**Sodium and Potassium Intake in Multiethnic Populations:
Associations with Genes and Blood Pressure**

by

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**DEDICATION**

I dedicate this dissertation to my family and friends:

To my husband – Wonjoo Yun, you are my best decision that I've ever made in my life. Thanks for all your sacrifice during my Ph.D. period. I couldn't have done this without you. I am looking forward to opening our new chapter with our baby boy, TumTum.

To my family – mom, Seoung Sook Jae, you are my hero and the most beautiful person. I am always your biggest fan. Dad, Jaeho Kho, thanks for your sense of humor that made me laugh during my Ph.D. life. I love you both! Parents-in-law, thank you for your support along the way. I always feel lucky to have you both who always provide me with encouragement and inspiration to purse and complete my Ph.D.

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## ABSTRACT

Over 80 million adults in the United States have hypertension, one of the leading risk factors for cardiovascular disease (CVD) and stroke. Sodium and potassium intake are essential dietary components, but excess sodium intake and insufficient potassium intake are established risk factors for hypertension and CVD. To improve and target interventions to reduce the burden of hypertension and CVD, it is critical to identify factors that influence sodium and potassium intake. The overarching goal of this dissertation is to provide insight into the genetics of sodium and potassium intake with high-quality measurement as well as the role of gene-by-sodium interactions underlying blood pressure variation in multiethnic populations.

Aim 1 of the dissertation focuses on the identification of genomic regions associated with sodium intake, potassium intake, and sodium-to-potassium ratio in multiethnic populations. Using genome-wide genetic data imputed to the 1000 Genomes Project reference panel in five cohorts with European ancestry (N=7,363), one cohort with Asian ancestry (n=2,475), and one cohort with African Ancestry (n=1,246), we performed a genome-wide association study (GWAS) meta-analysis. We found a significant genetic locus, rs71639080, near the Fc fragment of IgG receptor genes (*FCGR2B-FCGR2C- FCGR3A*) on chromosome 1 from the meta-analysis of 24-hour urinary sodium excretion with a significance threshold of $P < 5 \times 10^{-8}$. Additionally, two genetic loci, rs77958157 on chromosome 5 and rs148459019 on chromosome 6, were significantly associated with sodium-to-potassium ratio. In Aim 2, we used sequence-kernel association methods to investigate gene-level associations from Aim 1 using both common and

rare genetic variants. In addition, we evaluated whether the gene-level associations were modified by demographic factors (age $\geq$ 65 years, sex, and college education) and found significant interactions in the regions of genes *TAPSAR1, CTC-228N24.1, RP11-433C9.2,* and *RP11-483H11.1* in a European American cohort. In Aim 3, we identified 12 genome-wide significant genetic loci ($P < 5 \times 10^{-8}$) through meta-analysis of a genome-wide gene-by-sodium intake interaction study on blood pressure measures using multiethnic cohort studies (N=6,020). One of the identified gene regions includes *NKAIN2* (chromosome 6), which is associated with the regulation of sodium and potassium ion transporting within or between cells.

Much research still remains to replicate and understand these initial findings in larger multiethnic populations to provide more insight into the underlying genetic variations and mechanisms by which these genomic regions are influencing the regulation of sodium and potassium intake, as well as blood pressure levels.

# CHAPTER I: Introduction

## 1.1 Introduction

Sodium intake is an essential dietary component, but excess sodium intake is an established risk factor for hypertension and cardiovascular disease [1-4]. In 2010, about 1.7 million, or 9.5%, of all deaths from cardiovascular causes were attributed to high sodium intake globally [5]. Potassium intake, however, is beneficial for controlling blood pressure [6, 7]. Recently, it was found that the ability to predict an increased risk of cardiovascular diseases (CVD) is stronger when using sodium-to-potassium intake ratio than using sodium or potassium alone [8, 9]. Thus, identifying factors that influence sodium intake, potassium intake, and sodium-to-potassium intake ratio is important and could be a basis for interventions to reduce the burden of hypertension and cardiovascular disease. A previous study in Korean participants showed that genetic factors contribute to variability in sodium intake (heritability = 34%) [5, 10-12]. However, there has been limited investigation into the specific genetic variants that influence sodium and potassium intake, and their role in blood pressure variation. Identifying predictors of sodium and potassium intake will allow better identification of individuals that are at high risk of excess sodium and low potassium intake, which is important for improved prevention of high blood pressure.

Sodium consumption is known to be disproportionately high among men, older people, and people with low education [13-15]. Potassium intake is also reported to be high among men and older people, but low among people with low education [16, 17]. Since the associations

between genes and sodium/potassium intake may differ as a function of environmental conditions, investigating potential gene-environment interactions with age, sex, and education on sodium and potassium intake is also critical. Additionally, examining the role of interactions between sodium intake and genomic factors in the explaining interindividual variation in blood pressure may provide additional insight into which subgroups of the population are particularly susceptible and may require more personalized intervention. In the section below, the overarching research aims of this dissertation are described. These aims address the need to identify genes and gene-environment interactions underlying sodium and potassium intake, and the relationship between sodium intake and blood pressure variation.

## 1.2 Research Aims

In this dissertation, we take advantage of high-quality measurements of sodium and potassium intake as well as genome-wide single nucleotide polymorphism (SNP) data from multiethnic epidemiologic studies to identify the genomic regions and genetic variants associated with sodium intake, potassium intake, and sodium-to-potassium intake ratio. We then investigate their interactions with factors underlying differences in sodium and potassium intake (age, sex, and education level), and their role in blood pressure variation. In Figure 1, we illustrate the overall conceptual model used to motivate and organize the findings across the three main aims of the dissertation.
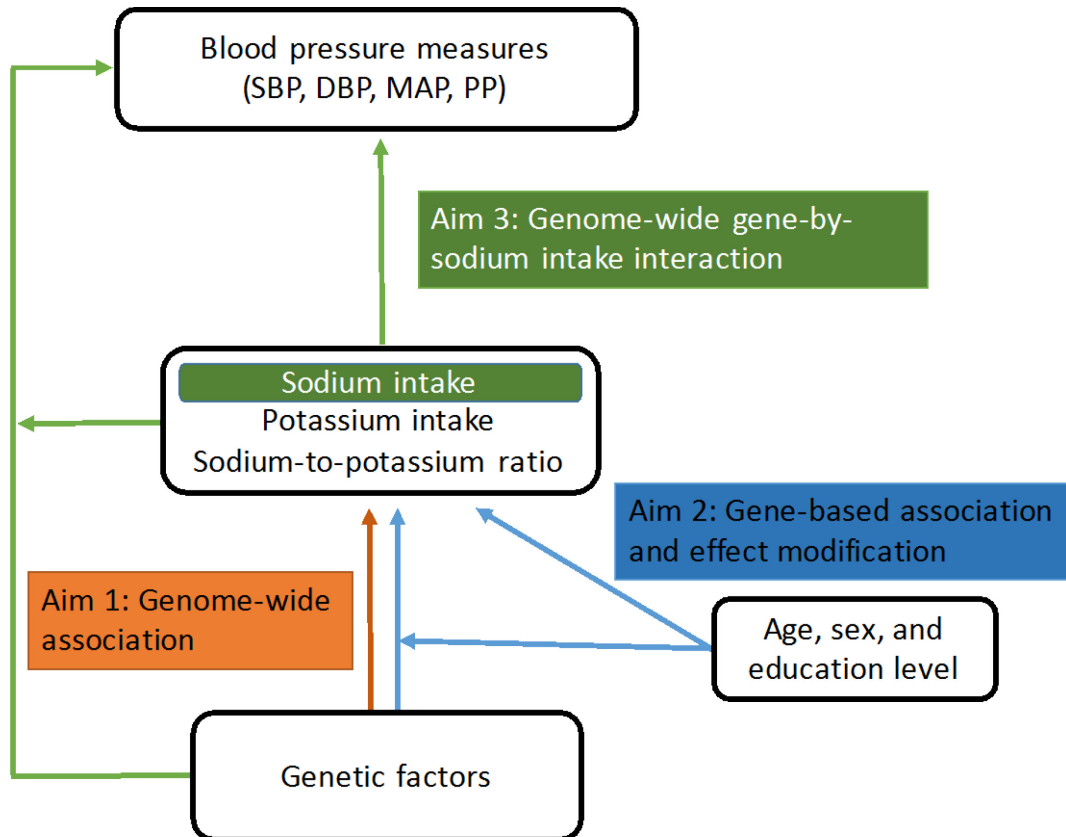
**Figure 1** Conceptual model for the proposed study describing the associations between genetic factors, sodium intake, potassium intake, sodium-to-potassium ratio, and blood pressure

Specifically, the three aims of this dissertation are:

Aim 1: Identify genetic factors associated with sodium intake, potassium intake, and sodium-to-potassium intake ratio by conducting a meta-analysis of genome-wide association studies (GWAS) in multi-ancestry cohorts.

*Hypothesis 1: Single nucleotide polymorphism (SNP) markers predict variation in sodium intake, potassium intake, and sodium-to-potassium ratio.*

Aim 2: Test gene-level associations from Aim 1 and gene-by-demographic factor (age, sex, and education level) interactions on sodium intake, potassium intake, and sodium-to-potassium intake ratio in multi-ancestry cohorts.

*Hypothesis 2: The genetic variants in a region and gene-by-demographic factor (age, sex, and education level) interactions explain significant variation in sodium intake, potassium intake, and sodium-to-potassium ratio.*

Aim 3: Evaluate gene-by-sodium intake interactions underlying blood pressure variation in multi-ancestry cohorts.

*Hypothesis 3: Significant interactions between sodium intake and SNP markers across the genome explain blood pressure variation in multi-ancestry cohorts.*

In the next section, we provide the background and significance underlying these aims.

**1.3 Background and significance**

**Importance of sodium intake, potassium intake, and sodium-to-potassium intake ratio in blood pressure, hypertension, and cardiovascular diseases**

On average, increments of 2.11 mm Hg in systolic blood pressure (SBP) and 0.78 mg Hg in diastolic blood pressure (DBP) are associated with each 1g sodium intake increment [12]. The average daily sodium intake for Americans is 3,608 mg per day from the National Health and Nutrition Examination Survey (NHANES) in 2014, which is much higher than the recommended levels by the American Heart Association (1,500mg/day) [18]. Potassium intake, however, is beneficial for controlling blood pressure [6, 7]. Each 1.72 g potassium intake increment is on average associated with decrement of 2.42 mm Hg in SBP and 1.57 mm Hg in DBP [19]. The average daily potassium intake for Americans is 2,155 mg per day from the NHANES in 2014, which is much lower than the recommended levels by the American Heart Association (4,700mg/day) [18]. Researchers have found that the ability to predict an increased risk of CVD is stronger when using sodium-to-potassium intake ratio than using sodium or potassium alone in prediction models [8, 9]. Since American consumption of sodium exceeds recommended levels while they fall short on their potassium intake by the American Heart Association (1500mg/day), investigating the underlying genetic factors and gene-environment interactions associated with sodium and potassium intake may allow a better understanding some of the molecular mechanisms driving dietary behavior and may provide potential intervention and prevention opportunities.

**Gold standard of sodium and potassium intake measurement**

Population and individual sodium and potassium intake are typically measured in one of two ways: 1) self-reported dietary intake data (i.e., dietary recalls, food records, food frequency questionnaires) and 2) urine biomarkers (i.e., 24-hour urine sample, half-day urine sample, and spot urine sample). Generally, 24-hour urinary excretion is regarded as the gold standard for intake assessment of sodium and potassium, and is more accurate than self-reported dietary intake data [20-22]. The 24-hour urinary excretion method does not allow electrolyte loss other than via the kidney. When comparing estimates of sodium intake from duplicate food portions (with sodium content measured by flame photometry) and 24-hour urinary sodium excretion, the sodium in the urine sample was only 5% on average lower than intake assessed by duplicate food portions [23]. However, intake measured by dietary records was much lower than the urinary estimates [23]. In another study, the difference between 24-hour urinary sodium excretion and sodium from duplicate food portions was 14% [24]. The remaining sodium is excreted through sweat and feces, which is a small portion under normal conditions. Regarding potassium intake, the level of potassium in 24-hour urine samples was 13.6% on average lower than intake assessed by duplicate food portions [23]. This is the scientific evidence that demonstrates that urinary sodium and potassium excretion is a gold standard for measuring sodium and potassium intake.

Collecting 24-hour urinary samples is, however, very challenging compared to using a dietary record. Thus, sodium excretions from half-day and spot urine samples are measured, and they have acceptable correlation coefficients with measures from 24-hour urine samples [11, 25, 26]. The Pearson product-moment correlation coefficient (r) between the measured and the estimated 24-h sodium excretion using simple volume-time linear extrapolation on half-day urine

samples was 0.837 in the Healthy Twin Study, Korea [11]. The correlation between the measured and the estimated 24-h sodium excretion and spot urine samples were previously reported as 0.53 - 0.82 [25, 26].

**Genetics of sodium and potassium intake**

There is a large amount of variability in sodium intake within and across populations, and many factors influence the level of sodium and potassium intake, including sex, age, socio-economic status, dietary habits, area of residence, and cultural factors [5, 10, 27]. Using the Healthy Twin Study, a twin-family cohort in Korea, I previously evaluated the null hypothesis that genetic factors do not play role in sodium intake level [11]. In the Healthy Twin Study, the intra-class correlation coefficients (ICCs) of 24-hour sodium excretion between family pairs were highest among the monozygotic twin pairs (0.47) and lowest among first-degree relative pairs (siblings combined with dizygotic twins: 0.09; parent-offspring: 0.07). Genetic versus environmental contributions were then estimated in terms of heritability ($h^2$), adjusting for associated factors (heritability: 34%). In this dissertation, we extend this research to identify genomic regions and genetic variants associated with sodium and potassium intake using a genome-wide association meta-analysis in five epidemiologic cohorts.

To our knowledge there has only been one GWAS for sodium and potassium concentration level (mEq/dl) measured from spot urine sample with limited sample size (N=3,095) in Japan that found one significant SNP but failed to replicate it in a replication set [9]. While research in this area has been limited, other studies have identified genes related to salt sensitivity, a measure of how individual blood pressure responds to salt intake [28, 29], and salt taste, ability to detect salt [30, 31].

**Gene-environment interaction in sodium and potassium intake**

Individual sodium and potassium intake has a wide range of individual variability [32, 33]. The determinants of sodium and potassium intake have not been fully defined but physiological phenotypes, physical characteristics, developmental factors, cultural factors, genetic factors, and environmental factors as well as interactions among them have been reported to influence individual sodium and potassium intake [16, 27, 34]. Thus, the associations between genes and sodium/potassium intake may differ as a function of environmental and other conditions. While there has been no study that investigates gene-environment interaction in sodium and potassium intake, to our knowledge, other studies have found gene-sodium intake interactions that affect blood pressure [35, 36].

**Gene-by-sodium/potassium intake interaction influencing blood pressure**

Blood pressure measures including SBP and DBP are heterogeneous traits because they are influenced by both genetic and environmental factors. GWAS have identified numerous SNPs that are associated with SBP and DBP, but the identified genetic loci explain only a small portion of trait variability (~2%) even though heritability is relatively high (~40-50%) [37-43]. Thus, identifying environmental factors that could modify the genetic effects of blood pressure is important and being actively researched [44-46]. High sodium intake and low potassium intake are strong and independent risk factors for high blood pressure, and the level of sodium and potassium intake has a large variation on both the individual and population level [32, 47, 48]. Thus, research on whether and how individual sodium and potassium intake modifies the genetics of blood pressure is important for identifying susceptible genetic groups in populations that are disproportionately affected by sodium and potassium intake. However, few studies have

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been conducted to evaluate the gene-by-sodium intake or gene-by-potassium intake interactions on blood pressure traits, especially using large-scale epidemiologic cohort data.

Studies using animal and human subjects have focused on the identification of genes that are involved in blood pressure responses to sodium intake mostly via genetic alterations in tubular sodium reabsorption [49]. Changwei et al conducted analyses of gene-by-sodium intake and gene-by-potassium intake interactions on blood pressure traits including SBP, DBP, mean arterial pressure (MAP), and pulse pressure (PP) and found multiple novel loci from GWAS and gene-based analysis in a Chinese population [50, 51]. A recent study in a Korean population found 6 loci near significant SNPs that had significant interactions with sodium intake, potassium intake, or their ratio on hypertension [52]. However, more studies of gene-by-sodium or potassium intake interactions on blood pressure traits in multiethnic populations are needed to better understand the mechanisms of blood pressure regulation by dynamic interrelationships among genes, sodium intake, and potassium intake across ancestry groups. This dissertation will help to provide additional insight into the genes that may interact with an individual's sodium intake to influence their blood pressure.

**CHAPTER II**: **Genome-wide meta-analysis of sodium intake, potassium intake, and their ratio in multiethnic cohorts**

## 2.1 Introduction

Sodium and potassium are essential dietary components, but excess sodium intake [2, 53] and low potassium intake [6, 7] are established risk factors for hypertension and cardiovascular disease (CVD). In 2010, about 1.7 million, or 9.5%, of all worldwide deaths from cardiovascular causes were attributed to high sodium intake [5]. Although sodium and potassium intake are well-known modifiable and targeted dietary factors in CVD prevention, American daily consumption of sodium is 2.2 times the recommended maximum 1500mg/day, while daily consumption of potassium is 2,000mg/day below the recommended minimum of 4,700mg/day [54]. Recently, the sodium-to-potassium ratio has been considered a more important risk factor for hypertension than sodium and potassium levels alone [55, 56]. Thus, identifying the factors associated with maintaining an optimal sodium-to-potassium ratio could provide a basis for interventions to reduce the burden of hypertension and CVD [8, 9, 57]. Since sodium and potassium intake are related to eating behavior, which is a complex trait, many factors influence the level of consumption, including sex, age, socio-economic status, dietary habits, area of residence, and cultural factors [5, 10, 58, 59]. A previous study of 2,209 Koreans in a twin-family study showed that genetic factors also contribute to variability in sodium intake (heritability = 30-35%) [11]. The intra-class correlation coefficients of 24-hour urinary sodium

excretion were the highest among monozygotic twin pairs (0.47) and the lowest among first-degree relative pairs (siblings combined with dizygotic twins: 0.09).

However, there has been limited investigation into the specific genetic variants that influence sodium and potassium intake, as well as their ratio. To our knowledge, there has only been one genome-wide association study (GWAS) for sodium and potassium concentration (mEq/dl) measured from spot urine samples in a Japanese population (N=3,095 for discovery sample, and N=5,716 for replication sample), which found one genome-wide significant locus but failed to replicate the genetic variant [9]. While research in this area has been limited, other studies have identified genes related to salt sensitivity, a measure of blood pressure responsiveness to salt intake [28, 29], salt taste, the ability to detect salt [30, 31].

To better understand the genetic architecture of sodium and potassium intake and their ratio, we conducted a GWAS meta-analysis using the rich combination of high-quality measurement of sodium and potassium intake and genotype data from seven cohorts comprising over 11,000 participants of European (GENOA, PREVEND, FHS, HyperGEN and HAPI heart), African American (HyperGEN), and Asian (HTS) ancestry (Appendix 1). Since there is a wide range of sodium and potassium intake across different cultures, the current study includes multiethnic populations to help us better understand and generalize our findings about the genetics of sodium and potassium intake across ancestry groups.


## 2.2 Methods

Aim 1 included the following European Ancestry cohorts in the discovery sample (N=7,363): Genetic Epidemiology Network of Arteriopathy (GENOA) [60], Prevention of REnal and Vascular ENd-stage Disease(PREVEND) [61], Hypertension Genetic Epidemiology

Network (HyperGEN) study European American (EA) [60], Heredity and Phenotype Intervention (HAPI) Heart Study [62], and the Framingham Heart Study (FHS) [63, 64]. The replication sample (N=3,721) included: HyperGEN African American (AA) [60], and Healthy Twin Study - Korea (HTS) [65]. The descriptions and acknowledgements for participating cohorts are described in Appendix 1. Each of these cohorts has high-quality measurements of sodium and potassium intake from urinary samples, enabling us to initiate an international collaboration of multiethnic genome-wide meta-analysis of sodium and potassium intake and their ratio. A brief description of each cohort is included below:

GENOA is a community-based study that aims to identify genes influencing blood pressure from Rochester, MN and Jackson, MS. It is a part of the NHLBI-sponsored Family Blood Pressure Program (FBPP) [66]. Sibships with at least two adults with clinically diagnosed essential hypertension before age 60 were recruited, and all siblings in the sibship were invited to participate [60]. Twenty-four hour urinary sodium and potassium excretion levels were collected from the participants [67].

PREVEND is an ongoing, community-based, and prospective cohort study initiated in 1997 in the Netherlands [61]. The PREVEND study was designed to investigate the predictive value of urinary albumin excretion for renal and cardiovascular disease progression [61]. Twenty-four-hour urinary sodium and potassium excretion levels were collected from the participants [68].

HyperGEN is part of the NHLBI-sponsored Family Blood Pressure Program (FBPP) [66]. Participants were recruited from multi-center (Framingham, MA; Minneapolis, MN; Salt Lake City, UT; Forsyth County, NC; and Birmingham, AL) to investigate the genetics of hypertension [66]. Individuals with onset of hypertension before age 60 and at least one

additional hypertensive sibling who could be enrolled in the study were recruited into the HyperGEN study [69]. Twenty-four-hour urinary sodium and potassium excretion levels of participants were estimated using sodium and potassium excretion levels from overnight urine samples.

In the HAPI Heart study, relatively healthy individuals and their family members who were 20 years old or older were recruited from the Amish community in Pennsylvania to investigate the response to short-term environmental exposures related to CVD [62]. Usual daily sodium and potassium levels were measured from the first-morning single spot urine specimen of participants [70].

The Framingham Offspring Study is a community-based longitudinal study examining CVD risk in the offspring of the original cohort participants of Framingham Heart Study (FHS) and their spouses [63, 64]. The analysis in this study was conducted using the data from the FHS investigators participating in the SNP Health Association Resource (SHARe) project and downloaded from the NIH Database of Genotypes and Phenotypes (dbGaP). 24-hour urinary sodium and potassium excretion were measured in Offspring Exam 9 and Omni 1 Exam 4.

The Healthy Twin Study, Korea is an ongoing community-based cohort study that has been running since 2005 [65]. Healthy Korean adult twins and their first-degree adult family members were recruited. Half-day and spot urine samples were collected from all participants [11]. Sodium and potassium excretion levels of participants were measured either from half-day urine samples ($\geq$ 8 hours) or spot urine samples.

**Measurements of sodium and potassium intake**

Urinary sodium and potassium excretion were quantified as continuous variables (mmol/day) from urine collections in each cohort. Sodium excretion from a 24-hour urinary

sample is the gold standard for the assessment of sodium intake [20-22], as its validity is much

higher than that from self-reported dietary methods, such as 24-hour recalls, dietary records, or

Food Frequency Questionnaires (FFQ) [20-22, 71]. The validity of urinary sodium excretions

from half-day/overnight or spot urine samples is lower than that of urinary sodium excretions

from 24-hour urine samples, but is still higher than that of self-reported dietary methods [22].

The correlation coefficient (r) between the measured 24-h sodium excretion (from the 24-hour

urine sample) and the estimated 24-h sodium excretion (using simple volume-time linear

extrapolation on the half-day urine samples) was 0.837 in Healthy Twin Study, Korea [11]. The r

between the measured and the estimated 24-h sodium excretion and spot urine samples was

previously reported as 0.53 - 0.82 [25, 26]. The measurement of the source of urinary sodium

and potassium excretion in each cohort is described in the study population section and in Table

1 and Table 2. If the duration of the sample was less than 24 hours, established formulas were

applied to estimate 24-hour sodium and potassium excretions; simple volume-time linear

extrapolation was used for half-day urine samples (HyperGEN and HTS), and the Kawasaki

formula for spot urine samples (HAPI Heart) [11, 25].

**Genotyping**

Genotypes for each cohort were obtained using either Affymetrix or Illumina genotyping

arrays (Table 3). Each cohort performed internal quality control (QC) assessments of initial

genotype data including excluding individuals with poor genotype call rate (i.e., <95%) and

checking for relatedness across individuals. Quality checks for single nucleotide polymorphisms

(SNPs) included exclusion of SNPs with poor call rate (i.e., <95%), SNPs with Hardy-Weinberg

disequilibrium $P<10^{-4}$, SNPs with high duplicate discordance rates, and monomorphic SNPs.

