6}	0.48	0.01	0.72	0.48	−0.02	2.06×10^{-4}	54,921
rs6565990	18	73350561	*GALR1, MBP*	T/G	0.49	0.05	1.51×10^{-6}	0.51	0.05	0.06	0.50	0.05	2.96×10^{-7}	39,236

The gene nearest the SNP is listed first. Coded allele equals effect allele. The SNPs rs12677356 on chromosome 8 and rs6565990 on chromosome 18 were not available in the LifeLines Cohort Study, and proxy SNPs with $r^2 > 0.6$ could not be identified. The SNPs rs11662617 and rs6565990 (both on chromosome 18) were not available in the MESA, and proxy SNPs with $r^2 > 0.6$ could not be identified. Because only directly genotyped SNP data were available from the MESA, we analyzed three proxy SNPs for stage 2 meta-analysis. For rs16846053, we used the summary statistics of rs12476631 (chromosome 2, position 162,275,182, distance =891 bp, $r^2 = 0.91$, $D' = 1$ with rs16846053). For rs9980, we analyzed rs39999 (chromosome 16, position 68,211,197, distance =83,772 bp, $r^2 = 1$, $D' = 1$ with rs9980), and for rs17074418, we analyzed rs1023104 (chromosome 13, position 29,675,301, distance =554 bp, $r^2 = 1$, $D' = 1$ with rs17074418).

[a]The gene nearest the SNP if the SNP is located in the gene.

remarkable enrichment for enhancer-specific histone modification, including H3K4me1 histone methylation consistent with enhancer function,[49] H3K27ac histone acetylation emblematic of active (in contrast to poised) enhancers,[50] and robust binding of a broad array of transcription factors (Figure 2). Our findings are consistent with the frequently observed effect of functional genetic variants on enhancer regions in disease pathogenesis[51–53] and the expression of quantitative traits.[54]

Bioinformatic data are consistent with a potential glial/astrocytic locus of action for *NFAT5* variant rs7193778 and the systemic sensing of plasma sodium concentration. Although neurons of the hypothalamus and lamina terminalis are known to have osmosensing roles,[37,38] a role for non-neuronal cells in the CNS has also been proposed. Specifically, a subset of glial cells (astrocytes) senses plasma sodium concentration *via* the Na_x channel.[35,36] Interestingly, a small DNaseI-hypersensitive region immediately upstream of rs7193778 in *NFAT5* is detected in astrocytes as one of only two of 125 ENCODE-tested cell lines. Moreover, the putative transcription factor binding sites affected by rs7193778 include those for *SOX* family members with expression highly enriched in glial tissue and glioma. Because enhancer-associated epigenomic marks are over-represented in trait-relevant tissues,[55] it is plausible that rs7193778 is an eQTL for *NFAT5* in glial cells and that the central sensor of plasma sodium concentration may reside in this tissue.

SLC4A10 encodes a brain-specific member of the sodium-bicarbonate transporter family, making this gene a biologically plausible participant in systemic water balance, despite lack of formal replication in stage 2 meta-analysis. The nominally significant signal at *SLC4A10* thus similarly implicates CNS glial tissue in systemic osmosensing. The protein is expressed predominantly in brain, and epigenomic functional annotations disproportionately map to brain and in particular, astrocytic, cell lines. Therefore, similar to the case for *NFAT5*, a glial cell–specific site of action for *SLC4A10* in central osmoregulation is plausible. Furthermore the lead variant at *SLC4A10* affects an intronic putative *NFAT5* DNA binding motif. Moreover, the variant affects the position weight matrix–defined fidelity score for the motif. Intronic enhancers have long been recognized,[56] including examples in genes coding for membrane transport proteins.[57–59] Notably, other members of the SLC4 family participate in volume regulation at the cellular level.[60]

Intriguingly, rs7193778, in LD with the lead variant at the *NFAT5* locus, has previously been identified in a meta-GWAS on plasma uric acid concentration.[61] Plasma uric acid level is influenced by systemic water balance and is often used to inform the diagnosis of a water-excess state, particularly in the context of the syndrome of inappropriate antidiuretic hormone.[62–64]

The minor allele of the *NFAT5* SNP rs9980 associates with hypertonicity and thus, a reduction in either the central sensing of water loss or renal water conservation, with similar effect sizes observed in all ethnicities studied. Thus, the relative absence of this variant in African ancestry (MAF 0.03 versus 0.14 in European populations) may hint at potential selection pressure in environments where chronic or seasonal