Imputation was performed using the 1000 Genomes Project Phase I Integrated Release Version 3 [March 2012] cosmopolitan reference panel in each cohort.

Since allele frequency differences in samples due to systemic ancestry differences can lead to false associations in GWASs, we adjusted for population stratification in each cohort using principal components (PCs) in the analysis [72]. In GENOA, the first 4 PCs were included in the model and were calculated using common SNPs shared by Affymetrix (Genome-Wide Human SNP Array 6.0) and Illumina (Human 1M-Duo, 660-Quad, or 610-Quad), with imputation quality ($R^2$) greater than or equal to 0.8 using unrelated individuals (570 individuals from 1,509 subjects).

**Statistical analysis**

**Genome-wide association study**

To identify the genetic loci that influence sodium intake, potassium intake, and their ratio across the genome, associations between each SNP and these traits were conducted with 1000 Genomes Project imputed genetic data. This GWAS analysis was conducted separately in each cohort and within each ethnicity. In the model, age and sex were included in addition to each SNP, coded additively as a dosage of the coded allele. PCs were also included to adjust for population stratification in each cohort. In a second model, BMI and height were added to the original models to approximate measures of interindividual variation of individual food intake (total energy intake). For family-based data, linear mixed effects modeling with "family" as a random intercept was conducted. The models in a family-based cohort are presented below:

$24 - hour\ sodium\ urinary\ sodium\ excretion_{ij},$

$24 - hour\ urinary\ potassium\ excretion_{ij},$

or $Sodium-to-potassium\ excretion\ ratio_{ij}$

$$= \beta_0 + \beta_1 \cdot age_{ij} + \beta_2 \cdot sex_{ij} + \beta_3 \cdot PC1_{ij} + \beta_4 \cdot PC2_{ij} + \beta_5 \cdot PC3_{ij} + \beta_6 \cdot PC4_{ij}$$

$$+ \beta_7 \cdot SNP_{ij} + u_j + \epsilon_{ij}$$

where $i$ is an individual, $j$ is a family, $\beta_0$ is a fixed intercept, $\beta_1 - \beta_7$ are fixed coefficients

representing the estimated effects of each following term, $u_j$ is a random intercept for family $j$,

and $\epsilon_{ij}$ is a random error for an individual $i$ in family $j$.

**Meta-analysis and replication**

Before conducting the meta-analysis, individual GWAS results were cleaned. This was

done using EasyQC software [73] to check the collected allele frequencies against the ancestry-

specific 1000 Genomes Reference panel, and to harmonize genetic marker names for consistency

across cohorts. To improve the power of GWAS and reduce false-positive results, a fixed-effect

meta-analysis using inverse-variance weightings was performed on summary statistics (beta

estimate from the association, and standard error of beta estimate) and corrected for study-

specific genomic control lambda when lambda was greater than 1. The only SNPs that were

included were the ones present in at least two participating studies with minor allele frequency

(MAF) greater than 0.01, and imputation quality greater than 0.3. We conducted a meta-analysis

across cohorts with European ancestry using the METAL package in R [74], and genomic

control correction was again applied after the meta-analysis. To adjust for the inflation of type I

error due to multiple testing, we used an alpha level of $5 \times 10^{-8}$ to declare significant association.

To assess the homogeneity of results across cohorts, we estimated the Cochran's Q statistic and

$I^2$ statistic for each SNP, and we calculated the percentage of total variation across studies that

was due to heterogeneity rather than chance [37, 38]. A cut-off of 25% was used to represent

minimal heterogeneity, 50% to represent moderate, and 75% to represent considerable heterogeneity [37, 38].

For SNPs with at least suggestive association in EA ($P < 5 \times 10^{-6}$), we examined the SNPs in cohorts with AA and Asian ancestry (overview shown in Figure 2). We considered $P < 0.05$ before correcting multiple comparison to represent replication.

## Discovery
[European n=7,363]

GENOA
HyperGEN EA
HAPI
PREVEND
FHS

Significant or suggestive SNPs selected for replication ($P < 5 \times 10^{-6}$)

## Replication
[Asian n=2,475]
[African American n=1,246]

HTS
HyperGEN AA
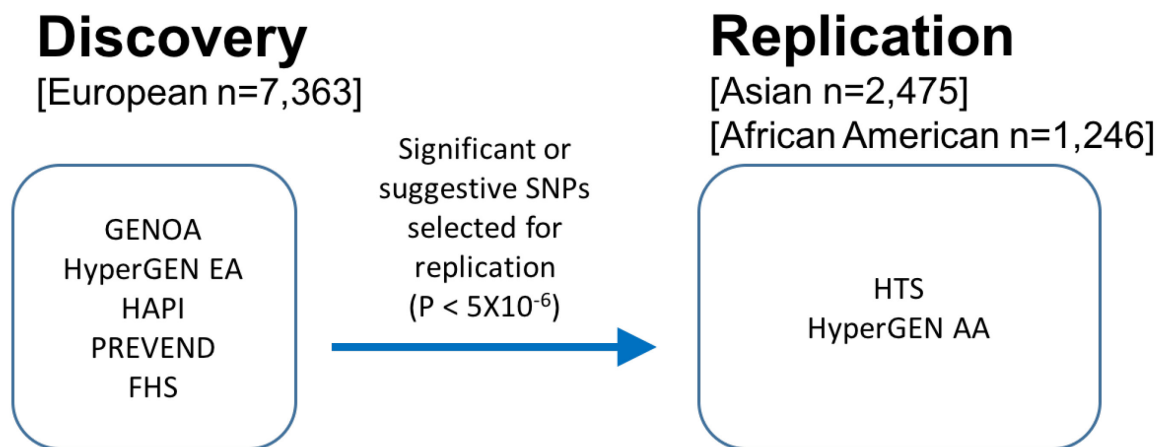
**Figure 2** Schematic of the study design

### 2.3 Results

Meta-analysis of 24-hour sodium excretion, potassium excretion, and their ratio was conducted in 7,363 participants of European ancestry from 5 cohorts. Only suggestive or significant SNPs ($P \leq 5 \times 10^{-6}$) were further tested for replication in the participants of African Americans (N=1,246) and Koreans (N=844). The descriptive characteristics of the cohorts are presented in the Table 1.  On average, the 24-hour urinary sodium excretions of participants were much higher in HyperGEN, HAPI Heart, and HTS (range: 203.3 -237.8 mmol/day) than in GENOA, REVEND, and FHS (range: 136.6 -144.9 mmol/day). In HyperGEN and HAPI Heart, the average sodium-to-potassium ratio ranged from 3.7-4.7, while in HTS, it was 2.7. The

prevalence of hypertension was greater than 50% in the American cohorts, except for in HAPI Heart (Amish cohort), and it lower (10 - 30%) in HTS and PREVEND, likely due to the participants' younger age.

**Discovery meta-analysis**

From the discovery meta-analyses (both with and without adjustment for BMI and height), we identified 52, 75, and 27 SNPs with at least suggestive association (P $<5x10^{-6}$) with 24-hour sodium excretion, 24-hour potassium excretion, and their ratio, respectively (Tables 4 and 5). Figure 3 shows the QQ plots of the meta-analysis results, and Figure 4 shows the Miami plots.

We found few genome-wide significant SNPs from the meta-analyses. The most significant SNP was in the *FCGR2B -FCGR2C-RP11-25K21.6-FCGR3A* gene cluster on chromosome 1 (rs71639080, P=6.88 $x10^{-9}$ and 6.21 $x10^{-9}$) from GWAS of 24-hour sodium excretion with and without adjustment for BMI and height, respectively. The most significant SNP from GWAS of 24-hour potassium excretion was rs111345501 near genes *PATZ1-RP3-400N23.6* on chromosome 22 with adjustment for BMI and height in the model (P=8.11 $x10^{-8}$). From the sodium-to-potassium ratio meta-analysis with adjustment for BMI and height, we found two genome-wide significant SNPs (rs77958157 on chromosome 5 with P=2.3 $x10^{-8}$, and rs148459019 on chromosome 6 with P=3.7 $x10^{-8}$). Regional plots for the significant SNPs are shown in Figure 5.
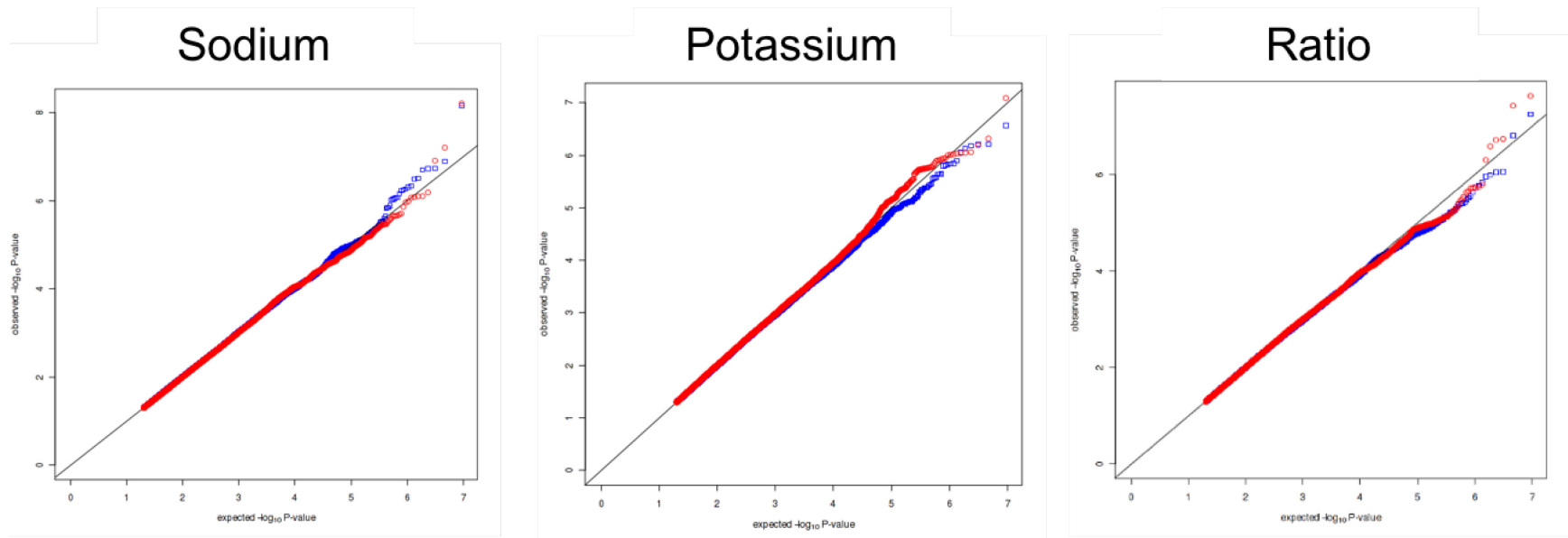
**Figure 3** QQ plots of discovery GWAS meta-analysis for 24-hour sodium excretion, 24-hour potassium excretion, and sodium-to-potassium ratio in Aim 1

Blue line: without BMI and height adjustment
Red line: with BMI and height adjustment

**Figure 4** Miami plots of discovery GWAS meta-analysis for 24-hour sodium excretion, 24-hour potassium excretion, and sodium-to-potassium ratio in Aim 1

Above Miami plot: without BMI and height adjustment
Below Miami plot: with BMI and height adjustment

## 24-hour sodium excretion
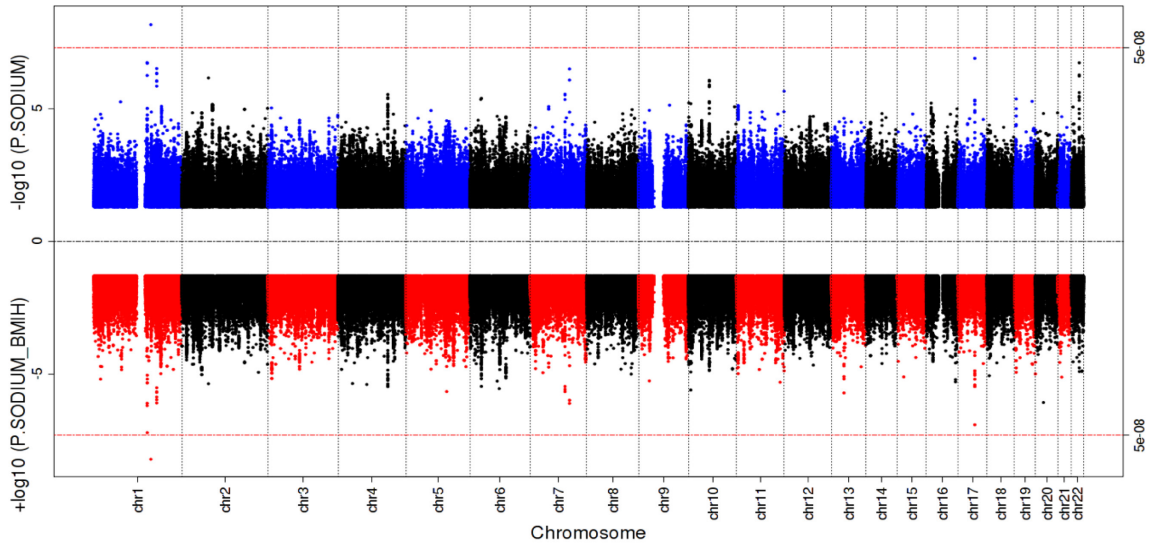


## 24-hour potassium excretion
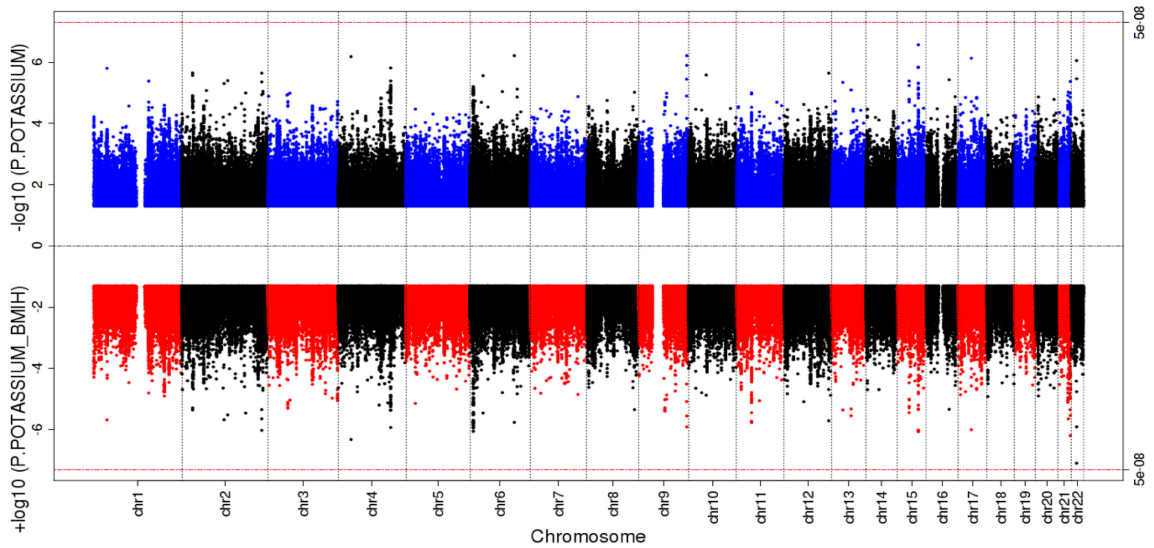
**Sodium-to-potassium ratio**
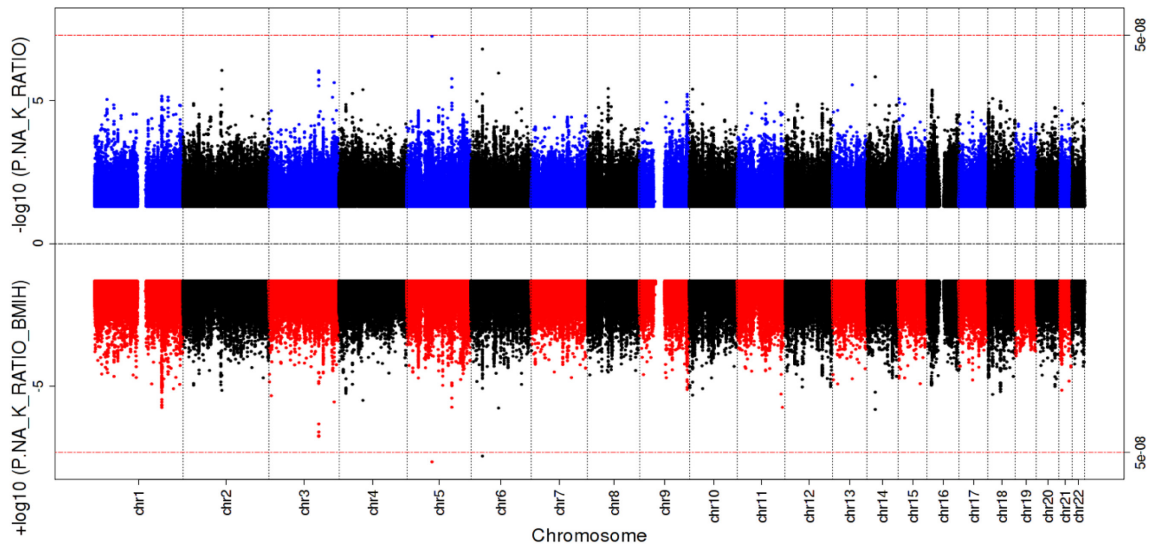
**Figure 5** Regional plots for the most significant loci from 24-hour sodium excretion, 24-hour potassium excretion, and sodium-to-potassium ratio using LocusZoom in Aim 1

**24-hour sodium excretion**

**24-hour potassium excretion**
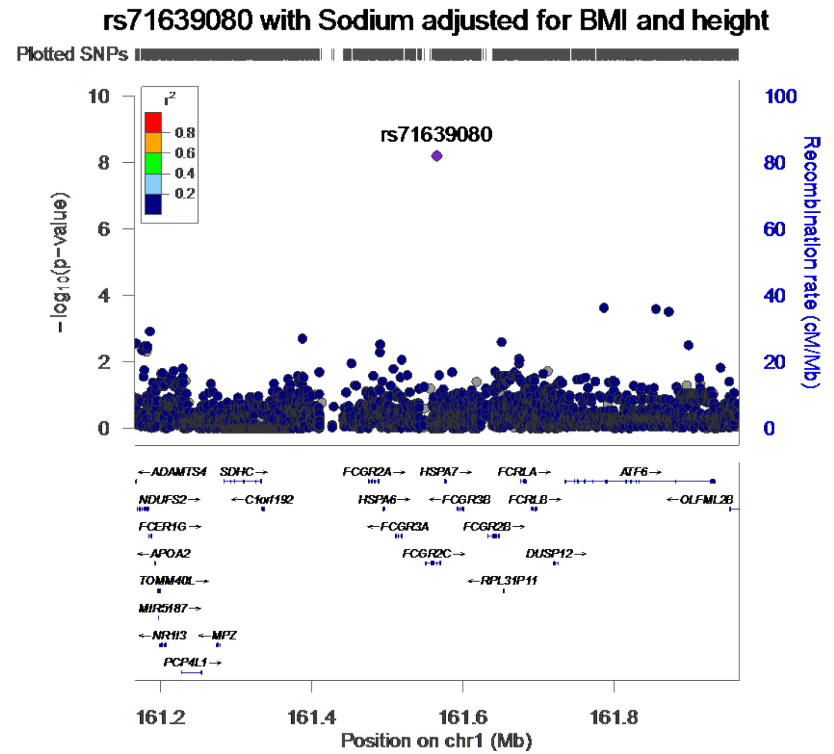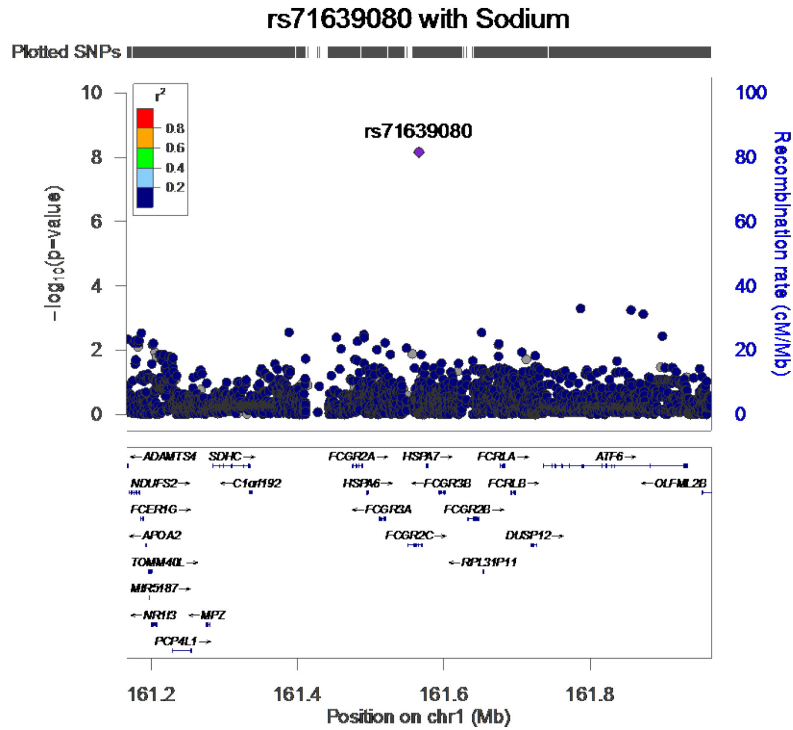
**Sodium-to-potassium ratio**
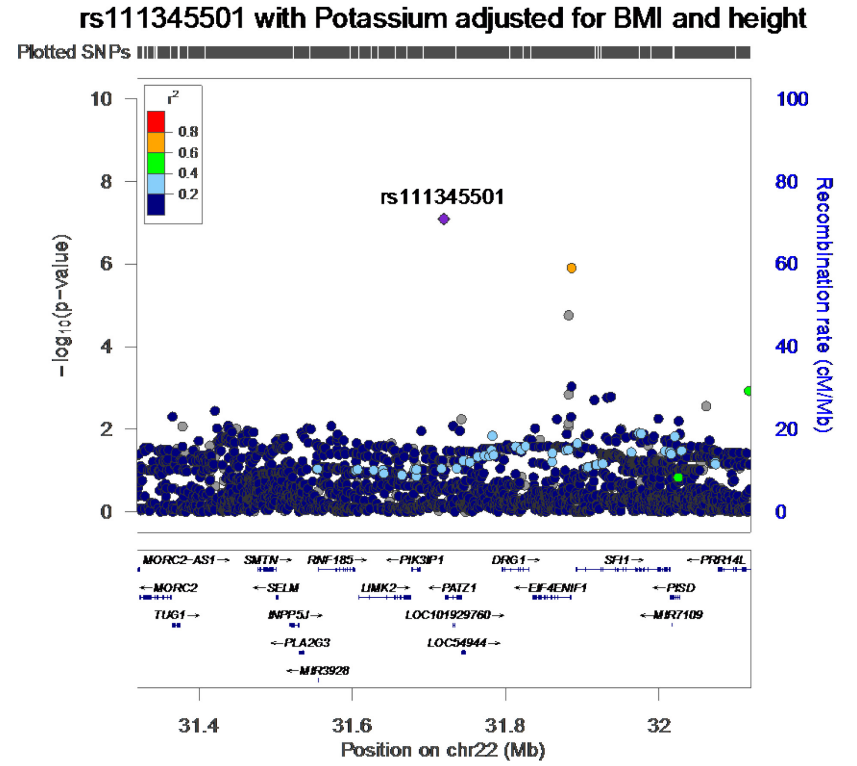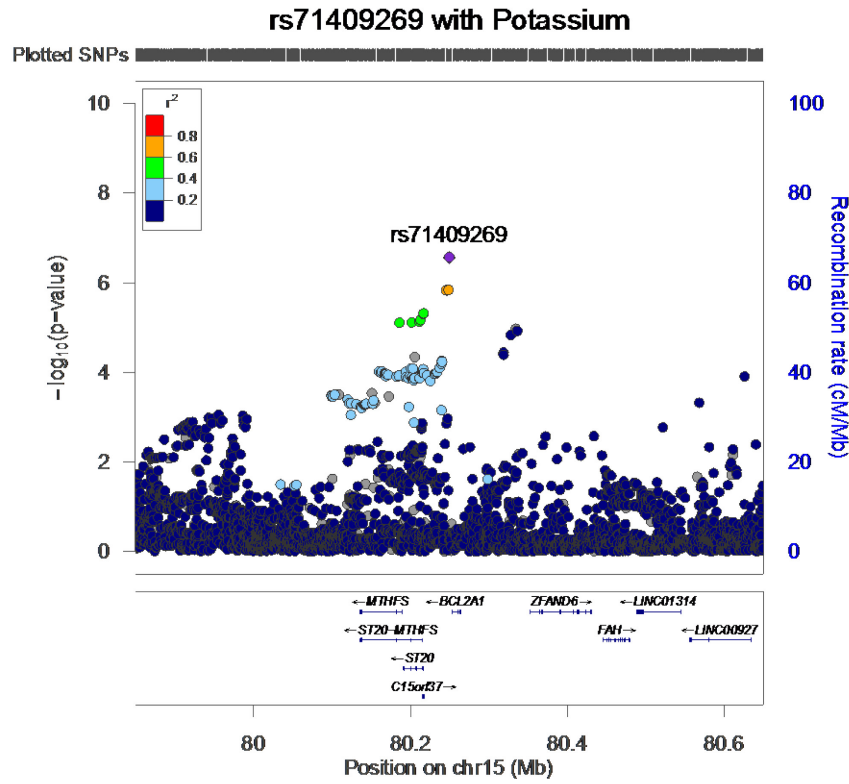
**Replication**

We conducted replication analysis of 154 SNPs with $P < 5 \times 10^{-6}$ from the European Ancestry cohorts (52 for 24-hour sodium excretion, 75 for 24-hour potassium excretion, and 27 for sodium-to-potassium ratio, respectively) in the African American and Asian ancestry populations (Table 6). One SNP, rs1033925 on chromosome 10 from the 24-hour sodium excretion GWAS replicated in the Asian cohort (P=0.031). From the 24-hour potassium excretion GWAS, 4 SNPs (rs200543390, rs201934692, rs143513312, and rs188284329) from the same locus on chromosome 11 replicated in the African American cohort (P=0.026 - 0.05), and one SNP, rs74459597 on chromosome 13, replicated in the Asian cohort (P=0.03).

**2.4 Discussion**

We conducted a GWAS meta-analysis of 24-hour sodium excretion, 24-hour potassium excretion, and sodium-to-potassium ratio using 5 European ancestry cohorts (N=7,363), followed by the analysis of replication in an African American cohort (N=1,246) and an Asian cohort (N=2,475). From the meta-analysis in European ancestry population, we found a total of 52, 75, and 27 SNPs with at least suggestive associations ($P < 5 \times 10^{-6}$) with 24-hour sodium excretion, 24-hour potassium excretion, and their ratio, respectively. Three of those SNPs were replicated either in African Americans or Asian populations (P<0.05). Although the total sample size is small compared to other large GWAS, this is the largest genome-wide investigation of these phenotypes to date.

Several of our identified loci are located in or near 69 gene regions from any of GWAS in Aim 1. Out of 69 genes, the 12 genes that have a known function are listed below. From the sodium excretion meta-analysis, the most significant SNPs were found near the Fc fragment of

IgG receptor genes (*FCGR2B-FCGR2C- FCGR3A*) on chromosome 1. The genes encode a receptor found on the surface of immune response cells, and mutations in these genes have been suggestively associated with autoimmune disease [75]. While excess sodium intake could induce excessive immune responses, which can be damaging to immune homeostasis in human body [76] [77], there is no known reason why these genes would be associated with sodium or potassium intake. Further studies are needed to elucidate the function of these genes, and their relationship with the genetics of sodium excretion and the immune system.

Multiple genes from the sodium excretion meta-analysis, including *GTPBP1* (GTP binding protein 1) on chromosome 22, and *CDC42SE1* (CDC42 small effector 1) on chromosome 1, have been suggestively associated with the activity of GTPases. GTPases are suggestively associated with blood pressure regulation, hypertension, kidney function, and other traits that are related with cardiovascular system and disease. Studies have identified GTPases as a mechanism for salt intake triggering hypertension and other cardiovascular damage [78] [79]. The gene *ARHGAP22* (GTPase activating protein 22) near the variant rs56319019 identified from the potassium excretion meta-analysis on chromosome 10 encodes Rho GTPase. The Rho GTPases have important roles in salt-sensitive hypertension [78] and renal tubular epithelial cell function [80].

The gene *CLMP* (CXADR like membrane protein) on chromosome 11 from the sodium excretion meta-analysis with adjustment for BMI and height has been suggestively involved in adipocyte maturation, intestinal development, body mass index, and development of diet-induced obesity [79]. Although the link between the gene, sodium intake, and obesity has not been well established, it is promising that this may support the positive association between sodium intake and obesity [81] [82].

We found multiple genes that have important roles in regulation of blood pressure and cardiovascular disease. The gene *DLEU2* (deleted in lymphocytic leukemia 2) on chromosome 13 identified from the potassium excretion meta-analysis is suggestively associated with angiotensin converting enzyme 2 (ACE 2) in the cell cycle of vascular endothelial cells [83]. ACE has important role in blood pressure regulation by controlling the volume of fluids in the body. In addition, multiple SNPs located in the intronic region of gene *CUL3* (cullin 3) on chromosome 2 were found from the potassium excretion meta-analysis. The mutation in the gene is associated with pseudohypoaldosteronism type two, a rare Mendelian syndrome involving hypertension [84]. The mechanisms of the disease have been suggestively associated with salt reabsorption and potassium secretion in the kidney [85]. We also found a suggestive SNP, rs145526382 near gene *ABO* (alpha 1-3-N-acetylgalactosaminyltransferase and alpha 1-3-galactosyltransferase) on chromosome 9 from the meta-analysis of potassium excretion. Previous GWAS found that SNPs near the *ABO* gene were associated with ACE activity [86] and venous thromboembolism (VTE) [87].

Several genes identified in suggestive GWAS regions identified appear to be associated with neuromuscular function. From the meta-analyses of sodium-to-potassium ratio, we found a suggestive SNP near gene *EIF2B5* (eukaryotic translation initiation factor 2B subunit epsilon) on chromosome 3. The gene has been suggestively associated with multiple sclerosis, a neurodegenerative disorder [56]. The important role of sodium and potassium ions in the human body involves their functions in the transmission of nerve impulses in neuron. The associations between sodium/potassium intake and multiple sclerosis have been inconclusive [88] [89] [90]. We also identified a suggestive SNP from the meta-analysis of sodium-to potassium ratio near *KIRREL3* (kirre like nephrin family adhesion molecule 3) on chromosome 11, which is involved

in encoding a member of the nephrine-like protein family that is present in kidney podocytes [91]. The main role of the nephrine protein is the proper functioning of the renal filtration barrier in the kidney. The nephrine proteins interacts with podocin, another important protein in renal filtration function, which is associated with the permeability of sodium and potassium in kidney ultrafiltration. *KIRREL3* has been also suggestively associated with human skeletal muscle and intellectual disability [92, 93]. While it may not seem that the sodium and potassium intakes are associated with those diseases, sodium and potassium are involved in transmitting nerve signals that induce muscle contraction, and sodium intake has been suggestively associated with skeletal muscle via loss of nitric oxide activity [94] [95]. In addition, studies have identified the potential role of *KIRREL3* in neurodevelopment [93] [96]. *KIRREL3* could potentially interact with *ATP1B1* that belongs to the family of sodium-potassium ATPases [93]. However, further studies are needed to elucidate the mechanism of how the genes are related to sodium and potassium intake, perhaps through neurological feedback systems that affect taste or hunger mechanisms.

To our knowledge, there has only been one genome-wide association study (GWAS) for sodium and potassium concentration (mEq/l) adjusted for age, sex, and BMI. The study had limited sample size (N=3,095 in discovery, and N=5,716 in replication using a subset of the same original cohorts) using only Japanese populations. In the Japanese study, sodium and potassium concentrations were measured from spot urine samples, which is a different phenotype from daily intake. The Japanese study found one genome-wide significant SNP, rs12092050 (P=1.35 X $10^{-8}$) on chromosome 1, for sodium concentration level, but failed to replicate the SNP (P= 0.618) [9]. We did replication analysis of rs12092050 in our sample, and the SNP had a significant P value from the sodium-to-potassium ratio GWAS results adjusted for age, sex, BMI, and height in Korean cohort, HTS (P=0.044, Table 7).

A notable strength of our research is that urinary sodium intakes were measured in populations with multiple ancestries (N=11,084). A large number of high quality samples may have helped us provide accurate identification of genetic factors for sodium and potassium intake. Since sodium and potassium intake are highly variable among different populations, it is important to include multiethnic populations in the analyses. The current study included multiple populations with both higher and lower mean sodium intakes, which allowed us to generalize these results across a variety of populations.

Our power to detect the genetic loci associated with sodium and potassium intake might have been limited due to our relatively small sample size. Generally, 24-hour urinary sodium excretion is regarded as the gold standard for intake assessment of sodium intake, and is more accurate than data measured from self-reported dietary questionnaires [20-22]. Collecting 24-hour urinary samples is, however, very challenging compared to using self-reported dietary questionnaires. Thus, sodium excretions from half-day and spot urine samples are measured instead, and they have reasonably high correlation coefficients with the excretions from 24-hour urine samples (0.837 and 0.53 – 0.82, respectively) [11, 25].

The low rate of replication from the European American meta-analysis in the African American and Asian cohorts may be due to the different linkage disequilibrium structure in each ancestry. SNPs found in different race/ethnicity groups may not be replicated in other groups even if the underlying genes that influence the trait are the same. Thus, a gene-based approach may be needed to replicate our findings in populations with different ancestry since the gene is a functional unit that does not vary by race/ethnicity group. Another reason for the low replication rate might be related to the different characteristics of participants in multiethnic populations, which includes different level of sodium potassium intake or different recruitment methods of

participants. It is possible that the genetic effects on high intakes of sodium or potassium is different than on low intakes of sodium or potassium. In addition, some of participants in Aim 1 were selected like in GENOA and HyperGEN that were targeting hypertensive subjects or subjects with a family history of hypertension.

The identification of genetic variants that influence sodium and potassium intake and corresponding susceptible groups may improve personalized nutritional recommendations by identifying individuals at high risk of excess sodium intake and low potassium intake, and by proactively recommending behavior modifications to reduce the risk of high blood pressure. These initial discoveries may shed light on the importance of the genetic architecture of sodium and potassium intake. Future work is now required to identify functional variants in these genomic regions, and to provide more insight to the regulation of sodium and potassium intake that may improve the health of multiple populations.

**Table 1** The basic characteristics of participating cohorts in Aim 1

| | GENOA | PREVEND | FHS | HyperGEN EA | HyperGEN AA | HTS | HAPI Heart |
|---|---|---|---|---|---|---|---|
| **Cohort** | Family-based | Population-based | Family-based | Family-based | Family-based | Family-based | Family-based |
| **Country** | USA | Netherlands | USA | USA | USA | South Korea | USA |
| **Total (N)** | 811 | 3,649 | 801 | 1,258 | 1,246 | 2,475 | 844 |
| **Female, %** | 57.6 | 51.5 | 53.2 | 50.4 | 67 | 64.0 | 46.6 |
| **Age in years** | 65.7 ± 9.1 | 49.6 ± 12.5 | 70.2 ± 7.62 | 50 ± 14 | 45 ± 13 | 44.1 ± 13.3 | 43.8 ± 14.0 |
| **Race/ethnicity** | EA | Europeans (Dutch) | EA | EA | AA | Asian | EA (Amish) |
| **SBP** | 146.7 ± 22.8 | 129.1±19.9 | 125.1 ± 16.2 | 123.5 ± 19.1 | 129.2 ± 22.2 | 116.8 ± 17.0 | 121.5 ± 14.6 |
| **DBP** | 84.1 ± 10.8 | 74.1±9.9 | 71.3 ± 9.6 | 70.7 ± 10.0 | 74.0 ± 11.6 | 73.7 ± 10.9 | 76.8 ± 8.7 |
| **Hypertension, %** | 88.2 | 34.4 | 52.6 | 52.2 | 63 | 10.7 | 13.6 |
| **BP lowering medication use, %** | 76.2 | 12.3 | 52.4 | 47.7 | 61.1 | 8.09 | 0.0 |
| **BMI** | 30.9 ± 5.9 | 26.1±4.3 | 28.1 | 29.47 ± 6.13 | 32.55 ± 8.04 | 23.7 ± 3.3 | 26.6 ± 4.5 |
| **Measurement of source** | 24-hour urine | 24-hour urine | 24-hour urine | Half-day urine | Half-day urine | Half-day & Spot urine | Spot urine |
| **24-h sodium excretion (mmol/day)** | 139.4 ± 58.3 | 144.9 ± 50.3 | 136.6 ± 57.0 | 203.3±107.3 | 237.8±121.9 | 212.8± 77.8 | 216.6 ± 50.8 |
| **24-h potassium excretion (mmol/day)** | 58.5 ± 22.9 | 73.6 ± 21 | 67.9 ± 23.2 | 65.1±36.3 | 65.7±41.4 | 84.0 ± 32.2 | 47.9 ± 13.4 |
| **Sodium-to-potassium excretion ratio** | 2.5 ± 1.0 | 2 ± 0.7 | 2.1 ± 0.9 | 3.7 ± 1.9 | 3.7 ± 2.3 | 2.7 ± 1.0 | 4.7 ± 1.2 |

For continuous variables: mean ± SD, For binary variables: %
Abbreviations: EA- European American, AA- African American, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BP: Blood pressure, BMI: Body Mass Index ($kg/m^2$), GENOA: Genetic Epidemiology of Arteriopathy, PREVEND: Prevention of REnal and Vascular ENd-stage Disease, FHS: Framingham Heart Study, HyperGEN: Family Blood Pressure Program, HTS: Healthy Twin Study, Korea, HAPI Heart: Heredity and Phenotype Intervention Heart Study

**Table 2** Urinary sodium and potassium excretion measurement methods of participating cohorts in Aim 1

| Cohort | Brief Description of Urinary Sodium and Potassium Excretion Measurement | Relevant References |
|---|---|---|
| Genetic Epidemiology Network of Arteriopathy (GENOA)<br><br>**USA** | In GENOA, participants completed at least one 24-hour urine collection at a CKD and/or GDUL study visit. A total of 333, 295, and 183 participants had a total of 1, 2, or 3 urine collections, respectively. For individuals with 2 or 3 urine collections, values were averaged for analysis. The mean time between the earliest CKD and latest GDUL urine collections was 1.73 years (range ¼ 0.9-3.6 years). The average time between the 2 GDUL collections was 22 days. Intraclass correlation coefficients for urine factors across collections revealed that most urine measures were relatively stable across time. Urine was collected with toluene as a preservative and twenty-four-hour urinary sodium and potassium excretion were measured in the Mayo Clinic Renal Testing Laboratory. | Lieske, John C., et al. "Heritability of dietary traits that contribute to nephrolithiasis in a cohort of adult sibships." Journal of nephrology 29.1 (2016): 45-51. |
| Prevention of REnal and Vascular ENd-stage Disease (PREVEND)<br><br>**Netherlands** | Urinary excretions of sodium and potassium were determined with a MEGA clinical chemistry analyzer (Merck, Darmstadt, Germany). Sodium and potassium were determined by indirect potentiometry. | Verhave, Jacobien C., et al. "Sodium intake affects urinary albumin excretion especially in overweight subjects." Journal of internal medicine 256.4 (2004): 324-330. |
| Hypertension Genetic Epidemiology Network (HyperGEN)<br><br>**USA** | An overnight urine sample was collected for sodium and potassium and extrapolated to 24-h urinary sodium and potassium excretion using the method of simple volume-time linear extrapolation. | Province, Michael A., et al. "Association between the α-adducin gene and hypertension in the HyperGEN Study." American journal of hypertension 13.6 (2000): 710-718. |
| Heredity and Phenotype Intervention (HAPI) Heart<br><br>**USA** | The HAPI Heart study participants collected the first morning void on the day they were scheduled to come in for Clinic Visit 1. Urine was measured for creatinine, sodium, and potassium at Quest Laboratories, Horsham, PA. These spot urines were used to estimate 24-hour creatinine, sodium, and potassium variables using the Kawasaki formula. | Mitchell, Braxton D., et al. "The genetic response to short-term interventions affecting cardiovascular function: rationale and design of the Heredity and Phenotype Intervention (HAPI) Heart Study." American heart journal 155.5 (2008): 823-828. |
| Framingham Heart Study (FHS)<br><br>**USA** | Twenty-four-hour urine sample was collected for sodium and potassium measurement. | |
| Healthy Twin Study, Korea (HTS)<br><br>**South Korea** | Half-day urine (HU) samples were collected from all participants in the Healthy Twin Study. HU collection started at ~1900 on the day before their visit, after the subjects had completely voided and discarded their urine; the exact time was recorded. Each participant's urine was collected in a bag until the next day's visit for his or her health examination. In the morning, at ~0900 on site, any remaining urine was further voided and the time and the total volume were reported as final records. The amount of sodium and potassium in the urine samples was measured by ion-selective electrode potentiometry in one central laboratory, which was certified and had passed all quality-control regulations set forth by the government. The 24-h sodium excretion level was estimated by using simple volume-time linear extrapolation on the HU samples or by using Kawasaki formula on the excretion level if the duration of urine collection is less than 8 hours. | Kho, M., Lee, J. E., Song, Y. M., Lee, K., Kim, K., Yang, S., ... & Sung, J. (2013). Genetic and environmental influences on sodium intake determined by using half-day urine samples: the Healthy Twin Study–. The American journal of clinical nutrition, 98(6), 1410-1416. |

**Table 3** Genotyping information for participating cohorts in Aim 1

| Cohort | Array type | Genotype calling | QC filters for genotyped SNPs used for imputation | Imputation Software | Data management and statistical analysis | Population stratification or principal components | Type of reported imputation quality |
|---|---|---|---|---|---|---|---|
| **GENOA** | Affymetrix Genome-Wide Human SNP Array 6.0 (91.9% of sample); Illumina Human 1M-Duo, 660-Quad, or 610-Quad (8.1% of sample) | Birdseed; Illumina Genome Studio | Call rate < 95% | IMPUTE version 2 | R | First 4 PCA | INFO |
| **PREVEND** | Illumina Cyto SNP12 v2 array | | HWE P <0.00001, MAF <1%, call rate <95% | IMPUTE2 version 2.2.0 | SNPtest V2.5 | First 5 PCA | INFO |
| **HyperGEN (EA)** | Affymetrix 5.0 | BRLMM | Mendelian errors, HWE $P<10^{-6}$ | MaCH/minimac | MMAP | N/A | Rsq |
| **HyperGEN (AA)** | Affymetrix 6.0 | Birdseed | Mendelian errors, HWE $P<10^{-6}$ | MaCH/minimac | MMAP | PC 1 | Rsq |
| **HAPI Heart** | Affymetrix 500K and Affymetrix 6.0 | BRLMM | HWE < 1e-6, Call rate ≤ 0.95, MAF < 0.01, mendelian errors, and sex mismatch | MaCH/minimac | MMAP | Kinship matrix based on 14-generation Amish pedigree | Rsq |
| **FHS** | Affymetrix 500K mapping array and the Affymetrix 50K gene-focused molecular imprinted polymer array | BRLMM | HWE < 1e-6, Call rate < 95%, MAF< 1% | MACH | R | N/A | Rsq |
| **HTS** | Affymetrix 6.0 | Birdseed | HWE <0.001, MAF <0.01, and genotype missing rate >0.05 | IMPUTE version 2 | GenABEL | Kinship matrix | INFO |

**Table 4** Meta-analysis results of 24-hour sodium excretion, 24-hour potassium excretion, sodium-to-potassium ratio for all loci brought forward for replication (P <5x10$^{-6}$ from discovery meta-analysis) in Aim 1

Chr, chromosome; A1, effect allele; A2, non-effect allele; EAF, effect allele frequency
Increasing beta indicates higher excretion of sodium and potassium
Nearest Gene: Genes near index SNP (± 5Kb Upstream/Downstream distance bp)
Gene names were obtained using variant effect predictor (VEP) from Ensembl using GRCh37
Genes with intragenic index variants bolded.
Direction of effect in GENOA, PREVEND, HpyperGEN EA, HAPI Heart, and FHS in European ancestry, respectively

## 24-hour sodium excretion

| SNP | Nearest Gene | Chr | Position | A1 | A2 | EAF | N | Direction | Beta | SE | P |
|---|---|---|---|---|---|---|---|---|---|---|---|
| rs71639080 | **FCGR2B** **FCGR2C** **RP11-25K21.6** **FCGR3A** | 1 | 161565867 | t | c | 0.02 | 1651 | +??+? | 71.03 | 12.26 | **6.88E-09** |
| rs188869607 | RPL9P28 CTD-2377D24.2 **CTD-2377D24.8** | 17 | 46764522 | a | t | 0.48 | 7344 | ++-++ | 5.14 | 0.97 | 1.28E-07 |
| rs117259059 | **MLLT11** CDC42SE1 | 1 | 151034164 | t | c | 0.02 | 6500 | +++?- | 19.78 | 3.79 | 1.84E-07 |
| rs7291524 | JOSD1 GTPBP1 | 22 | 39100545 | t | c | 0.04 | 7344 | +++++ | 12.54 | 2.41 | 1.87E-07 |
| rs145860590 | | 1 | 151325810 | d | i | 0.02 | 5699 | ++-?? | 21.75 | 4.18 | 1.97E-07 |
| rs16852403 | | 1 | 178039226 | t | c | 0.80 | 7344 | +++++ | 5.65 | 1.10 | 3.09E-07 |
| rs139574219 | | 7 | 110287083 | t | c | 0.99 | 1608 | -???- | -47.40 | 9.27 | 3.21E-07 |
| rs6703721 | | 1 | 178037791 | t | c | 0.21 | 7344 | ----- | -5.52 | 1.09 | 4.61E-07 |
| rs6662255 | | 1 | 178040083 | t | c | 0.21 | 7344 | ----- | -5.56 | 1.11 | 4.87E-07 |
| rs182773669 | **JOSD1** GTPBP1 | 22 | 39096945 | t | c | 0.96 | 6500 | ---?- | -14.45 | 2.88 | 5.40E-07 |
| rs192132524 | GABPB2 | 1 | 151064827 | t | c | 0.03 | 5243 | ++??- | 17.17 | 3.43 | 5.66E-07 |
| rs200660817 | TOMM22 JOSD1 **RP3-508I15.9** | 22 | 39077150 | d | i | 0.07 | 7344 | +++++ | 10.09 | 2.02 | 5.94E-07 |
| rs182605199 | | 2 | 74951285 | t | c | 0.02 | 5286 | ++?+? | 27.14 | 5.47 | 6.98E-07 |
| rs144955294 | | 7 | 110262691 | t | c | 0.01 | 1608 | +???+ | 46.59 | 9.46 | 8.37E-07 |
| rs1033925 | | 10 | 58606785 | t | c | 0.93 | 7344 | ----- | -9.14 | 1.86 | 8.55E-07 |
| rs11583320 | | 1 | 178042145 | t | c | 0.80 | 7344 | +++++ | 5.45 | 1.11 | 8.91E-07 |
| rs73289729 | | 10 | 58604226 | a | t | 0.93 | 7344 | ----- | -9.11 | 1.86 | 9.40E-07 |
| rs73049336 | | 1 | 178042298 | a | t | 0.80 | 7344 | +++++ | 5.44 | 1.11 | 9.46E-07 |
| rs1925315 | | 10 | 58591477 | a | t | 0.07 | 7344 | +++++ | 9.00 | 1.86 | 1.29E-06 |
| rs111674304 | | 1 | 178043192 | t | c | 0.80 | 7344 | +++++ | 5.35 | 1.11 | 1.42E-06 |
| rs73287651 | | 10 | 58580254 | a | g | 0.07 | 7344 | +++++ | 9.01 | 1.87 | 1.42E-06 |
| rs981155 | | 10 | 58573238 | a | c | 0.93 | 7344 | ----- | -9.00 | 1.87 | 1.50E-06 |
| rs72653410 | **GLB1L2** | 11 | 134216182 | a | c | 0.06 | 5286 | --?-? | -13.90 | 2.94 | 2.22E-06 |
| rs73159315 | NPTXR | 22 | 39213327 | t | c | 0.10 | 7344 | +++++ | 8.18 | 1.74 | 2.50E-06 |

| rs12538837 | | 7 | 97684468 | t | c | 0.72 | 7344 | ++++- | 4.66 | 1.00 | 2.86E-06 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| rs200302969 | **SETD7** | 4 | 140491783 | d | i | 0.32 | 7344 | +++++ | 4.79 | 1.03 | 2.93E-06 |
| rs3847055 | | 7 | 97680645 | a | g | 0.72 | 7344 | ++++- | 4.67 | 1.00 | 2.95E-06 |
| rs847573 | | 7 | 97681761 | t | c | 0.29 | 7344 | ----- | -4.59 | 0.98 | 3.04E-06 |
| rs5750620 | **DMC1** | 22 | 38952493 | a | t | 0.04 | 7344 | +++++ | 11.22 | 2.42 | 3.44E-06 |
| rs1292811 | **DMC1** | 22 | 38927886 | t | c | 0.04 | 7344 | +++++ | 11.42 | 2.47 | 3.76E-06 |
| rs7691513 | **SETD7** | 4 | 140498292 | t | c | 0.22 | 7344 | +++++ | 5.03 | 1.09 | 3.84E-06 |
| rs4713599 | TAP1 **PSMB8** TAP2 PSMB9 TAPSAR1 | 6 | 32811530 | a | c | 0.92 | 7344 | --+-- | -7.95 | 1.73 | 4.10E-06 |
| rs59849088 | **SETD7** | 4 | 140499281 | d | i | 0.22 | 7344 | +++++ | 5.00 | 1.09 | 4.20E-06 |
| rs200142350 | **AC005523.3** | 19 | 4786178 | d | i | 0.54 | 5286 | ++?-? | 5.32 | 1.16 | 4.34E-06 |
| rs181724901 | **MUC22** | 6 | 30989117 | a | g | 0.09 | 6087 | --?-- | -7.80 | 1.70 | 4.50E-06 |
| rs34262838 | | 7 | 97675148 | t | c | 0.28 | 7344 | ----+ | -4.61 | 1.01 | 4.55E-06 |
| rs144364970 | RPL9P28 CTD-2377D24.2 **CTD-2377D24.8** | 17 | 46772982 | d | i | 0.55 | 7344 | ----- | -4.15 | 0.91 | 4.74E-06 |
| rs5750666 | CBY1 TOMM22 **RP3-508I15.9** | 22 | 39073210 | a | g | 0.04 | 6500 | +++?+ | 13.48 | 2.95 | 4.87E-06 |
| rs10445381 | RPL9P28 CTD-2377D24.2 **CTD-2377D24.8** | 17 | 46766306 | a | g | 0.45 | 7344 | +++++ | 4.10 | 0.90 | 4.93E-06 |