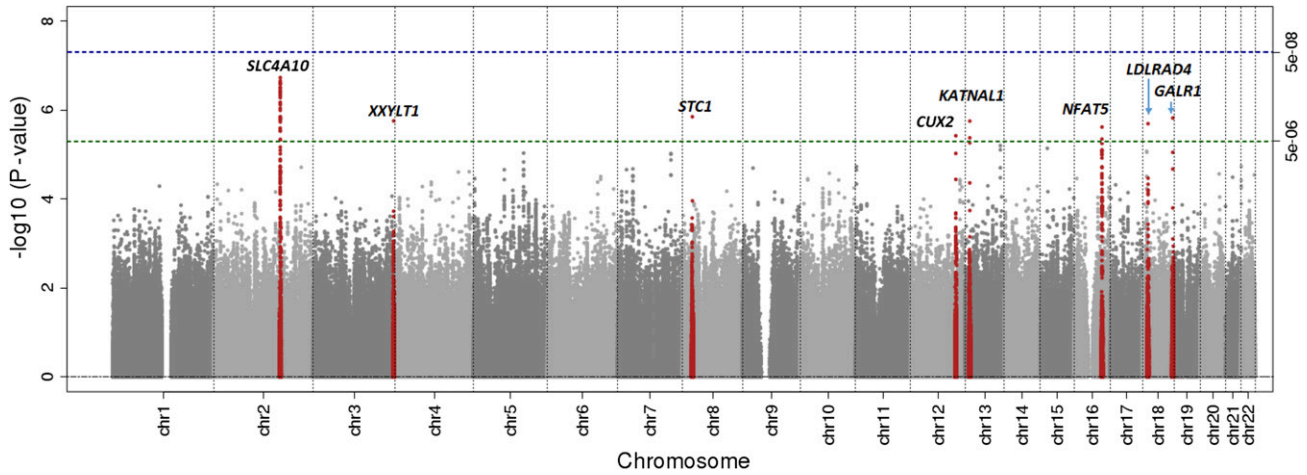

Figure 1. Stage 1 genome-wide association −log10 *P* value (Manhattan) plot identifies candidate loci. The green dotted line indicates the *P* value threshold for following SNPs in stage 2 meta-analysis ($P<5 \times 10^{-6}$). The blue dotted line indicates the genome-wide significance threshold ($P<5 \times 10^{-8}$).

water scarcity might occur. Similarly, the minor allele of rs16846053 in *SLC4A10* was under-represented in African ancestry (MAF 0.02 versus 0.10 in European populations).

Strengths of our work include the large sample size, the unbiased approach to identifying associated genetic loci by GWAS, and the bioinformatic characterization of the replicated loci. However, some limitations warrant mention. First, modest stage 2 replication and transethnic look-up sample size may have limited our ability to replicate additional loci. Second, the phenotype is based on a single measurement, potentially reducing statistical power. Third, the power for replication may have been limited by the poor imputation quality at the *GALR1* locus and the limited sample size at the *STC1* and *LDLRAD4* loci. Fourth, although the effect direction of the association of rs9980 with sodium was consistent across all analyzed ethnicities, the association was only borderline significant in Asian Indians and was not significant in those of African descent, possibly owing to limited power. Fifth, we did not directly replicate the functionally intriguing variant at the *NFAT5* locus (rs7193778), because it did not meet our *a priori* criteria for replication (*i.e.*, not independent from lead signal) and is in strong LD with the rs9980 variant ($D'=1$ and $r^2=0.9$). Finally, although we performed in-depth bioinformatic characterization of the identified loci, leading to important insights into potential mechanisms, the causal variant remains unknown, and we have not experimentally assessed the effects of the identified gene variants on gene function.

In summary, in this first well powered GWAS on plasma sodium concentration—the clinically measurable parameter of systemic water balance—we have identified genetic variants in *NFAT5* in individuals of European descent with validation by transethnic meta-analysis. Additionally, we identified a nominally significant association with an *SLC4A10* gene variant that may exert its effect through an intronic enhancer by altering its binding affinity for NFAT5. Our results and bioinformatic characterization point to a previously unknown role of genetic variation at *NFAT5* and *SLC4A10* in the regulation of systemic water balance *via* actions on gene expression within the central nervous system.

CONCISE METHODS

Data Management

An analysis plan, detailing phenotype derivation, exclusion criteria, genome-wide association testing, and data file formatting was distributed to all participating studies. Study-specific results files were uploaded to a central server for subsequent standardized central quality control and meta-analysis.[65]

Phenotype Definition

Plasma sodium concentration is the principal determinant of plasma osmolality. Plasma glucose concentration also contributes to plasma osmolality, and when elevated, it will obligate water entry into the intravascular space and render the plasma sodium concentration less reflective of true plasma osmolality. Thus, individuals with plasma glucose levels >150 mg/dl at the time of plasma sodium measurement

Table 3. Genetic association results of transethnic meta-analysis of rs9980 at *NFAT5*

Ethnic Group	Sample Size	Effect Allele	Other Allele	Effect Allele Frequency	β	*P* Value	Heterogeneity I^2, %
European descent	60,108	G	C	0.14	0.06	5.6×10^{-10}	0
Asian Indian	8760	G	C	0.12	0.05	0.02	0
African descent	5185	G	C	0.03	0.05	0.40	0
Transethnic	74,053	G	C	0.14	0.06	5.9×10^{-12}	27

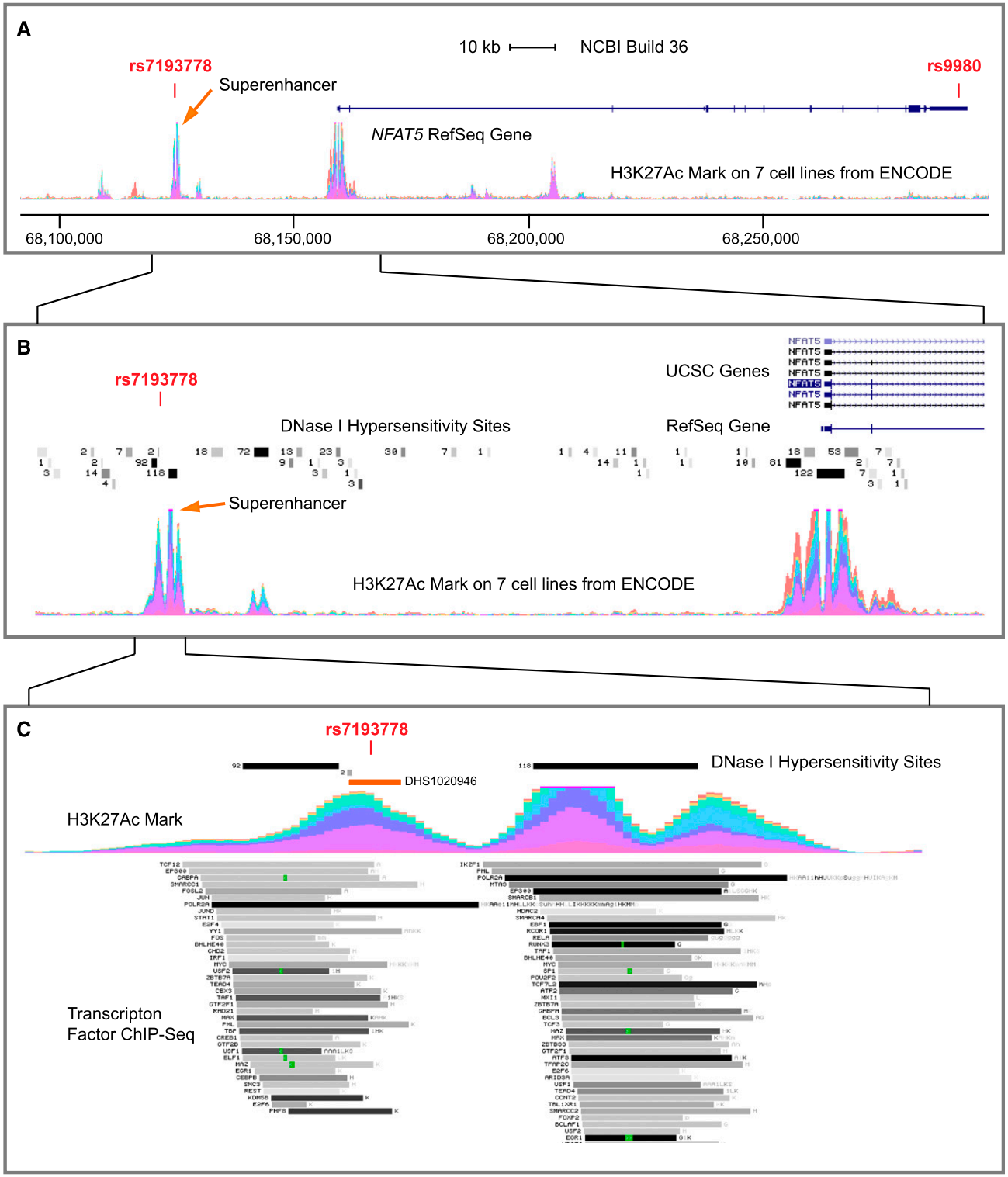

Figure 2. Sequence context of rs9980 and rs7193778 in the *NFAT5* region coincides with functional genomic annotation. Depicted are ENCODE data displayed in the UCSC Genome Browser. (A) shows *NFAT5* (exons connected by a blue line) and H3K27ac histone acetylation in the seven ENCODE cell lines (chromosome 16: 68087500–68307500 of human reference genome build NCBI build 36/hg18 and ENCODE histone modification track). Each color represents one of seven cell lines; peak height is the sum of activity in all cell types and proportional to the levels of enrichment of the H3K27ac histone mark across the genome as determined by ChIP-Seq assays. H3K27ac peaks coincide with the *NFAT5* promoter region and the vicinity of rs7193778. SNP rs9980 resides in the 3′ untranslated region. (B) illustrates an expanded view of approximately 40 kb upstream of the *NFAT5* TSS and depicts the H3K27ac triple peak of the *NFAT5* superenhancer as well as the locations of ENCODE/Epigenome Roadmap experimentally confirmed DNaseI-hypersensitive

were excluded. For plasma glucose concentration <150 mg/dl, we applied the formula of Katz: transformed sodium = plasma sodium (milliequivalents per liter) + (0.016 × (glucose [in milligrams per deciliter] −100)).[66] Transformed sodium was the trait used for the GWAS analysis. Because advanced CKD may impair water excretion, we excluded subjects with very low kidney function. We, thus, calculated eGFR on the basis of serum creatinine (eGFRcrea) using the four-variable Modification of Diet in Renal Disease Study equation[67] and excluded those with eGFRcrea below the age-specific mean minus 2 SD. Subjects were also excluded if they were not of the predominant ethnicity in the cohort or had missing phenotypic information.

Statistical Methods

Study Design, Genotypes, and Genotype Imputation