## 24-hour potassium excretion

| SNP | Nearest Gene | Chr | Position | A1 | A2 | EAF | N | Direction | Beta | SE | P |
|---|---|---|---|---|---|---|---|---|---|---|---|
| rs71409269 | BCL2A1 | 15 | 80249333 | t | c | 0.12 | 7346 | ++-++ | 2.82 | 0.55 | 2.70E-07 |
| rs139376539 | | 6 | 125681952 | c | g | 0.01 | 2099 | ??++? | 20.44 | 4.09 | 6.11E-07 |
| rs78755596 | ABO; RP11-430N14.4 | 9 | 136124590 | a | t | 0.06 | 7346 | +++++ | 4.79 | 0.96 | 6.15E-07 |
| rs114543420 | **RP11-431M7.2** | 4 | 36358412 | a | g | 0.99 | 1612 | -???- | -19.08 | 3.83 | 6.57E-07 |
| rs201920383 | LINC00672 | 17 | 37086244 | d | i | 0.08 | 5290 | ++?+? | 3.70 | 0.75 | 7.42E-07 |
| rs111345501 | PATZ1; **RP3-400N23.6** | 22 | 31719404 | t | g | 0.01 | 4890 | ?++?? | 12.70 | 2.58 | 8.85E-07 |
| rs145526382 | ABO; RP11-430N14.4 | 9 | 136121623 | t | c | 0.06 | 7346 | +++++ | 4.63 | 0.95 | 1.27E-06 |
| rs4262910 | BCL2A1 | 15 | 80248501 | a | g | 0.16 | 7346 | +++++ | 2.41 | 0.50 | 1.44E-06 |
| rs71409267 | | 15 | 80245221 | t | g | 0.83 | 7346 | ----- | -2.39 | 0.50 | 1.47E-06 |
| rs142142409 | | 15 | 80245922 | d | i | 0.17 | 7346 | +++++ | 2.39 | 0.50 | 1.48E-06 |
| rs6836562 | | 4 | 148278891 | t | c | 0.16 | 7346 | +++++ | 2.34 | 0.49 | 1.54E-06 |
| rs185185619 | | 1 | 37906000 | a | c | 0.99 | 4446 | --??? | -11.73 | 2.44 | 1.59E-06 |
| rs72857549 | | 2 | 30151870 | a | g | 0.98 | 7346 | +++++ | 6.71 | 1.42 | 2.24E-06 |
| rs4765208 | BRI3BP | 12 | 125519633 | t | c | 0.71 | 7346 | ----- | -1.87 | 0.40 | 2.27E-06 |
| rs78881198 | **CUL3** | 2 | 225434223 | t | c | 0.01 | 2056 | ??+?+ | 19.13 | 4.04 | 2.28E-06 |
| rs56319019 | ARHGAP22 | 10 | 49866788 | a | g | 0.02 | 6502 | +++?+ | 7.39 | 1.57 | 2.61E-06 |
| rs13419091 | | 2 | 30150824 | a | t | 0.02 | 7346 | ----- | -6.64 | 1.41 | 2.68E-06 |
| rs184017158 | | 6 | 37383326 | t | c | 0.97 | 6502 | --+?- | -7.41 | 1.58 | 2.76E-06 |

| SNP | Nearest Gene | Chr | Position | A1 | A2 | EAF | N | Direction | Beta | SE | P |
|---|---|---|---|---|---|---|---|---|---|---|---|
| rs112414910 | **EIF4ENIF1; SFI1; DRG1** | 22 | 31886109 | c | g | 0.98 | 6502 | +--?+ | -7.66 | 1.65 | 3.46E-06 |
| rs79591115 | **DDX31** | 9 | 135486329 | c | g | 0.01 | 5247 | --??- | -11.12 | 2.40 | 3.59E-06 |
| rs72788784 | | 16 | 64818665 | a | g | 0.01 | 6502 | +++?+ | 9.46 | 2.04 | 3.75E-06 |
| rs189560660 | | 2 | 129472735 | t | c | 0.99 | 4446 | ++??? | 12.87 | 2.79 | 4.00E-06 |
| rs6836525 | | 4 | 148278846 | t | c | 0.18 | 7346 | +++++ | 2.01 | 0.44 | 4.11E-06 |
| rs79332849 | UNC13C | 15 | 54301716 | c | g | 0.03 | 7346 | ----- | -4.47 | 0.97 | 4.14E-06 |
| rs199583567 | **ASH1L;** snoU13 | 1 | 155381361 | d | i | 0.25 | 7346 | +---- | -2.10 | 0.46 | 4.16E-06 |
| rs76323568 | **TSPEAR; KRTAP10-11; KRTAP12-4** | 21 | 46070028 | a | g | 0.04 | 6091 | ++?++ | 4.92 | 1.07 | 4.28E-06 |
| rs78761110 | **CUL3** | 2 | 225429316 | t | g | 0.99 | 2056 | ??-?- | -18.28 | 3.98 | 4.43E-06 |
| rs138370749 | **DLEU2** | 13 | 50617864 | t | c | 0.99 | 1612 | -???- | -16.87 | 3.67 | 4.54E-06 |
| rs71409262 | | 15 | 80216516 | a | c | 0.86 | 7346 | ----- | -2.24 | 0.49 | 4.80E-06 |
| rs34149442 | ST20-MTHFS; ST20; C15orf37 | 15 | 80216176 | t | g | 0.14 | 7346 | +++++ | 2.24 | 0.49 | 4.98E-06 |
| rs200218912 | | 2 | 119115839 | d | i | 0.89 | 7346 | ----- | -3.83 | 0.84 | 4.98E-06 |

## Sodium-to-potassium ratio

| SNP | Nearest Gene | Chr | Position | A1 | A2 | EAF | N | Direction | Beta | SE | P |
|---|---|---|---|---|---|---|---|---|---|---|---|
| rs77958157 | | 5 | 71166807 | a | c | 0.01 | 4441 | ++??? | 0.51 | 0.09 | 5.53E-08 |
| rs148459019 | | 6 | 32836582 | t | g | 0.01 | 4436 | ?+??+ | 0.41 | 0.08 | 1.56E-07 |
| rs72824746 | **SH3RF3** | 2 | 110034953 | t | c | 0.08 | 7339 | +++++ | 0.17 | 0.03 | 8.67E-07 |
| rs142729205 | | 3 | 140538834 | d | i | 0.90 | 7339 | +++++ | 0.14 | 0.03 | 9.04E-07 |
| rs72987180 | | 3 | 140538648 | a | g | 0.90 | 7339 | +++++ | 0.14 | 0.03 | 1.02E-06 |
| rs189926695 | | 6 | 78194765 | a | g | 0.17 | 6495 | --+?- | -0.12 | 0.03 | 1.08E-06 |
| rs117738029 | | 14 | 43033528 | a | t | 0.96 | 7339 | +++++ | 0.25 | 0.05 | 1.46E-06 |
| rs114631099 | RP11-483H11.1; **CTC-228N24.1** | 5 | 127126945 | a | g | 0.99 | 4888 | ?++?? | 0.43 | 0.09 | 1.68E-06 |
| rs115322212 | | 3 | 140538274 | c | g | 0.92 | 7339 | +++++ | 0.15 | 0.03 | 1.83E-06 |
| rs201948417 | **RP11-433C9.2; EIF2B5; RP11-433C9.2** | 3 | 184133284 | d | i | 0.92 | 7339 | --+-- | -0.15 | 0.03 | 2.33E-06 |
| rs181723052 | **KLF12** | 13 | 74294499 | t | c | 0.99 | 1607 | +???+ | 0.78 | 0.17 | 2.78E-06 |
| rs57782376 | | 3 | 140537390 | a | g | 0.92 | 7339 | +++++ | 0.15 | 0.03 | 3.00E-06 |
| rs115979281 | **CTC-228N24.1** | 5 | 127143872 | t | c | 0.01 | 4888 | ?--?? | -0.43 | 0.09 | 3.35E-06 |
| rs17790795 | | 8 | 57835147 | a | t | 0.10 | 7339 | ++-++ | 0.11 | 0.02 | 3.76E-06 |
| rs147099958 | **SH3RF3** | 2 | 110037118 | c | g | 0.08 | 7339 | +++++ | 0.15 | 0.03 | 3.88E-06 |
| rs201412779 | | 10 | 8545238 | d | i | 0.34 | 7339 | ----+ | -0.07 | 0.02 | 3.93E-06 |
| rs113045433 | | 4 | 67219961 | t | c | 0.01 | 7339 | +++++ | 0.31 | 0.07 | 4.08E-06 |
| rs113574066 | | 16 | 14080683 | c | g | 0.02 | 6495 | +++?+ | 0.26 | 0.06 | 4.19E-06 |
| rs111794147 | | 16 | 14087498 | t | c | 0.02 | 6495 | +++?+ | 0.27 | 0.06 | 4.38E-06 |
| rs143925020 | | 16 | 14084386 | a | g | 0.98 | 6495 | ---?- | -0.26 | 0.06 | 4.94E-06 |

**Table 5** Meta-analysis results of 24-hour sodium excretion, 24-hour potassium excretion, sodium-to-potassium ratio with adjustment for BMI and height for all loci brought forward for replication (P <5x10$^{-6}$ from discovery meta-analysis) in Aim 1

Chr, chromosome; A1, effect allele; A2, non-effect allele; EAF, effect allele frequency
Increasing beta indicates higher excretion of sodium and potassium
Nearest Gene: Genes near index SNP (± 5Kb Upstream/Downstream distance bp)
Gene names were obtained using variant effect predictor (VEP) from Ensembl using GRCh37
Genes with intragenic index variants bolded.
Direction of effect in GENOA, PREVEND, HpyperGEN EA, HAPI Heart, and FHS in European ancestry, respectively

### 24-hour sodium excretion

| SNP | Nearest Gene | Chr | Position | A1 | A2 | EAF | N | Direction | Beta | SE | P |
|------|------|------|------|------|------|------|------|------|------|------|------|
| rs71639080 | **FCGR2B** **FCGR2C** RP11-25K21.6 **FCGR3A** | 1 | 161565867 | t | c | 0.02 | 1651 | +??+? | 69.41 | 11.94 | **6.21E-09** |
| rs145860590 | | 1 | 151325810 | d | i | 0.02 | 5670 | ++-?? | 21.55 | 3.98 | 6.22E-08 |
| rs188869607 | RPL9P28 CTD-2377D24.2 **CTD-2377D24.8** | 17 | 46764522 | a | t | 0.48 | 7315 | ++-++ | 4.93 | 0.93 | 1.23E-07 |
| rs117259059 | **MLLT11** **CDC42SE1** | 1 | 151034164 | t | c | 0.02 | 6471 | +++?- | 17.96 | 3.61 | 6.46E-07 |
| rs139574219 | | 7 | 110287083 | t | c | 0.99 | 1608 | -???- | -43.49 | 8.81 | 7.88E-07 |
| rs192132524 | **GABPB2** | 1 | 151064827 | t | c | 0.03 | 5214 | ++??- | 16.10 | 3.26 | 7.95E-07 |
| rs16852403 | | 1 | 178039226 | t | c | 0.80 | 7315 | +++++ | 5.21 | 1.06 | 8.21E-07 |
| rs202066699 | | 20 | 22448711 | d | i | 0.99 | 5707 | ?---? | -29.34 | 5.96 | 8.52E-07 |
| rs144955294 | | 7 | 110262691 | t | c | 0.01 | 1608 | +???+ | 43.85 | 8.98 | 1.04E-06 |
| rs6662255 | | 1 | 178040083 | t | c | 0.21 | 7315 | ----- | -5.16 | 1.06 | 1.08E-06 |
| rs6703721 | | 1 | 178037791 | t | c | 0.21 | 7315 | ----- | -5.06 | 1.05 | 1.38E-06 |
| rs73192435 | | 13 | 53525710 | a | g | 0.92 | 7315 | +++++ | 7.75 | 1.63 | 1.96E-06 |
| rs11583320 | | 1 | 178042145 | t | c | 0.80 | 7315 | +++++ | 5.04 | 1.06 | 2.05E-06 |
| rs73049336 | | 1 | 178042298 | a | t | 0.80 | 7315 | +++++ | 5.03 | 1.06 | 2.17E-06 |
| rs149456297 | **COMMD10** | 5 | 115468458 | a | g | 0.98 | 6514 | ++++? | 24.05 | 5.08 | 2.20E-06 |
| rs3847055 | | 7 | 97680645 | a | g | 0.72 | 7315 | ++++- | 4.53 | 0.96 | 2.20E-06 |
| rs12538837 | | 7 | 97684468 | t | c | 0.72 | 7315 | ++++- | 4.52 | 0.96 | 2.21E-06 |
| rs4750189 | | 10 | 6299461 | a | t | 0.99 | 6471 | +++?+ | 23.58 | 5.01 | 2.51E-06 |
| rs847573 | | 7 | 97681761 | t | c | 0.29 | 7315 | ----+ | -4.42 | 0.94 | 2.66E-06 |
| rs190632626 | **IBTK** | 6 | 82935144 | a | t | 0.94 | 5257 | --?-? | -16.48 | 3.52 | 2.83E-06 |
| rs111674304 | | 1 | 178043192 | t | c | 0.80 | 7315 | +++++ | 4.96 | 1.06 | 3.06E-06 |
| rs7691513 | **SETD7** | 4 | 140498292 | t | c | 0.22 | 7315 | ++++- | 4.82 | 1.04 | 3.38E-06 |
| rs10445381 | RPL9P28 CTD-2377D24.2 **CTD-2377D24.8** | 17 | 46766306 | a | g | 0.45 | 7315 | +++++ | 4.00 | 0.86 | 3.41E-06 |
| rs34262838 | | 7 | 97675148 | t | c | 0.27 | 7315 | ----+ | -4.47 | 0.96 | 3.43E-06 |
| rs4713599 | TAP1 **PSMB8** | 6 | 32811530 | a | c | 0.92 | 7315 | ----- | -7.70 | 1.66 | 3.46E-06 |

| | TAP2 PSMB9 TAPSAR1 | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| rs144364970 | RPL9P28 CTD-2377D24.2 **CTD-2377D24.8** | 17 | 46772982 | d | i | 0.55 | 7315 | ----- | -4.03 | 0.87 | 3.46E-06 |
| rs3096643 | RPL9P28 CTD-2377D24.2 **CTD-2377D24.8** | 17 | 46769448 | t | g | 0.55 | 7315 | ----- | -4.00 | 0.86 | 3.66E-06 |
| rs59849088 | **SETD7** | 4 | 140499281 | d | i | 0.22 | 7315 | ++++- | 4.80 | 1.04 | 3.69E-06 |
| rs112609688 | **CTD-2377D24.8** | 17 | 46775760 | t | c | 0.45 | 7315 | +++++ | 4.04 | 0.88 | 3.91E-06 |
| rs184839545 | **ANTXR2** | 4 | 81038950 | a | c | 0.01 | 7315 | ++-++ | 21.30 | 4.62 | 4.07E-06 |
| rs706327 | **SETD7** | 4 | 140508093 | a | g | 0.27 | 7315 | ++++- | 4.49 | 0.98 | 4.27E-06 |
| rs182605199 | | 2 | 74951285 | t | c | 0.02 | 5257 | ++?+? | 23.99 | 5.22 | 4.33E-06 |
| rs75040643 | **RBM47** | 4 | 40577657 | c | g | 0.03 | 7315 | ----- | -15.89 | 3.46 | 4.41E-06 |
| rs77416301 | **PI4KB** ZNF687 | 1 | 151266354 | t | c | 0.03 | 6471 | +++?- | 15.07 | 3.29 | 4.63E-06 |
| rs181407375 | | 1 | 151455888 | a | t | 0.96 | 7315 | --+-- | -12.86 | 2.81 | 4.70E-06 |
| rs185109580 | **CLMP** | 11 | 122951118 | t | c | 0.99 | 1608 | -???- | -47.79 | 10.46 | 4.93E-06 |

## 24-hour potassium excretion

| SNP | Nearest Gene | Chr | Position | A1 | A2 | EAF | N | Direction | Beta | SE | P |
|---|---|---|---|---|---|---|---|---|---|---|---|
| rs111345501 | PATZ1 **RP3-400N23.6** | 22 | 31719404 | t | g | 0.01 | 4861 | ?++?? | 13.58 | 2.53 | 8.11E-08 |
| rs114543420 | **RP11-431M7.2** | 4 | 36358412 | a | g | 0.99 | 1608 | -???- | -19.12 | 3.80 | 4.79E-07 |
| rs76323568 | **TSPEAR** KRTAP10-11 KRTAP12-4 | 21 | 46070028 | a | g | 0.04 | 6058 | ++?++ | 5.28 | 1.06 | 6.42E-07 |
| rs4262910 | BCL2A1 | 15 | 80248501 | a | g | 0.16 | 7313 | +++++ | 2.43 | 0.49 | 8.69E-07 |
| rs139944666 | OFCC1 | 6 | 9725540 | a | g | 0.73 | 7313 | +++++ | 1.84 | 0.37 | 8.94E-07 |
| rs71409269 | BCL2A1 | 15 | 80249333 | t | c | 0.12 | 7313 | ++-++ | 2.66 | 0.54 | 9.09E-07 |
| rs71409267 | | 15 | 80245221 | t | g | 0.83 | 7313 | ----- | -2.40 | 0.49 | 9.28E-07 |
| rs78881198 | | 2 | 225434223 | t | c | 0.01 | 2056 | ??+?+ | 19.63 | 4.00 | 9.55E-07 |
| rs142142409 | | 15 | 80245922 | d | i | 0.16 | 7313 | +++++ | 2.40 | 0.49 | 9.75E-07 |
| rs201920383 | LINC00672 | 17 | 37086244 | d | i | 0.09 | 5257 | ++?+? | 3.61 | 0.74 | 1.00E-06 |
| rs12206466 | OFCC1 | 6 | 9726060 | a | t | 0.70 | 7313 | +++++ | 1.74 | 0.36 | 1.14E-06 |
| rs1410361 | OFCC1 | 6 | 9720100 | t | c | 0.71 | 7313 | +++++ | 1.75 | 0.36 | 1.16E-06 |
| rs6836562 | | 4 | 148278891 | t | c | 0.16 | 7313 | +++++ | 2.34 | 0.48 | 1.19E-06 |
| rs78755596 | ABO RP11-430N14.4 | 9 | 136124590 | a | t | 0.06 | 7313 | +++++ | 4.61 | 0.95 | 1.24E-06 |
| rs112414910 | **EIF4ENIF1** **SFI1** **DRG1** | 22 | 31886109 | c | g | 0.98 | 6469 | +--?+ | -7.84 | 1.62 | 1.24E-06 |
| rs56067143 | OFCC1 | 6 | 9718581 | t | c | 0.71 | 7313 | +++++ | 1.74 | 0.36 | 1.30E-06 |
| rs10456766 | OFCC1 | 6 | 9723199 | a | g | 0.70 | 7313 | +++++ | 1.72 | 0.36 | 1.42E-06 |
| rs4498339 | OFCC1 | 6 | 9720266 | a | g | 0.29 | 7313 | ----- | -1.73 | 0.36 | 1.57E-06 |
| rs73723509 | OFCC1 | 6 | 9734887 | a | g | 0.70 | 7313 | +++++ | 1.71 | 0.36 | 1.66E-06 |
| rs79278948 | OFCC1 | 6 | 9718880 | a | g | 0.70 | 7313 | +++++ | 1.73 | 0.36 | 1.67E-06 |
| rs200543390 | | 11 | 42492593 | d | i | 0.12 | 7313 | +++++ | 2.51 | 0.53 | 1.71E-06 |
| rs10949284 | OFCC1 | 6 | 9750430 | t | c | 0.70 | 7313 | ??++? | 1.71 | 0.36 | 1.75E-06 |