Details of each cohort's study design are shown in Supplemental Table 3. Details of each cohort's genotyping methods and quality control criteria are provided in Supplemental Table 4. In stage 1, 20 studies each imputed approximately 2.5 million SNPs on NCBI build 36 with external European haplotype reference samples (HapMap release 22). One study used the HapMap release 21 reference haplotypes on NCBI build 35 (KORA F3). In stage 2, one study (the LifeLines Cohort Study) contributed association statistics on the basis of genotypes imputed with HapMap CEU release 24 haplotypes on NCBI build 36. Two studies (FINCAVAS and DIACORE) in stage 2 imputed genotypes with 1000 Genomes reference haplotypes on GRCh build 37. One study (MESA) contributed association statistics on the basis of genotyped variants annotated on NCBI build 36. We transformed the SNP information of imputed genotypes on NCBI build 35 or GRCh build 37 to NCBI build 36 to match the data with HapMap-imputed genotypes of the other studies.

Studies of individuals of African descent and Asian Indians used cosmopolitan reference haplotypes to reflect the predominant ancestry in the study: two studies of individuals of African descent used the combined CEU and YRI haplotypes from HapMap release 22 on NCBI build 36, one study of individuals of African descent used the haplotypes from the June of 2010 release of the 1000 Genomes project on NCBI build 36 (HUFS), and one study of individuals of African descent used the 1000 Genomes Phase I interim data released in June of 2011 (on GRCh build 37) and transformed SNP information to NCBI build 36. All studies of Asian Indians used the combined HapMap release 22 CEU + CHB + JPT + YRI haplotypes on NCBI build 36. Imputed genotypes were coded as the estimated number of copies of a specified allele (dosage).

GWAS

In each study, standardized residuals were obtained by applying *z*-score transformation on plasma sodium concentration with the covariates sex, age, the interaction of sex with age, and eGFRcrea. GWAS was then performed assuming additive genetic effects using linear regression, with the standardized residuals as the dependent variable and the SNP genotype dosage as the independent variable, including cohort-specific covariates where applicable (*e.g.*, recruitment site and genetic principal components).

Stage 1 Meta-Analysis

A total of 21 studies of European ancestry contributed to the stage 1 meta-analysis. The summary statistics estimated from each cohort's GWAS were combined using inverse variance weighted fixed effects meta-analysis implemented in METAL software.[68] The genomic inflation factor λ[69] was estimated for each study, and genomic control (GC) correction was applied if $\lambda > 1$ (first GC correction). After the meta-analysis, a second GC correction on the aggregated results was applied if $\lambda_{aggregated} > 1$. Between-study heterogeneity was assessed by the I^2 statistic. SNPs were selected for stage 2 meta-analysis if they were available in at least 50% of all studies, they did not show an excess of heterogeneity ($I^2 > 50\%$), and they had a stage 1 discovery meta-analysis $P \leq 5 \times 10^{-6}$. The SNP with the lowest *P* value within a window of ± 1 Mb was selected for stage 2 meta-analysis and defined as the index SNP.

Stage 2 Meta-Analysis

In stage 2, SNPs identified in stage 1 meta-analysis were followed up in four study cohorts of European ancestry using the same analysis protocol as described for stage 1 meta-analysis. If the association statistics of the lead SNP in a susceptibility locus were not available, a proxy SNP with the highest LD and D' was used for the association analysis using the SNAP lookup tool in the HapMap release 22 dataset (https://www.broadinstitute.org/mpg/snap/ldsearch.php).[70] A SNP was considered to have replicated if its effect direction was consistent with stage 1 meta-analysis, it showed a significant one-sided *P* value after Bonferroni correction for multiple testing ($P < [0.05/\text{number of analyzed SNPs in stage 2}]$), and the *P* value of the stages 1 and 2 combined meta-analysis was lower than the stage 1 meta-analysis *P* value.

Genetic Associations in Studies of Individuals of African Descent and Asian Indians

For SNPs replicated in stage 2 meta-analysis, additional validation was sought among individuals of non-European ancestry (*i.e.*, African

sites above the H3K27ac peaks. The darkness of each site is proportional to the maximum signal strength observed in any cell line, and the adjacent numbers indicate numbers of tissues and cell lines in which hypersensitivity was detected (of a total of 125 tested tissues/cells). C illustrates the approximately 3-kb H3K27ac triple peak of the *NFAT5* superenhancer region, depicting rs7193778 relative to H3K27ac marks, DNaseI-hypersensitive sites, and a partial list of the 115 ChIP-Seq–confirmed transcription factor binding sites (of 161 tested) as gray boxes. The darkness of the boxes is proportional to the maximum signal strength observed in any cell line contributing to the cluster. The small DNaseI-hypersensitive region immediately 5′ of rs7193778 (marked 2) was detected in only astrocytes of the CNS (spinal cord; HA-sp cell line) and pancreatic islets (not shown: expression of *SLC4A10* is restricted to CNS and pancreatic islets). A DNaseI-sensitive region (DHS1020946) identified through the Regulatory Elements Database (http://dnase.genome.duke.edu/index.php; in the text) crosses the variant (orange bar) and maps to a cluster of motifs operative to astrocytes.

descent and Asian Indian cohorts) using the same protocols for GWAS and meta-analysis as described for the cohorts of European ancestry. Replication was defined by a significant one-sided *P* value after Bonferroni correction for multiple testing ($P<0.05$ divided by the number of replicated SNPs). There was little inflation in the genome-wide association meta-analysis of subjects of African and Asian ancestry ($\lambda=1.02$ in both analyses). Supplemental Tables 8 and 9 provide the summary statistics of all SNPs associated with sodium with a $P<10^{-5}$ within each ethnicity.

Transethnic Meta-Analysis

We performed a transethnic meta-analysis of replicated SNPs combining summary statistics from studies of individuals of European, African, and Asian Indian descent and following the same analysis protocol as described for stage 1 meta-analysis in individuals of European descent.

Visualization of LD Blocks

To illustrate the amount of LD between highly correlated variants, we visualized LD blocks with the R package snp.plotter (https://cran.r-project.org/web/packages/snp.plotter) with the individual genotype data of the population-based KORA F4 Study ($n=1814$).

Functional Characterization of Replicated Loci

We evaluated SNPs at replicated loci for potential relevance to gene expression by examining for overlap with functionally annotated genomic regions from the ENCODE[71] and Epigenomics Roadmap[55] projects. The former was queried *via* the UCSC Genome Browser, whereas the latter was accessed through the WashU Epigenome Browser (http://epigenomegateway.wustl.edu/) and RoadMap Epigenome Browser (http://epigenomegateway.wustl.edu/browser/roadmap/). SNPs in LD with lead SNPs ($r^2>0.8$)—and their corresponding functional annotations in ENCODE and the RoadMap Epigenome Project—were identified through HaploReg v4.0[32] citing Zou *et al.*[33] and RegulomeDB.[72] Genomic functional annotations in these public resources included the presence of DNase I-hypersensitive sites, chromatin modification (*e.g.*, histone methylation and acetylation), transcription factor binding, RNA-Seq expression data, and algorithmically assigned chromatin functional state (*e.g.*, active TSS, strong transcription, and enhancer region[55]; http://egg2.wustl.edu/roadmap/web_portal/chr_state_learning.html) in over 300 human tissues and cell lines (depending on assay platform). Putative transcription factor binding motifs were identified *via* JASPAR 2016 (http://jaspar.genereg.net/).[34] This resource uses a predefined position weight matrix to identify a potential binding motif and assign a score reflecting the fidelity of the sequence to the canonical motif. As an alternative to the more simplistic consensus sequence, the position weight matrix reflects the frequency of occurrence of each of the four nucleotides at each position in the motif.[73] *In silico* analysis of the *NFAT5* superenhancer in the vicinity of the rs7193778 sequence context ($\pm$50 bp; obtained from dbSNP) in the JASPAR 2016 screen, with the major (*t*) allele, identified 21 putative transcription factor binding sites crossing the variant, of which eight corresponded to SOX family members (SOX2, -3, -5, -6, -10 [$n=2$], and -17 and SRY). Apart from SRY (for which there were no expressed sequence tag (EST) data presented in the UNIGENE EST Profile Viewer), all of these SOX family transcription factors were expressed in brain and 2–28 other tissues (of a total of 45 tissues tested). For SOX2, -3, -5, and -6, brain expression was relatively enriched by up to 20-fold (for SOX3). Enrichment was quantified as normalized brain EST counts/total normalized EST counts for all 45 tissues. Expression in glioma was enriched by 2.5- to 25-fold for SOX2, -3, -6, and -10 (normalized glioma EST counts/total normalized EST counts for all 26 tumor types tested). EST counts were obtained from the UNIGENE EST profile viewer (*e.g.*, http://www.ncbi.nlm.nih.gov/UniGene/clust.cgi?UGID=155082&TAXID=9606&SEARCH=sox3).