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| rs139376539 | | 6 | 125681952 | c | g | 0.01 | 2099 | +++++ | 19.58 | 4.09 | 1.75E-06 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| rs6919349 | OFCC1 | 6 | 9743243 | a | t | 0.70 | 7313 | +++++ | 1.70 | 0.36 | 1.78E-06 |
| rs6936947 | OFCC1 | 6 | 9743225 | t | g | 0.30 | 7313 | ----- | -1.70 | 0.36 | 1.78E-06 |
| rs7765635 | OFCC1 | 6 | 9751165 | t | g | 0.70 | 7313 | +++++ | 1.70 | 0.36 | 1.80E-06 |
| rs12197949 | OFCC1 | 6 | 9740445 | t | g | 0.70 | 7313 | +++++ | 1.70 | 0.36 | 1.82E-06 |
| rs10949276 | OFCC1 | 6 | 9743309 | a | t | 0.70 | 7313 | +++++ | 1.70 | 0.36 | 1.82E-06 |
| rs6906634 | OFCC1 | 6 | 9748140 | a | c | 0.70 | 7313 | +++++ | 1.70 | 0.36 | 1.86E-06 |
| rs201934692 | | 11 | 42492594 | d | i | 0.12 | 7313 | +++++ | 2.50 | 0.52 | 1.87E-06 |
| rs143513312 | | 11 | 42492595 | d | i | 0.12 | 7313 | +++++ | 2.50 | 0.52 | 1.87E-06 |
| rs10949277 | OFCC1 | 6 | 9743509 | t | c | 0.70 | 7313 | +++++ | 1.70 | 0.36 | 1.88E-06 |
| rs4765208 | BRI3BP | 12 | 125519633 | t | c | 0.71 | 7313 | ----- | -1.86 | 0.39 | 1.97E-06 |
| rs12194264 | OFCC1 | 6 | 9738557 | t | c | 0.70 | 7313 | +++++ | 1.70 | 0.36 | 2.04E-06 |
| rs185185619 | | 1 | 37906000 | a | c | 0.99 | 4413 | --??? | -11.36 | 2.39 | 2.10E-06 |
| rs200218912 | | 2 | 119115839 | d | i | 0.89 | 7313 | ----- | -3.91 | 0.82 | 2.12E-06 |
| rs150588856 | | 21 | 40450627 | d | i | 0.06 | 2900 | ??+++ | 6.17 | 1.31 | 2.27E-06 |
| rs78761110 | **CUL3** | 2 | 225429316 | t | g | 0.99 | 2056 | ??-?- | -18.63 | 3.94 | 2.28E-06 |
| rs145526382 | ABO RP11-430N14.4 | 9 | 136121623 | t | c | 0.06 | 7313 | +++++ | 4.43 | 0.95 | 2.82E-06 |
| rs143562963 | | 13 | 73815106 | a | g | 0.01 | 6506 | ?+-++ | 7.68 | 1.64 | 2.86E-06 |
| rs79810257 | **TSPEAR** KRTAP12-2 | 21 | 46083419 | t | c | 0.04 | 6058 | ++?++ | 4.83 | 1.03 | 2.92E-06 |
| rs189560660 | | 2 | 129472735 | t | c | 0.99 | 4413 | ++??? | 12.89 | 2.76 | 3.04E-06 |
| rs12195113 | OFCC1 | 6 | 9754520 | a | t | 0.30 | 7313 | ----- | -1.67 | 0.36 | 3.05E-06 |
| rs199783078 | OFCC1 | 6 | 9760632 | d | i | 0.70 | 7313 | +++++ | 1.67 | 0.36 | 3.20E-06 |
| rs3038005 | OFCC1 | 6 | 9760633 | d | i | 0.70 | 7313 | +++++ | 1.67 | 0.36 | 3.24E-06 |
| rs12212374 | OFCC1 | 6 | 9754467 | c | g | 0.30 | 7313 | ----- | -1.67 | 0.36 | 3.38E-06 |
| rs113305219 | | 2 | 179948126 | a | c | 0.01 | 1651 | +??+? | 14.53 | 3.13 | 3.50E-06 |
| rs184017158 | | 6 | 37383326 | t | c | 0.97 | 6469 | --+?- | -7.20 | 1.55 | 3.51E-06 |
| rs79332849 | UNC13C | 15 | 54301716 | c | g | 0.03 | 7313 | ----- | -4.44 | 0.96 | 3.60E-06 |
| rs188284329 | | 11 | 42538203 | a | c | 0.91 | 7313 | ----- | -2.81 | 0.61 | 3.60E-06 |
| rs719947 | OFCC1 | 6 | 9760323 | t | c | 0.70 | 7313 | +++++ | 1.66 | 0.36 | 3.71E-06 |
| rs11142909 | RPL35AP21 | 9 | 74207717 | t | c | 0.04 | 2900 | ??+++ | 6.19 | 1.34 | 4.10E-06 |
| rs11142908 | RPL35AP21 | 9 | 74207715 | t | g | 0.96 | 2900 | ??--- | -6.19 | 1.34 | 4.11E-06 |
| rs11142910 | RPL35AP21 | 9 | 74207739 | t | c | 0.04 | 2900 | ??+++ | 6.19 | 1.34 | 4.11E-06 |
| rs72737924 | RPL35AP21 | 9 | 74208364 | t | c | 0.04 | 2900 | ??+++ | 6.19 | 1.34 | 4.13E-06 |
| rs28623525 | | 4 | 148291243 | t | c | 0.82 | 7313 | ----- | -1.96 | 0.43 | 4.32E-06 |
| rs6836525 | | 4 | 148278846 | t | c | 0.18 | 7313 | +++++ | 1.98 | 0.43 | 4.34E-06 |
| rs28720373 | | 4 | 148291242 | t | c | 0.18 | 7313 | +++++ | 1.96 | 0.43 | 4.37E-06 |
| rs11142911 | RPL35AP21 | 9 | 74207812 | a | g | 0.04 | 2900 | ??+++ | 6.18 | 1.35 | 4.38E-06 |
| rs138370749 | **DLEU2** | 13 | 50617864 | t | c | 0.99 | 1608 | -???- | -16.74 | 3.65 | 4.43E-06 |
| rs72857549 | | 2 | 30151870 | a | g | 0.98 | 7313 | +++++ | 6.42 | 1.40 | 4.44E-06 |
| rs4819363 | | 21 | 45421448 | c | g | 0.96 | 1651 | -??-? | -9.54 | 2.08 | 4.51E-06 |
| rs149875098 | | 8 | 134673221 | t | c | 0.02 | 4407 | ?-??- | -9.26 | 2.02 | 4.54E-06 |
| rs116446684 | **CUL3** | 2 | 225384862 | t | c | 0.01 | 2863 | +?+?+ | 14.55 | 3.17 | 4.55E-06 |

| rs67929684 | | 15 | 80336031 | t | g | 0.95 | 7313 | ----- | -3.67 | 0.80 | 4.60E-06 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| rs72788784 | | 16 | 64818665 | a | g | 0.01 | 6469 | +++?+ | 9.24 | 2.02 | 4.65E-06 |
| rs71308048 | | 15 | 80333868 | d | i | 0.95 | 7313 | ----- | -3.62 | 0.79 | 4.75E-06 |
| rs74459597 | | 13 | 73795820 | a | g | 0.02 | 5257 | -+?+? | 8.84 | 1.93 | 4.79E-06 |
| rs72737927 | | 9 | 74218054 | t | c | 0.04 | 2900 | ??+++ | 6.16 | 1.35 | 4.88E-06 |

## Sodium-to-potassium ratio

| SNP | Nearest Gene | Chr | Position | A1 | A2 | EAF | N | Direction | Beta | SE | P |
|---|---|---|---|---|---|---|---|---|---|---|---|
| rs77958157 | | 5 | 71166807 | a | c | 0.01 | 4413 | ++??? | 0.52 | 0.09 | **2.33E-08** |
| rs148459019 | | 6 | 32836582 | t | g | 0.01 | 4407 | ?+??+ | 0.42 | 0.08 | **3.71E-08** |
| rs142729205 | | 3 | 140538834 | d | i | 0.90 | 7311 | +++++ | 0.15 | 0.03 | 1.81E-07 |
| rs72987180 | | 3 | 140538648 | a | g | 0.90 | 7311 | +++++ | 0.15 | 0.03 | 1.91E-07 |
| rs115322212 | | 3 | 140538274 | c | g | 0.92 | 7311 | +++++ | 0.16 | 0.03 | 2.59E-07 |
| rs57782376 | | 3 | 140537390 | a | g | 0.92 | 7311 | +++++ | 0.16 | 0.03 | 4.93E-07 |
| rs117738029 | **CTD-2307P3.1** | 14 | 43033528 | a | t | 0.97 | 7311 | +++++ | 0.24 | 0.05 | 1.59E-06 |
| rs189926695 | | 6 | 78194765 | a | g | 0.17 | 6467 | --+?- | -0.12 | 0.02 | 1.78E-06 |
| rs4845198 | RP11-398M15.1 | 1 | 189786356 | a | g | 0.19 | 7311 | ---+- | -0.09 | 0.02 | 1.85E-06 |
| rs184355489 | **KIRREL3** | 11 | 126822059 | a | t | 0.99 | 1651 | -??-? | -0.88 | 0.19 | 1.88E-06 |
| rs114631099 | RP11-483H11.1; **CTC-228N24.1** | 5 | 127126945 | a | g | 0.99 | 4859 | ?++?? | 0.42 | 0.09 | 1.90E-06 |
| rs9427449 | RP11-398M15.1 | 1 | 189786693 | a | g | 0.18 | 7311 | ---+- | -0.09 | 0.02 | 2.19E-06 |
| rs1339433 | **RP11-398M15.1** | 1 | 189783443 | a | g | 0.82 | 7311 | +++-+ | 0.09 | 0.02 | 2.28E-06 |
| rs4845199 | RP11-398M15.1 | 1 | 189786362 | a | g | 0.18 | 7311 | ---+- | -0.09 | 0.02 | 2.88E-06 |
| rs201948417 | **RP11-433C9.2; EIF2B5** | 3 | 184133284 | d | i | 0.92 | 7311 | --+-- | -0.14 | 0.03 | 2.92E-06 |
| rs113045433 | | 4 | 67219961 | t | c | 0.02 | 7311 | +++++ | 0.30 | 0.07 | 3.31E-06 |
| rs2418519 | | 1 | 189818353 | t | c | 0.22 | 7311 | ---+- | -0.08 | 0.02 | 3.55E-06 |
| rs115979281 | **CTC-228N24.1** | 5 | 127143872 | t | c | 0.01 | 4859 | ?--?? | -0.42 | 0.09 | 3.97E-06 |
| rs73007388 | | 3 | 6445318 | a | g | 0.97 | 6467 | --+?- | -0.22 | 0.05 | 4.80E-06 |

**Table 6** Replication of SNPs from the meta-analysis results of 24-hour sodium excretion, 24-hour potassium excretion, sodium-to-potassium ratio in African Americans and Asians (P <5x10$^{-6}$ from discovery meta-analysis) in Aim 1.

**Replication in African Americans**

| Analysis | SNP | Chr | Position | A1 | A2 | N | Beta | SE | P |
|---|---|---|---|---|---|---|---|---|---|
| Potassium (adjusted for BMI and height) | rs200543390 | 11 | 42492593 | I | D | 1244 | -6.82 | 3.06 | **0.026** |
| Potassium (adjusted for BMI and height) | rs201934692 | 11 | 42492594 | I | D | 1244 | -6.79 | 3.06 | **0.027** |
| Potassium (adjusted for BMI and height) | rs143513312 | 11 | 42492595 | I | D | 1244 | -6.79 | 3.06 | **0.026** |
| Potassium (adjusted for BMI and height) | rs188284329 | 11 | 42538203 | A | C | 1244 | -12.46 | 6.36 | **0.050** |

**Replication in Asians**

| Analysis | SNP | Chr | Position | A1 | A2 | N | Beta | SE | P |
|---|---|---|---|---|---|---|---|---|---|
| Sodium | rs72653410 | 11 | 134216182 | C | A | 869 | 6.82 | 3.34 | **0.031** |
| Potassium (adjusted for BMI and height) | rs74459597 | 13 | 73795820 | G | A | 2221 | 5.08 | 2.46 | **0.031** |

Chr, chromosome; A1, effect allele; A2, non-effect allele
Increasing beta indicates higher excretion of sodium and potassium
Results displayed for SNPs with P value ≤ 0.05 in replication analysis

**Table 7** Replication of previously identified SNP rs12092050 from Tabara et al. 2015 in Aim 1

| Outcome | Race/Ethinicity | Covariates | EA | N | Beta | SE | P |
|---------|-----------------|------------|-----|------|-------|------|-------|
| **GWAS results of sodium, potassium, and sodium-to-potassium ratio** | | | | | | | |
| Sodium | European Ancestry | age, sex | a | 7344 | -0.02 | 0.96 | 0.985 |
| Sodium | African American | age, sex | a | 1246 | 3.37 | 6.09 | 0.580 |
| Sodium | Asian (Korean) | age, sex | g | 2458 | 0.68 | 2.53 | 0.774 |
| Potassium | European Ancestry | age, sex | a | 7346 | 0.11 | 0.36 | 0.764 |
| Potassium | African American | age, sex | a | 1246 | 1.70 | 2.14 | 0.428 |
| Potassium | Asian (Korean) | age, sex | g | 2462 | -1.42 | 0.86 | 0.085 |
| Sodium-to-potassium ratio | European Ancestry | age, sex | a | 7339 | 0.00 | 0.02 | 0.804 |
| Sodium-to-potassium ratio | African American | age, sex | a | 1233 | 0.00 | 0.13 | 0.999 |
| Sodium-to-potassium ratio | Asian (Korean) | age, sex | g | 2417 | 0.07 | 0.04 | 0.058 |
| **GWAS results of sodium, potassium, and sodium-to-potassium ratio adjusted for BMI and height** | | | | | | | |
| Sodium | European Ancestry | age, sex, BMI, height | a | 7315 | 0.16 | 0.92 | 0.865 |
| Sodium | African American | age, sex, BMI, height | a | - | - | - | - |
| Sodium | Asian (Korean) | age, sex, BMI, height | g | 2458 | 1.03 | 2.50 | 0.657 |
| Potassium | European Ancestry | age, sex, BMI, height | a | 7313 | 0.11 | 0.36 | 0.751 |
| Potassium | African American | age, sex, BMI, height | a | 1244 | 1.63 | 2.14 | 0.447 |
| Potassium | Asian (Korean) | age, sex, BMI, height | g | 2462 | -1.42 | 0.85 | 0.086 |
| Sodium-to-potassium ratio | European Ancestry | age, sex, BMI, height | a | 7311 | 0.01 | 0.02 | 0.709 |
| Sodium-to-potassium ratio | African American | age, sex, BMI, height | a | 1231 | 0.00 | 0.13 | 0.993 |
| Sodium-to-potassium ratio | Asian (Korean) | age, sex, BMI, height | g | 2417 | 0.07 | 0.04 | **0.044** |

Results in European ancestry are from the meta-analysis
Significant P value (P<0.05) bolded
EA: Effect allele

**CHAPTER III: Gene-based associations and effect modification underlying variation in sodium intake, potassium intake, and their ratio in two European American cohorts**

## 3.1 Introduction

Excess sodium intake and insufficient potassium intake are established risk factors for hypertension and cardiovascular disease (CVD) [2, 53, 97]. In 2010, about 1.7 million, or 9.5%, of all deaths from cardiovascular causes were attributed to high sodium intake globally [5]. On the other hand, potassium is a established protective factor for hypertension and related CVD. Individual sodium intake and potassium intake have a wide range of variability in the human population and are influenced by many factors. [32, 33]. The determinants of sodium and potassium intake have not been fully defined, but physiological, physical, developmental, cultural, genetic, and environmental factors as well as the interactions among these factors have been reported to influence variation in individual sodium and potassium intake [16, 27, 34]. In this Aim, we use gene-level association methods to better understand the relationship between genetic variation in genomic regions and variation in individual sodium and potassium intake, including the potential for interaction with sex, age, and education, since consumption differs from recommended values for men, older people, and people with low education [10].

Although many common disease risk factors have high heritability, genetic variants discovered from GWAS usually explain only a small portion of heritability, a phenomenon typically called "missing heritability." Identifying gene-environment interactions, as well as rare genetic variants that have not been detected by GWAS, could reduce the gap between estimated

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heritability and the portion of trait variation explained by genetic factors [98, 99]. To characterize susceptible populations and better explain the variation in sodium and potassium intake, it is necessary to identify genetic effects and gene-by-environment interactions on sodium and potassium intake using common and rare genetic variants data [10]. However, to our knowledge, no study exists that investigates gene-environment interaction for sodium and potassium intake. In the present study, we investigate whether the effects of genetic factors that influence sodium and potassium intake differ based on an individual's age, sex, and education level.

## 3.2 Methods

### Study populations

The analyses were conducted using two European American cohorts. The Genetic Epidemiology Network of Arteriopathy (GENOA) study [60] is a community-based study that aims to identify genes influencing blood pressure in participants from Rochester, MN and Jackson, MS. The study recruited sibships with at least two adults with clinically diagnosed essential hypertension before 60 years of age and then enrolled all available siblings within the family [60]. The Framingham Heart Study (FHS) is a community-based study that began in 1948 with the recruitment of an original cohort to identify risk factors for CVD and other chronic disease from the town of Framingham, MA, who had not yet developed CVD. The FHS cohort continued to recruit the second generation of study participants (children and spouses of children of the original cohort) in 1971 and a third generation of study participants (children of offspring cohort participants) in 2002-2005. Urinary sodium and potassium excretions were measured in the Offspring Study participants approximately every 4 years [64]. The analyses included a total

of 811 GENOA and 766 FHS participants who had genotype data and measurements of 24-hour urinary sodium excretion, 24-hour urinary potassium excretion, and adjustment variables including age, sex and education level.

**Measurements**

Sodium and potassium intake were quantified as continuous variables (mmol/day) from urine collections. In GENOA, urine was collected with toluene as a preservative, and twenty-four-hour urinary sodium and potassium excretions were measured in the Mayo Clinic Renal Testing Laboratory [100]. In FHS, the urinary sodium and potassium excretions were measured using an automated Ion-Selective Electrode (ISE) in the Offspring cohort. In each study, 24-hour sodium and potassium excretion measures were checked for normality, and outliers ± 4 standard deviations from the mean were removed.

For age, participants were grouped as age 65 and older or less than 65. For education level, participants were characterized as having less than a college/university education or having at least a college/university education.

**Genotyping and imputation**

GENOA participants were genotyped using the Affymetrix 6.0 (91.9 % of sample) arrays or the Illumina Human 1M-Duo, 660-Quad, or 610-Quad (8.1% of sample) genotyping arrays as well as the Illumina HumanExome Beadchip. In FHS, the genotyping was measured using the Affymetrix 500K/50K array and the Illumina HumanExome Beadchip. Each cohort performed internal quality control (QC) assessments of initial genotype data including excluding individuals with poor genotype call rate (i.e., <95%) and checking for relatedness across individuals. Quality

checks for single nucleotide polymorphisms (SNPs) included exclusion of SNPs with poor call rate (i.e., <95%), SNPs with Hardy-Weinberg disequilibrium $P<10^{-4}$, SNPs with high duplicate discordance rates, and monomorphic SNPs. Imputation for the Affymetrix genotype data and the Illumina Human 1M-Duo genotype data was performed using the 1000 Genomes Project Phase I Integrated Release Version 3 [March 2012] cosmopolitan reference panel using IMPUTE version 2 in GENOA and MACH in FHS. Genotyping variants with imputation quality less than 0.3 were excluded before the analysis.

**Statistical analysis**

We investigated gene-level associations and their interactions with age, sex, and education level in gene regions near SNPs that had significant ($P<5X10^{-8}$) or suggestive ($P<5X10^{-6}$) association with 24-hour urinary sodium excretion, potassium intake, and sodium-to-potassium intake ratio in GWAS from Aim 1. For those genes near SNPs with at least suggestive significance ($P<5X10^{-6}$) in Aim 1, we first tested the gene-level associations with each trait, and then evaluated the effect modification by sex, age, and education level on the gene-level associations in GENOA and FHS. We used a powerful set of kernel-based methods to test gene-level associations and gene-by-age, gene-by-sex, and gene-by-education level interactions [101, 102].

In order to use the existing SKAT and iSKAT program that were developed for unrelated samples, we transformed 24-hour urinary sodium and potassium excretion measured from related samples (GENOA and FHS) using GRAMMAR+ before the analysis [103]. SKAT is a supervised, flexible, and efficient score-based variance-component test to evaluate association between genetic variants and traits in a gene- or genomic-region [101, 102]. All position

information was based on genome assembly GRCh37, and the start and end position of each gene was defined by GENCODE annotation version 19. All SNPs within a gene region were used for each gene in the SKAT analysis. In GENOA, age, sex, and 4 principal components (PCs) were included as covariates for SKAT analysis. In FHS, age and sex were included as covariates. For gene-environment interactions, we used the interaction sequence kernel association test (iSKAT), which is an extension of SKAT methods [104, 105]. Similar to SKAT, iSKAT uses the score statistic after adjusting for the main effects of the gene and factors underlying differences in sodium and potassium intake (age, sex, and education level). In the analysis evaluating gene-by-age $\geq 65$ interactions, sex was included in the model as a covariate, and when evaluating the gene-by-sex interaction, age was included in the model as a covariate. For an analysis of gene-by-education interactions, both age and sex were included in the model, and the analysis was only conducted in GENOA. In GENOA, 4 PCs were additionally added to the models. The results for genes with number of genetic markers greater than 1,000 were excluded to have reliable results in the SKAT and iSKAT analyses. For weighting methods in SKAT and iSKAT, we used beta (1, 25) to upweight the rare variants from exome chip data, and beta (1, 1) to give equal weight to all variants from 1000G data. To resolve the multiple comparison problem, we calculated FDR adjusted P values, and all variants with FDR adjusted P value less than 0.1 were considered significant.

**3.3 Results**

The characteristics of the participants from the two European American cohorts, GENOA and FHS, are shown in Table 8. The participants in FHS were, on average, 4.5 years younger than those in GENOA (70.2 years in FHS and 65.7 years in GENOA). In GENOA, more than

95% of participants had at least a high school education, and almost 20% of participants had at least a college/university education. Additionally, almost 90% of participants in GENOA were hypertensive while only 52.6% of FHS participants were hypertensive. The 24-hour urinary sodium excretion level in GENOA was 139.4 on average and that of FHS was 136.5 mmol/day. On the other hand, the 24-hour urinary potassium in GENOA was 58.5 mmol/day on average and that of FHS was 67.9. As a result, the average sodium-to-potassium ratio was 2.5 in GENOA and 2.1 in FHS.

*Gene-based associations with 24-hour sodium excretion, 24-hour potassium excretions, and sodium-to-potassium ratio*

We had a total of 26, 23, and 6 genes to evaluate the gene-based association using SKAT and iSKAT with 24-hour urinary sodium excretion, 24-hour potassium excretion, and sodium-to-potassium ratio, respectively (Table 9). Table 10 and Table 12 show the P-values of gene-based association between genes and 24-hour urinary sodium excretion, 24-hour potassium excretion, and sodium-to-potassium ratio using 1000G and exome chip data in GENOA and FHS.

In GENOA, we found 4 and 2 genes that had at least a marginal significance (P<0.05) for 24-hour sodium excretion and 24-hour potassium excretion, respectively, using the gene-based analysis. Of the 6 genes, 3 genes had P values that passed FDR correction (FDR adjusted P value < 0.1): 1) *SETD7* gene-region on chromosome 4 from the SKAT analysis of 24-hour urinary sodium excretion using 1000G data (P value=0.004); 2) genes *ASH1L* on chromosome 1 and *RP11-431M7.2* on chromosome 4 from the SKAT analysis for 24-hour urinary potassium excretion using exome chip data (P=0.007 and 0.002, respectively).

In FHS, we found 2 gene-based associations with P-value <0.05 for each excretion trait (24-hour urinary sodium excretion, 24-hour potassium excretion, and sodium-to-potassium ratio). Out of 6 genes, *BRO3BP* and *LINC00672* genes had FDR adjusted P-value <0.1 in the gene-based association analysis for 24-hour potassium excretion (P=0.003 and 0.002, respectively), and *RP11-433C9.2* gene also had FDR adjusted P-value <0.1 for sodium-to-potassium ratio in the gene-based association analysis (P=0.016).

*Gene-by-age interactions, gene-by-sex interactions, and gene-by-college education interactions with 24-hour sodium excretion, 24-hour potassium excretions, and sodium-to-potassium ratio*

In the analysis of gene-by-environment interactions, 13 genes had at least marginally significant interactions (P<0.05) with age ≥ 65 years, sex, or college education on any of three outcome traits (24-hour urinary sodium excretion, 24-hour potassium excretion, and sodium-to-potassium ratio) in GENOA (Table 11). Of the genes, gene TAPSAR1 had P-value that passed FDR correction (FDR adjusted P-value <0.1) from the analysis of gene-by-age ≥65 years interactions using exome chip data. *CTC-228N24.1* had FDR adjusted P-value <0.1 from the both analysis of gene-by-sex interactions using 1000G data and gene-by-college education interactions using exome chip data. The genes *RP11-433C9.2* and *RP11-483H11.1* also had FDR adjusted P-value <0.1 from the analysis of gene-by-sex interactions using 1000G data and gene-by-college education using exome chip data, respectively.

In FHS, we found three genes that had at least a marginal significance (P<0.05) in the analyses of gene-by-age ≥65 years interactions (*CDC42SE* and *MLLT11*) or gene-by-sex interactions (*PSMB9*) on 24-hour sodium excretion using 1000G data, but none of the interactions had P-value that passed FDR correction (Table 11, FDR adjusted P-value <0.05)

**3.4 Discussion**

In the present study, we evaluated the association between gene-regions and outcomes from a previous GWAS including 24-hour urinary sodium excretion, 24-hour urinary potassium excretion, and sodium-to-potassium ratio in two European ancestry cohorts, GENOA and FHS. To do this, we used a gene-based approach with genetic variants from both 1000G imputed data and exome chip data. In GENOA, we found 4 and 2 gene-regions that had P value less than 0.05 in the SKAT analysis with 24-hour urinary sodium excretion or 24-hour urinary potassium excretion, respectively. In FHS, 2, 2, and 1 genes that had P-value less than 0.05 in the SKAT analysis with 24-hour urinary sodium excretion, 24-hour urinary potassium excretion, or their ratio, respectively. We also evaluated the interaction between genes and three demographic variables (age ≥ 65 years, sex, and college education) on 24-hour urinary sodium excretion, 24-hour urinary potassium excretion, or their ratio using iSKAT and found 16 interactions in GENOA, and 3 in FHS that had P value less than 0.05.