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DISCLOSURES

None.

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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

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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 ($p<5x10^{-8}$).

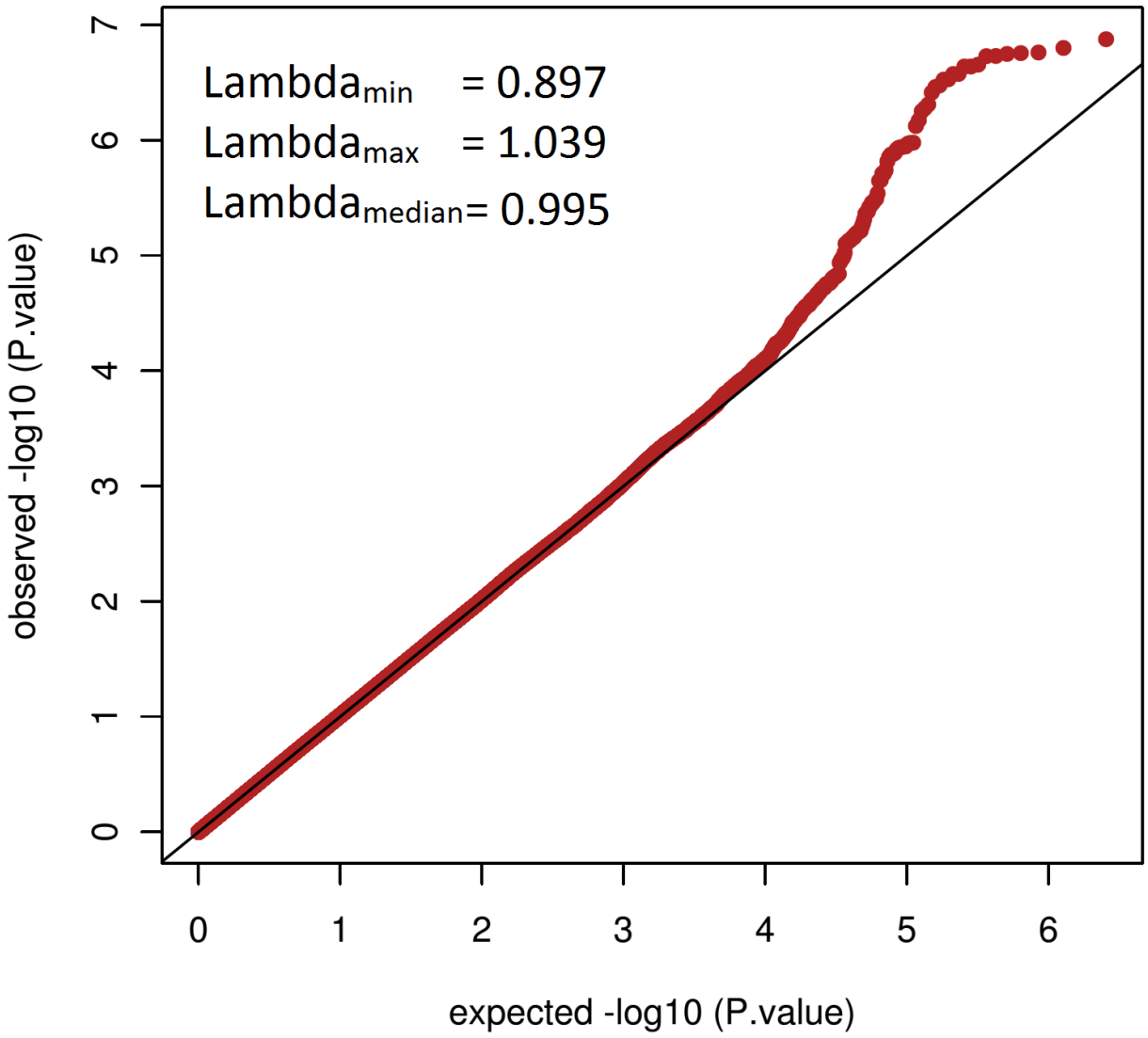
Supplementary Figure 2a: *NFAT5* locus in individuals of European descent (stage 1 GWAS meta-analysis results). The SNP rs7193778 is the SNP implicated by functional genomic annotation that is in near- perfect linkage disequilibrium with rs9980.