To identify the SNPs most strongly driving the association between the gene-region and three outcome phenotypes (24-hour sodium excretion, 24-hour potassium excretion, sodium-to-potassium ratio) or gene-by-demographic factors (age ≥ 65 years, sex, and college education), each SNP-outcome phenotype association and SNP-by-demographic factor interaction were modeled within a gene-region with P-value less than 0.5 from SKAT and iSKAT analysis using 1000 Genome imputed data (Figure 6 and 7). In the association analysis between the single SNP and the outcome variable, each SNP with the strongest signal was in linkage disequilibrium (LD) with multiple other SNPs in the regions of SETD7 and JOSD1 (24-hour sodium excretion) in GENOA, and BRI3BP and LINC00672 (24-hour potassium excretion) in FHS, respectively

(Figure 6). In the single SNP analysis of gene-by-sex on sodium to potassium ratio, each top

SNP (rs245177 and rs6443960) was in high LD with multiple other SNPs in each gene-region of

CTC-228N24.1 and RP11-433C9.2 in GENOA (Figure 7).

We used the gene-level approach to reduce the burden of multiple testing of individual

SNPs from Aim 1, and improve the power to detect significant effect modification in genetic

associations with factors including age, sex, and education. Another benefit of using the gene-

based strategy lies in the characteristic of a gene-level analyses. It is well known that the SNPs

that influence a trait may differ across ethnicities, even if the underlying genetic mechanisms are

the same. However, genes are a functional unit, so they do not vary across race/ethnicity, even

though allele frequency and linkage disequilibrium patterns may differ. These differences are

due to the ancestral origins of mutation and linkage disequilibrium (SNP correlation) patterns

that differ across ethnic groups. Although we used significant or suggestive SNPs from meta-

analysis in European American populations, we may replicate the significant SNPs from one

ancestry group in a different ancestry group in the future.

We set the age group cut-off at age 65 due to the aging process in human body. Many

studies have examined the change in prevalence of disease in individuals age 65 and over and

have found increased disease burden. For education level, we set the cut-off as completion of

college/university education. This is because most of our participants had completed a high

school education, and we wanted to evaluate the impact of a higher-level education in the

association between gene and sodium/potassium sodium intake level.

To illustrate the interaction effects, we created plots of interaction between top single

SNPs (rs245177 for *CTC-228N24.1* and rs6443960 for *RP11-433C9.2*) from the analysis of

single SNP-by-sex interactions, and sex on sodium-to-potassium ratio in GENOA (Figure 7).

Average predicted sodium-to-potassium ratio values by top SNP genotype, adjusted for age and the top 4 PCs for each sex group are presented in the bottom of Figure 7. The average predicted sodium-to-potassium ratio level increased with each additional copy of C in female group, but not in male group for rs245177 genotype from *CTC-228N24.1*. In the stratified analyses by sex, rs6443960 genotype from *RP11-433C9.2* was only associated with sodium-to-potassium level in male participants, and not in female participants in GENOA after adjusting for age and 4PCs (P in male group = 0.006 and P in female group = 0.26). Both *CTC-228N24.1* (coiled-coil domain containing 192) on chromosome 5 and *RP11-433C9.2* (long intergenic non-protein coding RNA 2054) on chromosome 3 are protein coding genes, but there has been no research that supports the mechanism of how these genes would be associated with sodium-to-potassium ratio.

The 24-hour urinary sodium and potassium excretion level were measured from related samples in GENOA and FHS. Although SKAT is able to work with correlated phenotypes using its advanced option of using a kinship matrix of the sample, the method has not been developed for iSKAT. Fortunately, the GRAMMAR+ from GeneABEL R package is able to transform traits from related samples into independent observations. The results from the standard SKAT analyses using the decorrelated phenotypes generated from GRAMMAR+ looked very similar to those from the advanced SKAT analyses that incorporated the familiar kinship matrix of samples.

The strengths of this present study include: 1) evaluation and confirmation of the genetic association from Aim 1 using state-of-the-art gene-based approach with improved power, 2) using both rare and common variants in the analyses of association, 3) testing multiple interactions with gene and epidemiological factors including age, sex, and education level.

However, we could not evaluate the associations and interactions in several genes including KRTAP10-11 and KRTAP12-4 when using rare variants from exome chip data, since our data set did not include variants located in the gene-regions. We decided on this selection of genes using the meta-analysis where the two cohorts in current study were included (not from independent cohorts), which could lead the increase of type 1 error. However, in the results of Aim 2, only a few genes had an FDR-adjusted P-value less than 0.1 with sodium and potassium excretion levels and their ratio. The low rate of replication in this gene-based approach may be due to inadequate sample sizes because only two out of the five European ancestry cohorts from Aim 1 were used in Aim 2. In future studies, we will extend the gene-based analyses to other cohorts, and SKAT results will be combined by conducting a meta-analysis using skatMeta R package, which will improve the power in future analyses [106, 107]. Another potential reason that the majority of genes had weak associations or interactions with outcome phenotypes is that the number of markers for each gene in 1000G exceeded the recommend level by SKAT program (the number of recommended markers is smaller than the sample size divided by 3).

The present study might help us better understand the genetics of sodium and potassium intake and explain missing heritability by using both common and rare variants as well as using advanced gene-based analytic strategies. Much more research is needed with larger cohorts, as we did not see significant replication of the gene-level findings in these two European cohorts. However, identifying preliminary evidence of effect modification of genetic effects on sodium and/or potassium intake by traditional epidemiological factors such as age, sex, and education does raise the important long-range question about how to tailor messaging about dietary behaviors to be more precise in order to have the desired health benefits for those individuals.

**Table 8** The basic characteristics of participating cohorts from GENOA and FHS in Aim 2

|  | **GENOA (N=811)** | **FHS (N=766)** |
|---|---|---|
| Cohort | Family-based | Family-based |
| Country | USA | USA |
| Race/ethnicity | European American | European American |
| Female (%) | 57.6 | 53.1 |
| Age in years | $65.7 \pm 9.1$ | 70.2 |
| Age $\geq$ 65 years (%) | 57.5 | 77.3 |
| Education |  |  |
| $\geq$ College/University (%) | 19.5 | - |
| Hypertension, % | 88.2 | 52.6 |
| Blood pressure lowering medication use, % | 76.2 | 52.4 |
| 24-h sodium excretion (mmol/day) | $139.4 \pm 58.3$ | $136.5 \pm 57.0$ |
| 24-h potassium excretion (mmol/day) | $58.5 \pm 22.9$ | $67.9 \pm 23.4$ |
| Sodium-to-potassium excretion ratio | $2.5 \pm 1.0$ | $2.1 \pm 0.9$ |
| Measurement of source | 24-hour urine | 24-hour urine |

For continuous variable: mean $\pm$ SD, For binary variable: %
Abbreviations:  EA- European American; GENOA- Genetic Epidemiology Network of Arteriopathy; FHS- Framingham Heart Study

**Table 9** Genes near genome-wide significant or suggestive SNPs from Aim 1 and number of genetic markers from 1000G and exome chip data available for each gene in Aim 2 analysis

CHR: chromosome, START: start position of gene based on genome assembly GRCh37, END: end position of gene based on genome assembly GRCh37, 1000G: 1000 Genomes Project imputed data, Exome: exome chip data

**24-hour sodium excretion**

| | | | | | GENOA | | FHS | |
|---|---|---|---|---|---|---|---|---|
| | | | | Gene size (kb) | 1000G Marker N | Exome Marker N | 1000G Marker N | Exome Marker N |
| Gene | CHR | START | END | | | | | |
| CDC42SE1 | 1 | 151023447 | 151042801 | 19.4 | 89 | 2 | 39 | 2 |
| MLLT11 | 1 | 151030234 | 151040970 | 10.7 | 53 | 1 | 21 | 1 |
| GABPB2 | 1 | 151043054 | 151098018 | 55.0 | 345 | 12 | 165 | 12 |
| RP11-25K21.6 | 1 | 161482966 | 161574889 | 91.9 | 460 | 6 | 4 | 7 |
| FCGR3A | 1 | 161511549 | 161600917 | 89.4 | 513 | 6 | 0 | 6 |
| FCGR2B | 1 | 161551101 | 161648444 | 97.3 | 579 | 5 | 26 | 5 |
| FCGR2C | 1 | 161551129 | 161575452 | 24.3 | 133 | 2 | 0 | 2 |
| SETD7 | 4 | 140417095 | 140527853 | 110.8 | 592 | 7 | 412 | 7 |
| MUC22 | 6 | 30978251 | 31003179 | 24.9 | 529 | 46 | 568 | 40 |
| TAP2 | 6 | 32781544 | 32806599 | 25.1 | 369 | 63 | 369 | 61 |
| PSMB8 | 6 | 32808494 | 32812480 | 4.0 | 28 | 8 | 33 | 9 |
| TAPSAR1 | 6 | 32811863 | 32814272 | 2.4 | 26 | 6 | 28 | 6 |
| PSMB9 | 6 | 32811913 | 32827362 | 15.4 | 183 | 47 | 200 | 47 |
| TAP1 | 6 | 32812986 | 32821755 | 8.8 | 120 | 35 | 133 | 35 |
| GLB1L2 | 11 | 134201768 | 134248235 | 46.5 | 315 | 16 | 122 | 19 |
| CTD-2377D24.8 | 17 | 46760729 | 46781844 | 21.1 | 154 | 2 | 119 | 2 |
| CTD-2377D24.2 | 17 | 46767843 | 46767986 | 0.1 | 0 | 2 | 0 | 2 |
| RPL9P28 | 17 | 46768478 | 46769056 | 0.6 | 7 | 2 | 5 | 2 |
| AC005523.3 | 19 | 4785132 | 4791219 | 6.1 | 52 | 2 | 12 | 2 |
| DMC1 | 22 | 38914954 | 38966291 | 51.3 | 206 | 3 | 106 | 3 |
| CBY1 | 22 | 39052641 | 39069859 | 17.2 | 127 | 3 | 84 | 3 |
| RP3-508I15.9 | 22 | 39063590 | 39077825 | 14.2 | 109 | 3 | 84 | 3 |
| TOMM22 | 22 | 39077953 | 39080818 | 2.9 | 13 | 4 | 10 | 4 |
| JOSD1 | 22 | 39081548 | 39097561 | 16.0 | 61 | 2 | 29 | 2 |
| GTPBP1 | 22 | 39101728 | 39134304 | 32.6 | 138 | 4 | 83 | 4 |
| NPTXR | 22 | 39214457 | 39239987 | 25.5 | 156 | 6 | 97 | 5 |

## 24-hour potassium excretion

| Gene | CHR | START | END | Gene size (kb) | GENOA | | FHS | |
| | | | | | 1000G Marker N | Exome Marker N | 1000G Marker N | Exome Marker N |
|---|---|---|---|---|---|---|---|---|
| ASH1L | 1 | 155305059 | 155532598 | 227.5 | 636 | 33 | 259 | 33 |
| CUL3 | 2 | 225334867 | 225450110 | 115.2 | 507 | 1 | 551 | 1 |
| RP11-431M7.2 | 4 | 36312812 | 36394032 | 81.2 | 627 | 5 | 652 | 5 |
| DDX31 | 9 | 135468384 | 135545788 | 77.4 | 396 | 37 | 377 | 38 |
| ABO | 9 | 136125788 | 136150617 | 24.8 | 320 | 36 | 268 | 32 |
| RP11-430N14.4 | 9 | 136125788 | 136130950 | 5.2 | 59 | 2 | 46 | 2 |
| ARHGAP22 | 10 | 49654077 | 49864310 | 210.2 | 1332 | 20 | 1255 | 19 |
| BRI3BP | 12 | 125478246 | 125515777 | 37.5 | 307 | 3 | 217 | 3 |
| DLEU2 | 13 | 50601269 | 50699856 | 98.6 | 349 | 2 | 396 | 2 |
| UNC13C | 15 | 54305101 | 54920806 | 615.7 | 4471 | 41 | 4855 | 42 |
| ST20-MTHFS | 15 | 80137537 | 80216096 | 78.6 | 617 | 15 | 698 | 14 |
| ST20 | 15 | 80191182 | 80216044 | 24.9 | 275 | 3 | 299 | 2 |
| C15orf37 | 15 | 80215113 | 80217194 | 2.1 | 22 | 2 | 21 | 1 |
| BCL2A1 | 15 | 80253231 | 80263788 | 10.6 | 59 | 7 | 49 | 7 |
| LINC00672 | 17 | 37081421 | 37084310 | 2.9 | 14 | 2 | 5 | 2 |
| TSPEAR | 21 | 45917775 | 46131495 | 213.7 | 2025 | 81 | 872 | 70 |
| KRTAP10-11 | 21 | 46066331 | 46067564 | 1.2 | 13 | 1 | 2 | 0 |
| KRTAP12-4 | 21 | 46074130 | 46074576 | 0.4 | 3 | 2 | 2 | 0 |
| RP3-400N23.6 | 22 | 31688485 | 31734007 | 45.5 | 242 | 3 | 197 | 3 |
| PATZ1 | 22 | 31721790 | 31742218 | 20.4 | 104 | 7 | 76 | 7 |
| DRG1 | 22 | 31795509 | 31924726 | 129.2 | 728 | 18 | 679 | 17 |
| EIF4ENIF1 | 22 | 31832963 | 31892094 | 59.1 | 334 | 16 | 326 | 15 |
| SFI1 | 22 | 31884674 | 32014572 | 129.9 | 862 | 44 | 806 | 43 |

## Sodium-to-potassium ratio

| Gene | CHR | START | END | Gene size (kb) | GENOA | | FHS | |
| | | | | | 1000G Marker N | Exome Marker N | 1000G Marker N | Exome Marker N |
|---|---|---|---|---|---|---|---|---|
| SH3RF3 | 2 | 109745804 | 110262207 | 516.4 | 2585 | 16 | 2527 | 17 |
| EIF2B5 | 3 | 183852826 | 184402546 | 549.7 | 3332 | 197 | 2204 | 195 |
| RP11-433C9.2 | 3 | 184119325 | 184157436 | 38.1 | 291 | 2 | 187 | 2 |
| CTC-228N24.1 | 5 | 127039082 | 127277326 | 238.2 | 996 | 2 | 1128 | 2 |
| RP11-483H11.1 | 5 | 127120310 | 127122734 | 2.4 | 11 | 2 | 13 | 2 |
| KLF12 | 13 | 74260226 | 74708394 | 448.2 | 2755 | 9 | 2452 | 9 |

**Table 10** P-values for gene-based association between genes and 24-hour sodium excretion, 24-hour potassium excretion, and sodium-to-potassium ratio in GENOA and FHS in Aim 2

**GENOA**

| Gene | 24-hour sodium excretion | | 24-hour potassium excretion | | Sodium-to-potassium ratio | |
|---|---|---|---|---|---|---|
| | 1000G (N=807) | Exome (N=784) | 1000G (N=811) | Exome (N=788) | 1000G (N=806) | Exome (N=783) |
| CDC42SE1 | **0.042** | 1.000 | | | | |
| MLLT11 | **0.048** | 1.000 | | | | |
| SETD7 | **0.004*** | 0.541 | | | | |
| JOSD1 | **0.029** | 1.000 | | | | |
| ASH1L | | | 0.490 | **0.007*** | | |
| RP11-431M7.2 | | | 0.410 | **0.002*** | | |

**FHS**

| Gene | 24-hour sodium excretion | | 24-hour potassium excretion | | Sodium-to-potassium ratio | |
|---|---|---|---|---|---|---|
| | 1000G (N=766) | Exome (N=753) | 1000G (N=766) | Exome (N=753) | 1000G (N=766) | Exome (N=753) |
| GABPB2 | 0.519 | **0.041** | | | | |
| GTPBP1 | 0.461 | **0.020** | | | | |
| BRI3BP | | | **0.003*** | 1.000 | | |
| LINC00672 | | | **0.002*** | 0.328 | | |
| RP11-433C9.2 | | | | | 0.328 | **0.016*** |

1000G: Variants from 1000 Genomes Project imputed data
Exome: Variants from exome chip data
P-values bolded if < 0.05
* indicates its FDR adjusted P-value <0.1

**Table 11** P-values for gene-by-age ≥ 65, gene-by-sex, and gene-by-college education interactions on 24-hour sodium excretion, 24-hour potassium excretion, and sodium-to-potassium ratio in GENOA and FHS in Aim 2

**GENOA**

| Outcome | Gene | gene-by-age ≥65 interactions | | gene-by-sex interactions | | gene-by-college interactions | |
|---|---|---|---|---|---|---|---|
| | | 1000G | Exome | 1000G | Exome | 1000G | Exome |
| 24-hour sodium excretion | PSMB9 | 0.057 | **0.030** | **0.030** | 0.603 | | |
| 24-hour sodium excretion | TAPSAR1 | **0.028** | **0.007*** | | | | |
| 24-hour sodium excretion | TAP1 | **0.008** | **0.020** | | | | |
| 24-hour sodium excretion | CTD-2377D24.8 | **0.038** | 0.323 | | | | |
| 24-hour sodium excretion | RPL9P28 | **0.034** | 0.323 | | | | |
| 24-hour sodium excretion | PSMB8 | **0.037** | 0.127 | | | | |
| 24-hour sodium excretion | SETD7 | | | 0.263 | **0.029** | | |
| 24-hour sodium excretion | GLB1L2 | | | | | 0.579 | **0.020** |
| 24-hour potassium excretion | ASH1L | | | 0.854 | **0.048** | | |
| Sodium-to-potassium ratio | CTC-228N24.1 | | | **0.005*** | 0.683 | 0.109 | **0.039*** |
| Sodium-to-potassium ratio | RP11-433C9.2 | | | **0.021*** | - | | |
| Sodium-to-potassium ratio | RP11-483H11.1 | | | | | 0.285 | **0.039*** |

**FHS**

| Outcome | Gene | gene-by-age ≥ 65 interactions | | gene-by-sex interactions | | gene-by-college interactions | |
|---|---|---|---|---|---|---|---|
| | | 1000G | Exome | 1000G | Exome | 1000G | Exome |
| 24-hour sodium excretion | CDC42SE1 | **0.020** | - | | | | |
| 24-hour sodium excretion | MLLT11 | **0.016** | - | | | | |
| 24-hour sodium excretion | PSMB9 | | | **0.041** | 0.52 | | |

1000G: Variants from 1000 Genomes Project imputed data
Exome: Variants from exome chip data
GENOA, Sample size for all SNPs/variants: 807; Sample size for rare variants: 784
FHS, Sample size for all SNPs/variants: 766; Sample size for rare variants: 753

P-values bolded if < 0.05
- : No results due to no genetic variation by environment variable
**\* indicates its FDR adjusted P-value <0.1**

**Table 12** Total list of P-values for gene-based association between each gene and 24-hour sodium excretion, 24-hour potassium excretion, and sodium-to-potassium ratio in GENOA and FHS in Aim 2

1000G: Variants from 1000 Genomes Project imputed data, Exome: Variants from exome chip data
P-values bolded if < 0.05
* indicates its FDR adjusted P-value <0.1

**24-hour sodium excretion**

| | GENOA | | | | FHS | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | 1000G | | Exome | | 1000G | | Exome | |
| Gene | N | P Value | N | P Value | N | P Value | N | P Value |
| CDC42SE1 | 807 | **0.042** | 784 | 1.000 | 766 | 0.602 | 753 | 1.000 |
| MLLT11 | 807 | **0.048** | 784 | 1.000 | 766 | 0.604 | 753 | 1.000 |
| GABPB2 | 807 | 0.071 | 784 | 0.501 | 766 | 0.519 | 753 | **0.041** |
| RP11-25K21.6 | 807 | 0.384 | 784 | 0.995 | 766 | 0.959 | 752 | 0.859 |
| FCGR3A | 807 | 0.550 | 784 | 1.000 | | | 753 | 1.000 |
| FCGR2B | 807 | 0.462 | 784 | 0.526 | 766 | 0.486 | 753 | 0.375 |
| FCGR2C | 807 | 0.108 | 784 | 1.000 | | | 753 | 1.000 |
| SETD7 | 807 | **0.004*** | 784 | 0.541 | 766 | 0.689 | 753 | 0.326 |
| MUC22 | 807 | 0.720 | 773 | 0.450 | 766 | 0.335 | 730 | 0.587 |
| TAP2 | 807 | 0.135 | 775 | 0.068 | 766 | 0.732 | 751 | 0.162 |
| PSMB8 | 807 | 0.546 | 784 | 0.158 | 766 | 0.515 | 753 | 0.095 |
| TAPSAR1 | 807 | 0.512 | 784 | 0.870 | 766 | 0.704 | 752 | 0.933 |
| PSMB9 | 807 | 0.538 | 784 | 0.522 | 766 | 0.458 | 749 | 0.142 |
| TAP1 | 807 | 0.421 | 784 | 0.844 | 766 | 0.367 | 750 | 0.336 |
| GLB1L2 | 807 | 0.655 | 784 | 0.878 | 766 | 0.309 | 752 | 0.256 |
| CTD-2377D24.8 | 807 | 0.193 | 784 | 0.109 | 766 | 0.313 | 753 | 0.639 |
| CTD-2377D24.2 | - | - | 784 | 0.109 | - | - | 753 | 0.639 |
| RPL9P28 | 807 | 0.899 | 784 | 0.109 | 766 | 0.901 | 753 | 0.639 |
| AC005523.3 | 807 | 0.119 | 784 | 0.882 | 766 | 0.165 | 753 | 0.860 |
| DMC1 | 807 | 0.142 | 784 | 1.000 | 766 | 0.760 | 753 | 0.488 |
| CBY1 | 807 | 0.067 | 784 | 0.512 | 766 | 0.483 | 753 | 0.314 |
| RP3-508I15.9 | 807 | 0.067 | 784 | 0.512 | 766 | 0.488 | 753 | 0.314 |
| TOMM22 | 807 | 0.093 | 784 | 1.000 | 766 | 0.563 | 753 | 1.000 |
| JOSD1 | 807 | **0.029** | 784 | 1.000 | 766 | 0.547 | 753 | 1.000 |
| GTPBP1 | 807 | 0.067 | 784 | 0.334 | 766 | 0.461 | 753 | **0.020** |
| NPTXR | 807 | 0.867 | 784 | 0.269 | 766 | 0.756 | 753 | 0.655 |

## 24-hour potassium excretion

| | GENOA | | | | FHS | | | |
|---|---|---|---|---|---|---|---|---|
| | 1000G | | Exome | | 1000G | | Exome | |
| Gene | N | P Value | N | P Value | N | P Value | N | P Value |
| ASH1L | 811 | 0.490 | 788 | **0.007*** | 766 | 0.063 | 752 | 0.729 |
| CUL3 | 811 | 0.261 | 788 | 0.780 | 766 | 0.500 | 753 | 0.495 |
| RP11-431M7.2 | 811 | 0.410 | 788 | **0.002*** | 766 | 0.233 | 753 | 0.340 |
| DDX31 | 811 | 0.858 | 788 | 0.270 | 766 | 0.144 | 753 | 0.932 |
| ABO | 811 | 0.579 | 772 | 0.347 | 766 | 0.334 | 744 | 0.656 |
| RP11-430N14.4 | 811 | 0.830 | 788 | 1.000 | 766 | 0.142 | 753 | 1.000 |
| ARHGAP22 | 811 | 0.231 | 784 | 0.407 | 766 | 0.691 | 752 | 0.912 |
| BRI3BP | 811 | 0.127 | 788 | 0.142 | 766 | **0.003*** | 753 | 1.000 |
| DLEU2 | 811 | 0.413 | 788 | 0.806 | 766 | 0.182 | 753 | 0.093 |
| UNC13C | 811 | 0.090 | 785 | 0.242 | 766 | 0.097 | 751 | 0.636 |
| ST20-MTHFS | 811 | 0.186 | 784 | 0.108 | 766 | 0.630 | 751 | 0.716 |
| ST20 | 811 | 0.165 | 784 | 0.845 | 766 | 0.773 | 752 | 0.400 |
| C15orf37 | 811 | 0.106 | 784 | 0.912 | 766 | 0.370 | 753 | 1.000 |
| BCL2A1 | 811 | 0.737 | 788 | 0.962 | 766 | 0.844 | 753 | 0.219 |
| LINC00672 | 811 | 0.198 | 788 | 0.965 | 766 | **0.002*** | 753 | 0.328 |
| TSPEAR | 811 | 0.103 | 787 | 0.946 | 766 | 0.416 | 751 | 0.849 |
| KRTAP10-11 | 811 | 0.113 | 788 | 0.684 | 766 | 0.386 | - | - |
| KRTAP12-4 | 811 | 0.206 | 788 | 0.684 | 766 | 0.351 | - | - |
| RP3-400N23.6 | 811 | 0.868 | 788 | 0.810 | 766 | 0.714 | 753 | 0.724 |
| PATZ1 | 811 | 0.818 | 788 | 0.810 | 766 | 0.885 | 753 | 0.925 |
| DRG1 | 811 | 0.687 | 787 | 0.693 | 766 | 0.695 | 753 | 0.969 |
| EIF4ENIF1 | 811 | 0.607 | 787 | 0.693 | 766 | 0.618 | 753 | 0.969 |
| SFI1 | 811 | 0.389 | 783 | 0.861 | 766 | 0.831 | 753 | 0.527 |