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

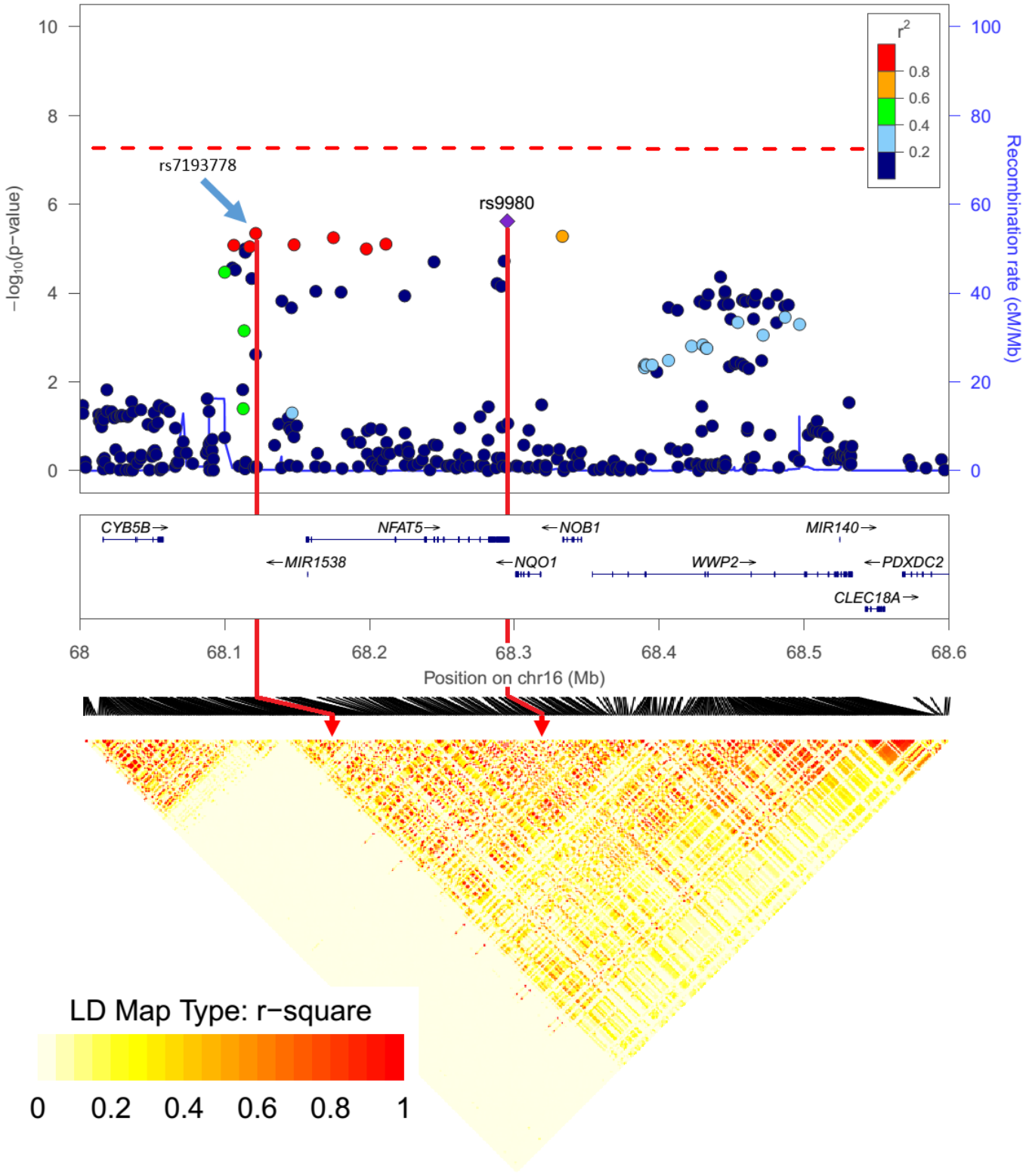
Supplementary Figure 3: Relation of the *NFAT5* SNP rs7193778 to H3K27ac histone acetylation in 107 tissues and cell lines in the Roadmap Epigenome Project.
Tissues exhibiting the most closely related H3K27ac histone acetylation pattern over the depicted genomic interval in the vicinity of rs7193778 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*,