## Sodium-to-potassium ratio

| | GENOA | | | | FHS | | | |
|---|---|---|---|---|---|---|---|---|
| | 1000G | | Exome | | 1000G | | Exome | |
| Gene | N | P Value | N | P Value | N | P Value | N | P Value |
| SH3RF3 | 806 | 0.785 | 783 | 0.817 | 766 | 0.462 | 749 | 0.734 |
| EIF2B5 | 806 | 0.605 | 765 | 0.677 | 766 | 0.256 | 746 | 0.639 |
| RP11-433C9.2 | 806 | 0.514 | 783 | 0.471 | 766 | 0.328 | 753 | **0.016*** |
| CTC-228N24.1 | 806 | 0.437 | 783 | 0.489 | 766 | 0.337 | 753 | 0.763 |
| RP11-483H11.1 | 806 | 0.203 | 783 | 0.489 | 766 | 0.910 | 753 | 0.763 |
| KLF12 | 806 | 0.184 | 783 | 0.993 | 766 | 0.240 | 753 | 0.333 |

**Figure 6** Regional plots of P-values for single SNP association analysis with 24-hour sodium excretion, 24-hour potassium excretion, and sodium-to-potassium ratio in Aim 2

**GENOA**

**24-hour sodium excretion using variants from 1000 Genomes Project imputed data**



*CDC42SE1*



*MLLT11*



*SETD7*



*JOSD1*
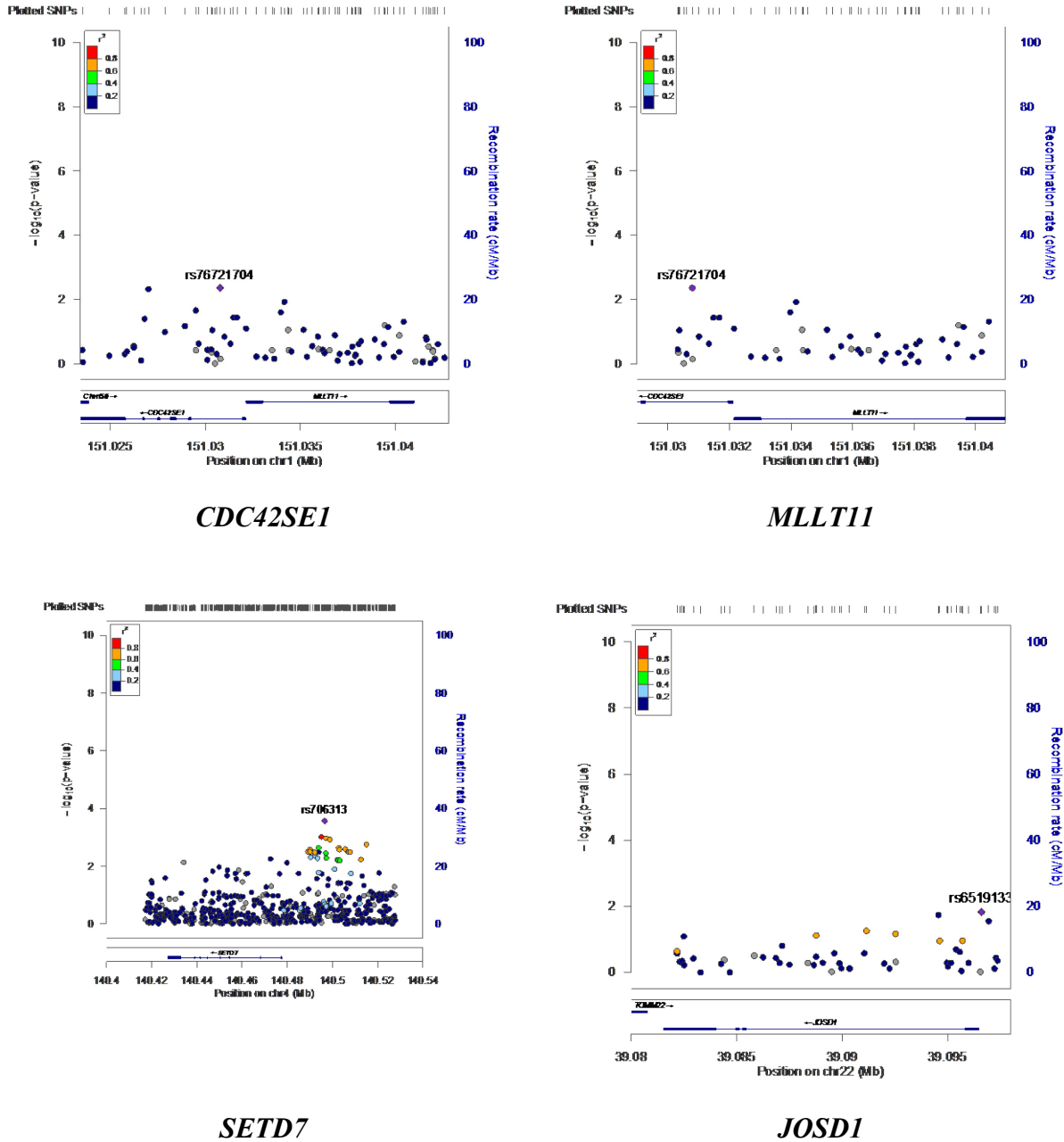
**FHS**

**24-hour potassium excretion using variants from 1000 Genomes Project imputed data**
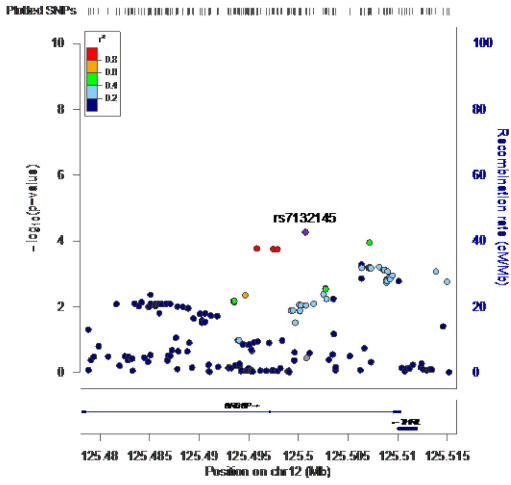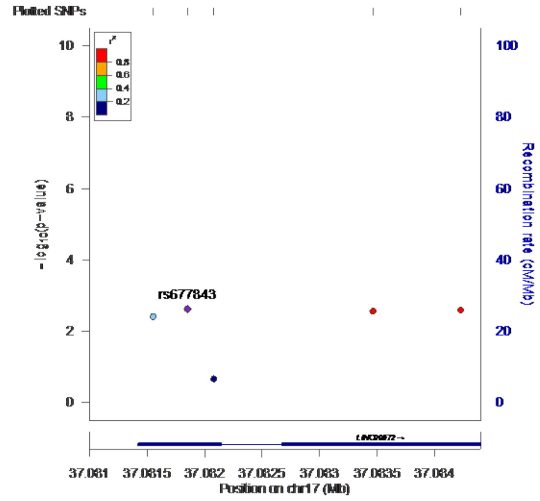


***BRI3BP***                           ***LINC00672***

**Figure 7** Plots of SNP-by-demographic factor interactions in Aim 2

**Regional Plot of p-values for single SNP analysis of gene-by-sex on sodium-to-potassium ratio in GENOA**



*CTC-228N24.1*
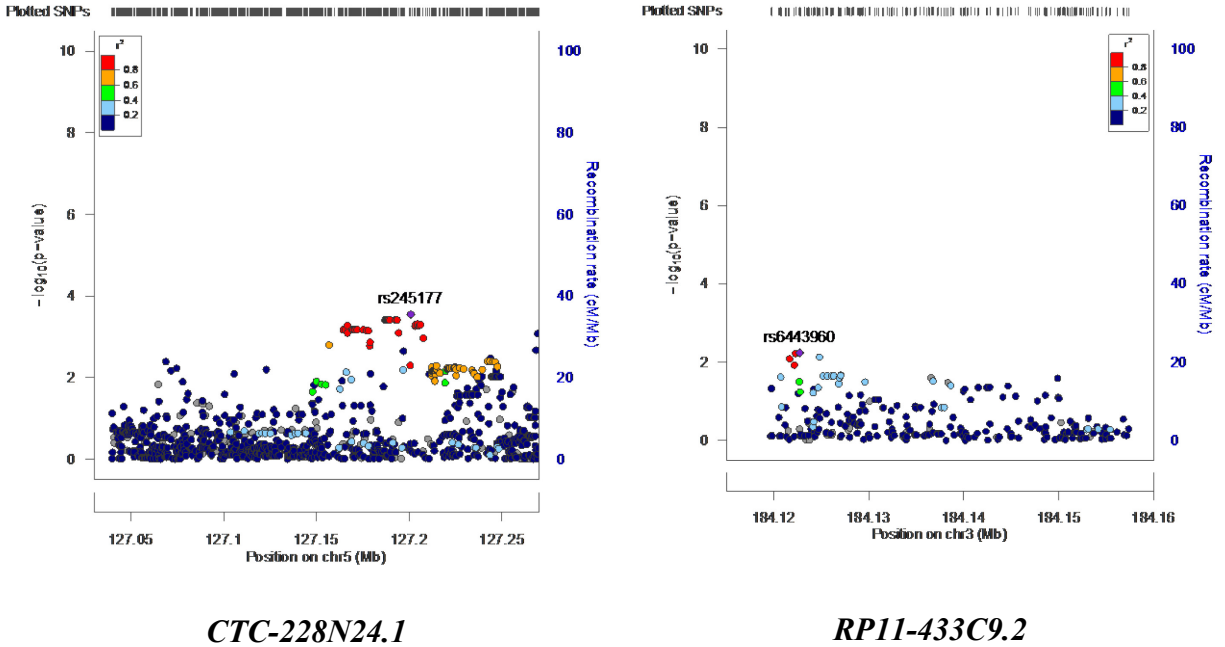
*RP11-433C9.2*

**Interaction between single SNP (rs245177 for *CTC-228N24.1* and rs6443960 for *RP11-433C9.2*) and sex on sodium-to-potassium ratio in GENOA**



*CTC-228N24.1*

*RP11-433C9.2*
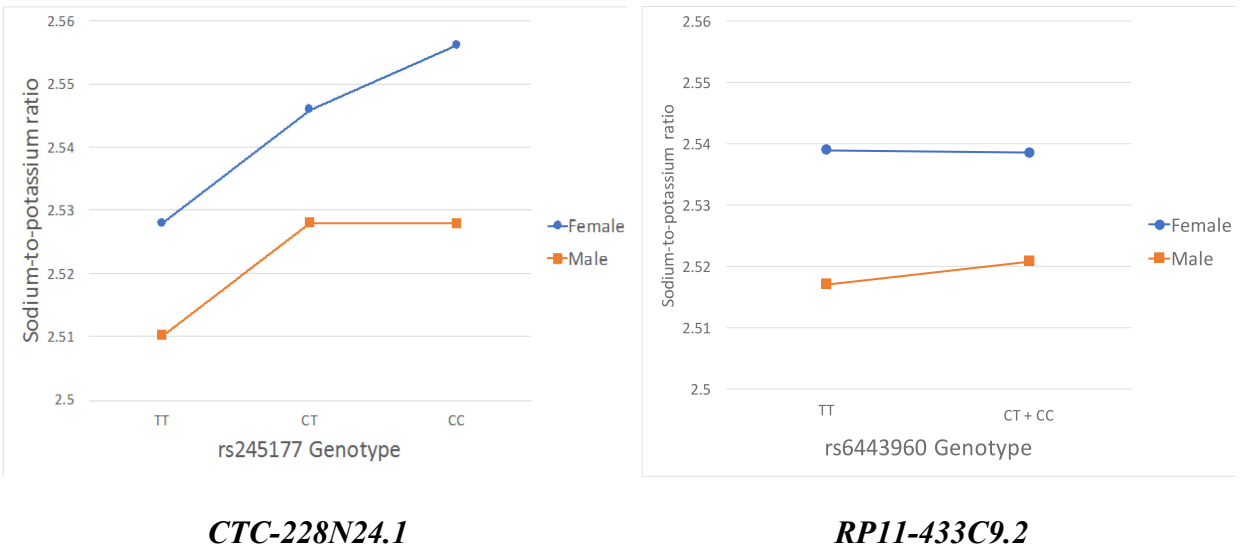
## CHAPTER IV: A multi-ancestry genome-wide study of gene-sodium interaction underlying blood pressure variation

### 4.1 Introduction

High blood pressure is strongly related to cardiovascular disease (CVD) and chronic kidney disease (CKD) [108]. Consequently, for preventative purposes, both systolic blood pressure (SBP) and diastolic blood pressure (DBP) are the most common intervention targets if one has been diagnosed with hypertension [109-111]. Mean arterial pressure (MAP), the average pressure in an individual's arteries during one cardiac cycle, and pulse pressure (PP), the difference between the systolic and diastolic pressure readings, are also often predictors of CVD [4, 112, 113].

Since measures of blood pressure (SBP, DBP, MAP, and PP) are complex phenotypes, identifying risk factors that could modify the genetic effects of blood pressure is being actively studied [44-46]. GWAS have identified numerous SNPs that are associated with SBP, but the identified associated genetic loci explain only a small portion of SBP and DBP variability, even though heritability is relatively high (~40-50%) [37-43]. Blood pressure is also influenced by an individual's lifestyle including lack of physical activity, diet, alcohol and smoking; these lifestyle factors have become important intervention targets [114-116]. In particular, high sodium intake is a strong and independent risk factor for high blood pressure, has a large variation at both the individual and population level [32, 47, 48]. Thus, it is important to research whether and how individual sodium intake modifies the genetics of blood pressure, and to investigate whether

there are susceptible genetic groups within a population that are disproportionately affected by sodium intake. In epidemiological samples, measuring sodium excretion using 24-hour or 12-hour urine collection is often used as a high-quality measure of sodium intake [117]. Li et al. recently conducted a study involving a genome-wide SNP-based and gene-based gene-sodium interaction analysis on SBP, DBP, MAP, and PP using one discovery cohort (N=1,876) and one replication cohort (N=775) in a Chinese population, and found 8 novel loci [118]. Sodium intake level was measured from a 24-hour urine sample in the discovery set and spot urine sample in replication set. Evaluating the gene-by-sodium intake interaction using larger multi-ethnic populations, including European and African ancestries with large sample sizes is needed to confirm and extend these preliminary findings.

To examine the role of interactions between sodium intake and genetic variations on blood pressure, we conducted a meta-analysis of a genome-wide gene-by-sodium interaction study on blood pressure measures, including SBP, DBP, MAP, and PP using high-quality measurements of sodium intake (i.e. 24-hour or half-day urine samples) from 6 cohorts comprising almost 6,000 participants of European, African, and Asian ancestry.

## 4.2 Methods

The study is part of a series of multi-ancestry genome-wide interaction projects conducted by the Gene-Lifestyle Interactions Working Group within the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) to assess the impact of genetic interactions with multiple lifestyle factors on cardiovascular traits [119]. Men and women between the ages of 18 and 80 from three ancestry groups were considered for analysis: 1) European ancestry (EA) - Genetic Epidemiology Network of Arteriopathy (GENOA), the

Hypertension Genetic Epidemiology Network (HyperGEN), and the Framingham Heart Study (FHS); 2) African ancestry (AA) – HyperGEN; and 3) Asian ancestry (AS) - Genetic Epidemiological Network of Salt-Sensitivity (GenSalt) study. The description of each study is included in Appendix 1. Participants were included if they had blood pressure measures, urinary sodium excretion measured from ≥ 8-hour urine sample, and imputed genotypes from the 1000 Genomes Project reference panel. A total of 6 cohorts were included (N=6,020) in this study, with 2,547 EA, 1,650 AA, and 1,823 AS participants.

**Preliminary study**

For gene-by-sodium interaction analyses, 24-hour urinary sodium excretion level was dichotomized at a particular cut-off point to ensure interpretability of the regression model. To identify the appropriate dichotomization threshold of 24-hour urinary sodium excretion for the interaction analyses, we evaluated the relationship between 24-hour urinary sodium excretion and blood pressure measures (SBP and DBP) using data from GENOA, FHS, HyperGEN (EA and AA), and GenSalt. In addition, we also examined whether the relationship between sodium excretion and blood pressure differed by diuretic use, since the relationship between diuretic use and sodium excretion is not well established. Diuretics, which are medications that are designed to increase the amount of water and sodium excreted as urine, may help lower blood pressure and may influence the relationship between sodium intake and blood pressure.

Participants were grouped by their 24-hour urinary sodium excretion levels: group 1 (<160 mmol/day, N=1,296), group 2 (≥160 and <220 mmol/day, N=1,373), group 3 (≥220 and <280 mmol/day, N=1,276), and group 4 (≥280 mmol/day, N=1,563). In each group, the weighted mean value for age- and sex-adjusted SBP and DPB values was first calculated by weighting by the sample size of each cohort. SBP and DBP differences in each sodium group were then

calculated by subtracting blood pressure in the reference group (sodium group 1) from blood pressure in each sodium group. We found linear relationships between blood pressure difference and sodium groups in all participants and in participants without diuretic use (Figure 8).

The preliminary results showed that 220 mmol/day was an appropriate cutoff for dichotomization. Approximately 40% of participants in the preliminary study had 24-hour urinary sodium ≥ 220 mmol/day. Since the associations between blood pressure measures and 24-hour urinary sodium excretion levels varied by use of diuretics, we decided to conduct the main analyses using 1) all participants and 2) participants without diuretic use.
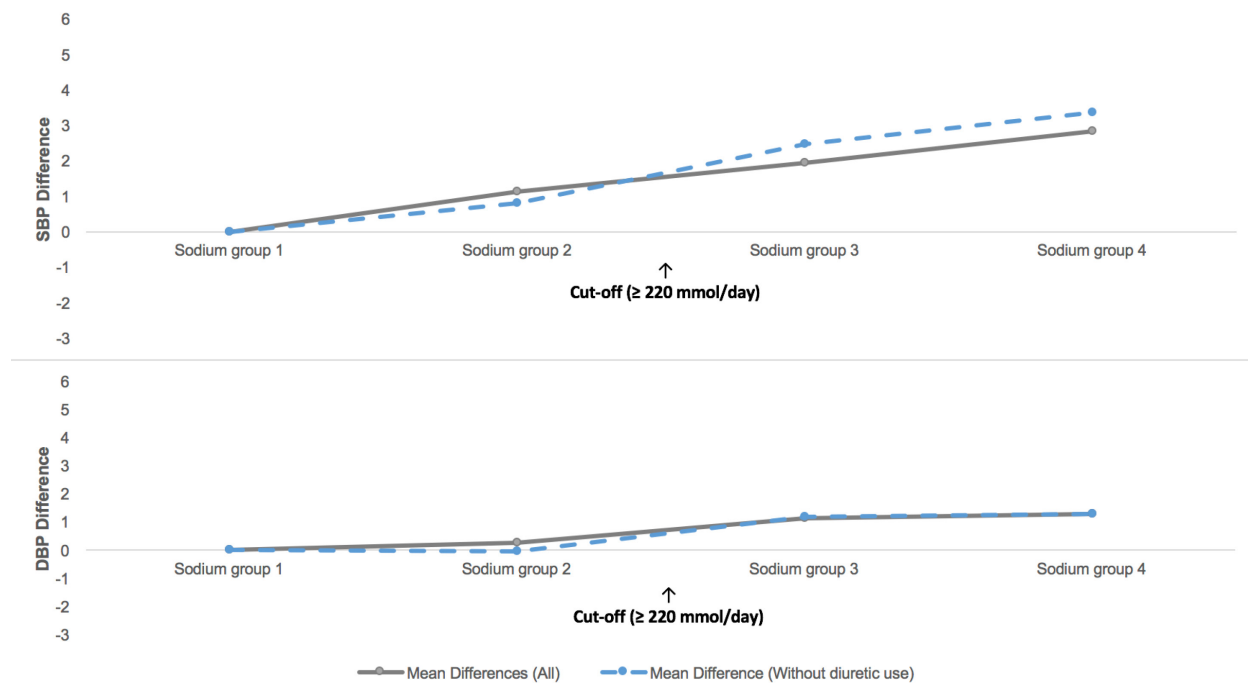


**Figure 8** The association between blood pressure difference and sodium groups in Aim 3

Twenty-four-hour urinary sodium excretion levels: group 1 (<160 mmol/day, N=1,296), group 2 (≥160 and <220 mmol/day, N=1,373), group 3 (≥220 and <280 mmol/day, N=1,276), and group 4 (≥280 mmol/day, N=1,563). SBP and DBP difference value for each sodium group = blood pressure in each sodium group - blood pressure in the reference group (sodium group 1)

**Phenotypes, urinary sodium excretion, and covariates**

Resting SBP (mmHg) and DBP (mmHg) were obtained. When multiple BP readings were available at the same visit, the average of all SBP readings and of all DBP readings were used. For subjects taking any blood pressure lowering medications, SBP and DBP values were adjusted by adding 15 mmHg to SBP and 10 mmHg to DBP [38, 120]. MAP (DBP + (SBP – DBP)/3) and PP (SBP – DBP) were also derived by using SBP and DBP values. SBP, DBP, MAP, and PP were analyzed separately. For each of the 4 blood pressure measures (SBP, DBP, MAP, and PP), outliers were set at 6 standard deviations (SD) from the mean.

Sodium excretion level was measured either from 24-hour or half-day urine samples (Table 13). If urinary sodium excretion was measured from half-day urinary samples (>8-hour duration), simple volume-time linear extrapolation was used to estimate 24-hour urinary sodium excretions. Dichotomous urinary sodium excretion (SODIUM) was defined as 0 if 24-hour urinary sodium excretion was <220 mmol/day, and as 1 if 24-hour urinary sodium excretion was ≥220 mmol/day. Information about covariates, including age, sex, and diuretic use, was also collected in each cohort.

**Genotyping**

The analyses for each cohort used the dosage of SNPs (chromosomes 1-22) imputed from the 1000 Genomes Project. For imputation, the ALL ancestry panel from 1000G Phase I Integrated Release Version 3 Haplotypes (March 2012) was used. The details of genotyping and genotype imputation for each cohort are described in Table 14. Each cohort applied a preliminary filter by excluding SNPs with very low imputation quality ($R^2$ or INFO <0.1) and low minor allele frequency (MAF<0.01). Principal components (PCs) were included in the analysis to adjust for population stratification in each cohort [72].

**Statistical analysis**

**Genome-wide association study in each cohort**

The genome-wide association study (GWAS) was conducted separately for each ancestry group within each cohort. Analyses were conducted separately for 1) all participants (ALL) and 2) participants not taking diuretic medications (WOD). For each BP trait, a total of six analyses were conducted within each ancestry group: three models were used (MODEL 1, MODEL 2, and MODEL 3).

In MODEL 1 (joint model), a regression model was used in each cohort that included both the genetic main effect and GxE interaction effects. MODEL 2 was additionally tested in each cohort to discern whether the SNP could be discovered without accounting for exposure and GxE interaction. MODEL 3, on the other hand, investigated the presence of G-E correlation. The models are as follows:

MODEL 1 (Joint analysis of main and interaction effects):

$$Y = \beta_0 + \beta_{E1} E + \beta_{G1} G + \beta_{GE} E * G + \beta_{C1} C$$

MODEL 2 (Analysis of main effect only):

$$Y = \beta_0 + \beta_{G2} G + \beta_{C2} C$$

MODEL 3 (Analysis of main effect adjusted for SODIUM):

$$Y = \beta_0 + \beta_{E3} E + \beta_{G3} G + \beta_{C3} C$$

where $Y$ is the medication-adjusted blood pressure phenotype value; $\beta_0$ is the intercept; $E$ is dichotomous urinary sodium excretion; $G$ is the dosage of the imputed genetic variant, coded additively; and $C$ is the vector of covariates including age, sex, study-specific confounders, and PCs.