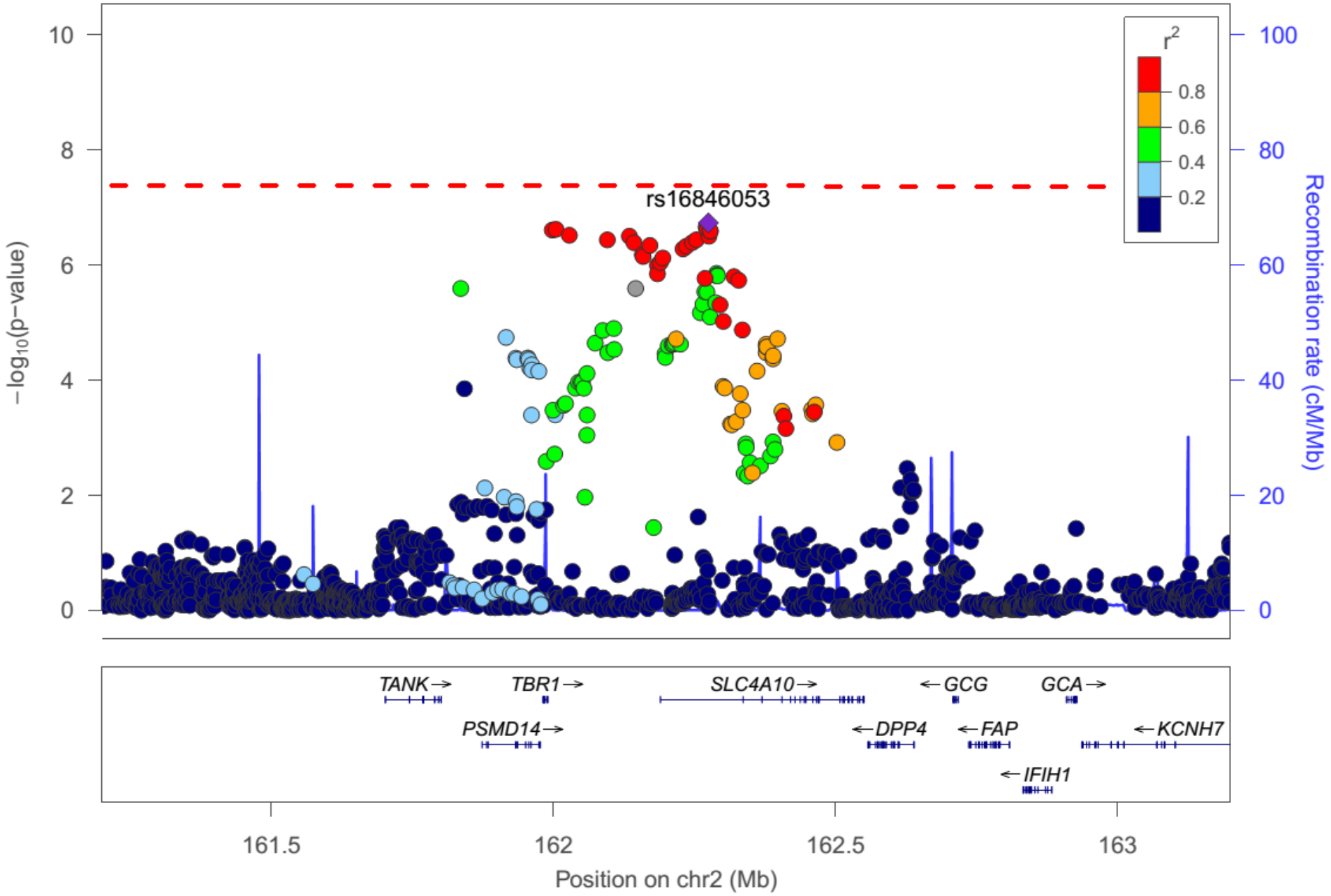
graphical representation of the position-weight matrix for *NFAT5* in JASPAR 2016. Remarkably, the variant was found to affect an *NFAT5* consensus motif. Presence of the minor allele (lower case “g”) reduces the JASPAR score, relative to the major allele (lower case “t”), for the motif (*Lower panel*).



Supplementary Figure 1

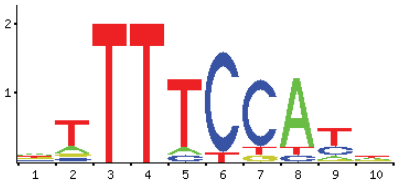


Supplementary Figure 2a



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