The genetic main effects ($\beta_{G1}$, $\beta_{G2}$, $\beta_{G3}$), the GxE interaction term effect $\beta_{GE1}$, their robust standard errors (SEs) and the robust covariance between the betas were collected in each cohort for each model. Robust estimates of SE and covariance were obtained because the error terms may not have the same variance across sodium excretion groups (heteroscedasticity) and there is a possibility of misspecification of the mean model [121, 122].

For association analyses in studies with unrelated subjects, linear regression with robust estimates of standard errors were conducted using ProbABEL [123]. For studies with related subjects, linear mixed models using a kinship matrix with a random polygenic component (for which the covariance matrix depends on the kinship matrix) were analyzed using ProbABEL or MMAP (Mixed Model Analysis in Pedigrees and Populations) [54] to account for family relationships.

**Quality Control (QC) before meta-analysis**

Before conducting the meta-analysis, individual GWAS results were cleaned by performing QC using the R package EasyQC [73]. In the study-level QC, the collected allele frequencies were checked against the ancestry-specific 1000 Genomes Project reference panel and genetic marker names were harmonized. In the meta-level QC, summary statistics for collected variables were compared in each specific analysis (e.g., SBP-Model1) across all cohorts. In addition, SE-N plot and QQ plots were used to check the errors in trait transformation, as well as other analytical problems.

If imputation quality was < 0.1 in a given cohort, the genetic variants were preliminarily excluded; if the measure was <0.5, the genetic variants were further excluded in the QC step. In addition, genetic variants with low MAF or low imputation quality measures were excluded if min (MAC0, MAC1) * imputation quality measure was < 10 in European and Asian ancestry

groups, or <15 in African ancestry, where MAC0 = 2 * $MAF_{E0}$ * $N_{E0}$ for the unexposed group (with $MAF_{E0}$ and sample size $N_{E0}$ for E=0 stratum) and MAC1 = 2 * $MAF_{E1}$ * $N_{E1}$ for the exposed group. This ensured that the study only included stable cohort-specific results with a large enough sample size for each genetic variant in the meta-analyses. For family studies, $N_E$ was computed as (n+N)/2 where n= the number of sibships with at least one exposed member, and N= the total number of exposed subjects across all sibships. This is a compromise between using n alone (which underestimates $N_E$ as multiple exposed subjects in a family are counted only once) or N alone (which overestimates $N_E$ as this ignores sibling correlation).

**GWAS meta-analysis**

Meta-analyses were conducted for those who did and did not use diuretics within each ancestry. For MODEL 1, two meta-analyses were performed in METAL: 1) 1 degree of freedom (DF) test of the interaction effect (SNP x E term) and 2) 2 DF test (joint fixed-effects) [124] that tested both the SNP main effect term and the SNP*E interaction term, while considering the covariance between them [74]. For the 1 DF test, a Wald test statistic was used that approximately follows a chi-squared distribution with 1 DF under $H_0$: $\beta_{GxE}$ = 0. For the 2 DF test, a Wald test statistic was used, which approximately follows a chi-squared distribution with 2 DF under $H_0$: $\beta_G = \beta_{GxE}$ = 0.

For MODELs 2 and 3, the fixed-effects inverse-variance weighted meta-analysis of the SNP main effect term was conducted in METAL [74]. In the meta-analysis, genomic control correction [125] was applied first for cohort-specific GWAS results when lambda value > 1, and then again to the meta-analysis results. From the meta-analysis results, genetic variants were excluded if they were represented by GWAS data in fewer than 2 cohorts. Genetic variants that

were genome-wide significant ($P < 5{\times}10^{-8}$) or suggestive ($P < 1{\times}10^{-6}$) in any of the meta-analyses will be replicated in independent cohorts in future studies.

## 4.3 Results

The characteristics of participating cohorts are shown in Table 13. All cohorts except JHS were family-based cohorts. The blood pressure measures and frequency of using diuretics were lowest in the Asian cohort (GenSalt). However, participants from GenSalt had highest portion of sodium excretion ≥220 mmol/day.

From the analyses using all participants, out of about 5-9 million SNPs from meta-analyses, we found 26 (EA), 91 (AA), and 17 (AS) genome-wide significant (2DF $P < 5{\times}10^{-8}$) or suggestive SNPs (2DF $P < 1{\times}10^{-6}$). When participants with diuretic use were excluded, 51 (EA), 44 (AA), and 25 (AS) genome-wide significant (2DF $P < 5{\times}10^{-8}$) or suggestive SNPs (2DF $P < 1{\times}10^{-6}$) were found in the meta-analyses (Table 16).

In Table 15, we present the most significant SNP at 12 independent genetic loci that reached genome-wide significance ($P < 5{\times}10^{-8}$) in meta-analyses using the 2DF interaction test. From the meta-analysis results in African ancestry, six significant genetic loci were found. The most significant locus in AA was rs113300617 near *FBXO10* and *RP11-613M10.8* on chromosome 9 (2DF P=$1.12{\times}10^{-10}$). In EA, found significant loci near genes *ZDHHC19* (rs11185517, 2DF P=$1.36{\times}10^{-8}$), *RUSC2* (rs17370852, 2DF P=$2.41{\times}10^{-12}$), *U3* (rs17753104, 2DF P=$2.49{\times}10^{-8}$), *RP11-507B12.2* (rs7179425, 2DF P=$9.40{\times}10^{-9}$), and *DCC* (rs7243864, 2DF P=$2.71{\times}10^{-8}$). The genetic variant rs6922858 on chromosome 6 had a genome-wide significant P-value (2DF P=$1.2{\times}10^{-8}$) from multiple analyses (DBP in both ALL and WOD, MAP in WOD) in the Asian cohort. Table 16 provides all genome-wide significant results.

In the presence of interaction, it is well known that the main effects of a simple linear regression are difficult to interpret. By examining the p-values associated with the genetic main effects ($\beta_{G1}$, $\beta_{G2}$, $\beta_{G3}$), the GxE interaction term effect $\beta_{GE1}$, and the 2 DF test in Table 15, we can begin to identify the genetic loci that appear to have both main and interactions effects, and separate them from the genetic loci that have only interactions effects. Out of 12 genome-wide significant loci in EA, only two loci had a genome-wide significant P-value in 1DF interaction test (rs17370852 with 1DF interaction P=$7.65 \times 10^{-13}$ on chromosome 9 and rs7179425 with 1DF interaction P=$3.21 \times 10^{-10}$ on chromosome 15).

Quantile-quantile (QQ) plots and Miami plots for each GWAS using the 2DF joint test are presented in Figures 9-12. Regional plots for the 12 significant loci using LocusZoom are shown in Figure 13.

## 4.4 Discussion

In this study, we identified 12 independent genome-wide significant genetic loci (P < 5 × $10^{-8}$) and 206 suggestive genetic SNPs from meta-analyses of a genome-wide gene-by-sodium interaction study on blood pressure measures (SBP, DBP, MAP, and PP) using 6 cohorts comprising more than 6,000 participants of European, African American, and Asian ancestry.

Most interestingly, we identified rs868549 in AA, which is in the intronic region of *NKAIN2* (sodium/potassium transporting ATPase interacting 2) that is expressed in the brain and in the heart [126]. The gene, which interacts with the beta subunit of Na, K-ATPase, has the important function of regulating sodium ion transport by modulating the frequency, rate or extent of the mobility of sodium ions (Na+) in/between cells [127]. Although it is clear that there is an apparent relationship between the gene and sodium, additional studies are needed to elucidate the

mechanism for how this promising genetic locus is associated with blood pressure regulation. At first glance, the genetic loci from EA have no apparent relationship with known blood pressure or sodium handling phenotypes. For example, the intronic variant rs11185517 on chromosome 3 is in a region of a protein coding gene, *ZDHHC19* (zinc finger DHHC-type containing 19), that is functionally associated with protein-cysteine S-palmitoyltransferase activity [126]. The gene is located in the cell membrane, and suggestively associated with proteins that influence endothelial nitric oxide synthase (eNOS), which is important for cardiovascular homeostasis [128]. From previous association studies, *ZDHHC19* has been associated with metabolism, erythrocyte indices, and hemoglobin [129, 130]. rs17370852 is an intronic variant in *RUSC2* (RUN and SH3 domain containing 2) on chromosome 9, which is expressed in the human brain. RUSC2 protein may interact with interacting with RAB GTPase binding, which plays a role in intracellular vesicular trafficking [131]. It has suggested that GTPases have important roles in renal tubular epithelial cell function [80]. For example, GTPases may be associated with the retention process of the sodium hydrogen exchanger (NHE3) at the surface of membranes in the renal proximal tubular epithelia; further, NHE3 is associated with renal and intestinal ion homeostasis and control of cellular volume [132]. Variant rs7243864 is located in the *DCC* (DCC netrin 1 receptor) on chromosome 18. The gene encodes a netrin 1 receptor, and is known to mediate axon outgrowth and steering response [133]. rs8101144 is an intronic genetic variant of the gene. Future studies are warranted to understand the potential functional relevance of the genes in the relationship between sodium intake and blood pressure.

When we compare the P-values from each meta-analysis, we have a better understanding of what kind of information each model could provide in Aim 3. In the study of the SNP association, the SNP effects are often first evaluated without accounting for exposure and gene-

by-environment interaction terms (main effect only model, Model 2) before conducting regressions of interaction terms like Model 1 in Aim 3 [124]. However, when both SNP main effect and interaction effect are jointly estimated in Model 1, we cannot separate the main effect from the interaction effect. From Model 1 where both the interaction and SNP main effect terms were included, the meta-analyses of 1DF interaction test and 2DF joint test were conducted. From the Manning et al paper, except for the extreme cases (no interaction effect or no SNP effects), 2DF joint test had the highest power. In simulations, the explained portion of outcome variation increased when both main and interaction effects were jointly evaluated in the model [124]. This might explain why there were no loci that had a genome-wide significant SNP main effect from Model 1 and 2 ($\beta_{G1}$ and $\beta_{G2}$, SNP main effect $P < 5 \times 10^{-8}$) and why there were only 2 significant loci from 1DF interaction test from Model 1 ($\beta_{GE}$, 1 DF interaction $P < 5 \times 10^{-8}$) where all loci had significant P-values from 2DF joint test in Table 15. In the paper of Manning et al, on the other hand, when there is an interaction effect with no or small main effect, the meta-analysis of the interaction alone ($\beta_{GE}$, 1DF interaction test) had the highest power because it has a lower degree of freedom (1DF) [124]. This might explain why locus 6 and 11 in Table 15 had a less significant P-value in the 2DF joint test when compared to the 1DF interaction test. In Model 3, the presence of correlation between genetic and environmental effects was investigated by adding the environment variable, SODIUM, and examining its impact on the 1DF SNP effect.

Despite the importance of gene-sodium intake interactions on blood pressure, there have been few studies in this area. Li et al recently found several novel loci using Chinese participants from GenSalt and MESA [118]. They did not have adequate power in their discovery sample to detect genome-wide significant effects, but detected significant SNPs from the combined results of discovery and replication samples. In addition, sodium intake was estimated from spot a urine

sample in the replication set, which could decrease the accuracy of the findings. We evaluated

the 3 novel loci (rs11104632 on chromosome 12, rs13211840 on chromosome 6, rs2567241 on

chromosome 4) from single variant analysis results in the Li et al study, using our European and

African ancestry meta-analysis (Table 17). None of loci were significant (P value<0.05) in any of

our analyses. Since different ancestry groups may have different linkage disequilibrium

structures, a SNP found in one ancestry group may not replicate in other ancestries. We did not

conduct the replication in AS since the results were from the same cohort, GenSalt.

Traditionally, the SNP-by-environment interactions have been evaluated for the subset of

SNPs with significant main effects [134]. This approach could improve power by limiting the

number of interaction tests performed, but its critical limitation is to prevent the identification of

genetic variants that are associated with diseases mainly through an interaction effect with no or

small marginal effects. In the interaction test with known blood pressure loci (until June 2017,

M=239) from previous large GWAS with successful replication that exist in our SNP list, only 3

loci out of 239 had an FDR adjusted P-value less than 0.1 from the 2DF joint test (Table 18). The

three loci included variant rs13139571 on chromosome 4 near genes GUCY1A3-GUCY1B3,

which was replicated with SBP and PP in AA participants (FDR adjusted P=0.069 and 0.059,

respectively) and with MAP in AA participants without diuretics (FDR adjusted P=0.021);

variant rs62012628 on chromosome 15 near gene ADAMTS7, which had a FDR adjusted

P=0.0369 with SBP; and variant rs743757 on chromosome 3 near gene CAC2D2, which also had

a FDR adjusted P=0.077 with DBP in EA participants without diuretics. This low rate of

replication highlights the importance of using the 2DF joint test in Aim 3 because the loci that

had significant P-values in our discovery analysis would not have been identified if we only used

known blood pressure loci for interaction testing.

The strength of this work includes using 1) multiethnic populations; 2) high-quality measurements (24-hour or half-day urinary sodium excretion); 3) a sensitivity analysis approach by conducting meta-analyses excluding participants with diuretic use; and 4) a powerful statistical approach in identifying gene-by-sodium environment interaction loci from meta-analyses (2DF joint test).

However, a limited number of cohorts had either a 24-hour or half-day urine samples as well as genotyping data since collecting 24-hour or half-day urine samples is expensive and time-consuming. Thus, the sample size limited our power to conduct the gene-sodium interaction meta-analyses. We also had only one Asian cohort.

To expand on our results, we are currently reaching out to additional cohorts to confirm suggestive or significant loci found from the discovery stage. Potential cohorts include 1) 24-hour urine sample: Prevention of REnal and Vascular ENd-stage Disease (PREVEND) (N=3,649) [61], 2) Spot urine sample: Heredity and Phenotype Intervention (HAPI) Heart Study (N=844) [70], Multiethnic Study of Atherosclerosis (MESA) cohort (N=2,462), [135] and UK Biobank (N=500,000) [136], and 3) FFQ: Health and Retirement Study (N=8,035) [137]. Identifying genetic variations that modify the relationship between sodium intake/excretion and blood pressure could have an effect on stratifying treatment and prevention recommendations for millions of adults who have high blood pressure or hypertension, since these gene variations would indicate which subgroups of the population have an increased risk of elevated blood pressure from excess sodium consumption.

**Table 13** Characteristics of participating cohorts in Aim 3

| | GENOA | FHS | HyperGEN EA | HyperGEN AA | JHS | GenSalt |
|---|---|---|---|---|---|---|
| **Race/ethnicity** | EA (N=2,547) | | | AA (N=1,650) | | AS (N=1,823) |
| **Cohort** | Family-based | Family-based | Family-based | Family-based | Population-based | Family-based |
| **Country** | USA | USA | USA | USA | USA | USA |
| **Total (N)** | 625 | 747 | 1,175 | 1,017 | 633 | 1,823 |
| **Diuretic use, %** | 49.9 | 19.3 | 23.5 | 38.2 | 41.4 | 0.4 |
| **24-hour urinary sodium excretion ≥ 220 mmol/day, %** | 11.7 | 10.2 | 36.9 | 47.9 | 19.6 | 58.4 |
| **SBP** | 154.3 ± 24.2 | 132.8 ± 18.3 | 131.5 ± 23.1 | 138.4 ± 25.0 | 136.6 ± 19.1 | 117.2 ± 14.1 |
| **DBP** | 83.7 ± 10.8 | 77.4 ± 9.9 | 76.0 ± 11.5 | 80.0 ± 13.0 | 81.2 ± 9.7 | 74.1 ± 10.2 |
| **MAP** | 107.2 ± 13.7 | 90.0 ± 9.6 | 94.5 ± 14.2 | 99.5 ± 15.9 | 100.0 ± 11.5 | 88.4 ± 10.8 |
| **PP** | 70.7 ± 19.5 | 52.9 ± 14.1 | 55.5 ± 16.8 | 58.4 ± 17.4 | 56.4 ± 15.3 | 43.1 ± 9.4 |
| **Urine Sample** | 24-hour | 24-hour | Half-day | Half-day | 24-hour | 24-hour |

For continuous variables: mean ± SD, For binary variables: % (N)

Abbreviations:  EA: European American, AA: African American, AS: Asian, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean Arterial Pressure, PP: Pulse Pressure, GENOA: Genetic Epidemiology of Arteriopathy, FHS: Framingham Heart Study, HyperGEN: Family Blood Pressure Program, JHS: Jackson Heart Study, GenSalt: Genetic Epidemiology Network of Salt Sensitivity

**Table 14** Genotyping information for participating cohorts in Aim 3

| Cohort | Ancestry | Study design | N PCs | Genotyping platform | Genotyping calling algorithm | Imputation software | Imputation: reference panel | Analysis Software |
|---|---|---|---|---|---|---|---|---|
| GENOA | EA | FB | 4 | Affymetrix Genome-Wide Human SNP Array 6.0 (91.9% of sample); Illumina Human 1M-Duo, 660-Quad, or 610-Quad (8.1% of sample) | Birdseed; Genome Studio | IMPUTE2 | 1000G Phase1 v3 | MMAP |
| FHS | EA | FB | 0 | Affymetrix 500K mapping array and the Affymetrix 50K gene-focused molecular imprinted polymer array | BRLMM | MACH | 1000G Phase1 v3 | MMAP |
| HyperGEN EA | EA | FB | 0 | Affymetrix Genome-Wide Human SNP Array 5.0 | BRLMM | MACH/ minimac | 1000G Phase1 v3 | MMAP |
| HyperGEN AA | AA | FB | 1 | Affymetrix Genome-Wide Human SNP Array 6.0 | Birdseed | MACH/ minimac | 1000G Phase1 v3 | MMAP |
| JHS | AA | PB | 10 | Affymetrix Genome-Wide Human SNP Array 6.0 | Birdseed2 | IMPUTE2 | 1000G Phase1 v3 | ProbABEL |
| GenSalt | AS | FB | N/A | Affymetrix Genome-Wide Human SNP Array 6.0 | Birdseed | Minimac | 1000G Phase1 v3 | ProbABEL |

Abbreviations:  EA: European American, AA: African American, AS: Asian, FB: Family-based, PB: Population-based, GENOA: Genetic Epidemiology of Arteriopathy, FHS: Framingham Heart Study, HyperGEN: Family Blood Pressure Program, JHS: Jackson Heart Study, GenSalt: Genetic Epidemiology Network of Salt Sensitivity

**Table 15** Genetic loci that were genome-wide significant ($P < 5\times10^{-8}$) from 2DF joint test in the discovery sample in Aim 3

| Locus[1] | Nearest Genes[2] | rsID | CHR:POS[3] | EA | EAF | N | Effect[4] G | Effect[4] GxE | Direction[5] G | Direction[5] GxE | 2 DF Joint | 1 DF Int. ($\beta_{GE}$) | Model 1 SNP ($\beta_{G1}$) | Model 2 SNP ($\beta_{G2}$) | Model 3 SNP ($\beta_{G3}$) | Most significant Analysis | Additional significant Analysis |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | *Y_RNA; ZDHHC19; SLC51A; PCYT1A* | rs11185517 | 3:195931583 | t | 0.20 | 916 | -0.40 | -11.38 | --(-) | --(+) | **1.36E-08** | 1.73E-06 | 6.52E-01 | 2.06E-01 | 2.84E-01 | EA.WOD.PP | |
| 2 | *RP11-313E19.1* | rs7678931 | 4:177545534 | t | 0.06 | 1650 | 1.27 | -8.49 | +- | -- | **4.82E-08** | 6.33E-06 | 3.87E-01 | 4.12E-02 | 3.64E-02 | AA.ALL.PP | |
| 3 | | rs6922858 | 6:888734 | a | 0.97 | 1816 | -1.17 | -8.90 | - | - | **1.20E-08** | 3.60E-04 | 5.30E-01 | 1.99E-06 | 1.70E-06 | AS.WOD.DBP | AS.ALL.DBP; AS.WOD.MAP |
| 4 | *NKAIN2* | rs868549 | 6:125027163 | t | 0.07 | 1650 | 0.89 | -8.65 | ++ | -- | **1.09E-09** | 3.03E-06 | 5.21E-01 | 1.85E-01 | 1.95E-01 | AA.ALL.PP | |
| 5 | *FOXP2* | rs6953359 | 7:114188174 | a | 0.93 | 1650 | -1.19 | -7.67 | -- | -- | **5.20E-09** | 3.55E-06 | 2.12E-01 | 2.24E-02 | 1.28E-02 | AA.ALL.DBP | AA.ALL.MAP |
| 6 | *RUSC2; RPL36AP33* | rs17370852 | 9:35510178 | a | 0.91 | 1800 | -0.31 | 9.76 | -(-)- | +(-)+ | **2.41E-12** | **7.65E-13** | 3.79E-01 | 5.79E-01 | 4.47E-01 | EA.ALL.SBP | EA.ALL.PP; EA.ALL.MAP |
| 7 | *FBXO10; RP11-613M10.8* | rs113300617 | 9:37544221 | a | 0.07 | 1650 | -0.69 | -6.75 | -- | -- | **1.12E-10** | 4.90E-05 | 5.80E-01 | 5.65E-03 | 6.25E-03 | AA.ALL.MAP | |
| 8 | *U3* | rs17753104 | 10:28700861 | a | 0.14 | 1372 | -0.87 | -12.47 | +-(+) | --(-) | **2.49E-08** | 5.20E-06 | 4.71E-01 | 9.46E-02 | 1.11E-01 | EA.ALL.SBP | |
| 9 | | rs115038395 | 12:11757330 | a | 0.08 | 1650 | -2.62 | -7.94 | -- | -- | **1.36E-08** | 3.42E-03 | 1.82E-01 | 1.00E-02 | 1.46E-02 | AA.ALL.SBP | |
| 10 | *AC067735.1* | rs189689705 | 12:39316220 | a | 0.93 | 1650 | 0.58 | 6.78 | -+ | ++ | **2.57E-08** | 6.90E-03 | 6.93E-01 | 2.18E-03 | 1.90E-03 | AA.ALL.MAP | |
| 11 | *RP11-507B12.2* | rs7179425 | 15:61595293 | t | 0.90 | 1800 | -1.83 | 6.71 | -(+)- | +(-)+ | **9.40E-09** | **3.21E-10** | 7.33E-03 | 5.38E-01 | 5.12E-01 | EA.ALL.DBP | |
| 12 | *DCC* | rs7243864 | 18:50713748 | t | 0.10 | 2547 | -2.34 | -2.42 | --- | -+- | **2.71E-08** | 4.88E-02 | 4.98E-05 | 1.90E-06 | 3.02E-06 | EA.ALL.MAP | |

[1]Each locus was determined through LD-based clumping, using ± 1 Mb around index variants, followed by LD threshold of r2 > 0.1; ancestry-specific LDs from 1000 Genomes Project were used when clumping within each ancestry

[2]Genes near index SNP (+/- 10K upstream/downstream distance bp). Gene names were obtained using variant effect predictor (VEP) from Ensembl. Genes with intragenic index variants bolded.

[3]Positions are based on build 37

[4]Effect is in mmHg unit

[5]Direction of effect in GENOA, FHS, and HyperGEN in European ancestry, respectively; Direction of effect in JHA and HyperGEN in African ancestry, respectively; in parenthesis if cohort was not included in a meta-analysis

[6]Genome-wide significant P-values ($P < 5\times10^{-8}$) bolded

Abbreviations: BP: blood pressure; SBP: systolic BP; DBP: diastolic BP; EA: effect allele; EAF: effect allele frequency; 1 DF Interaction P: P-value of the interaction test with 1 degree of freedom; 2 DF Joint P: P-value of the joint test with 2 degrees of freedom of genetic main and interaction effects; Model 2: P-value of SNP only model; Model 3: P-value of SNP in a model with SNP and E; EA: European ancestry; AA: African American ancestry; AS: Asian ancestry; G: Genetic Main; GxE: Interaction; Int.: Interaction; ALL: All participants; WOD: Subject without diuretic u

**Table 16** SNPs that are genome-wide significant (P < 5×10⁻⁸) or suggestive (P < 1×10⁻⁶) from 2DF joint test in meta-analysis without LD clumping in Aim 3

| Locus | rsID[1] | CHR | POS | EA | EAF | N | Effect[2] G | Effect[2] GxE | Direction[3] G | Direction[3] GxE | P value 2 DF Joint | P value 1 DF Interaction ($\beta_{GE}$) | P value Model 1 SNP ($\beta_{G1}$) | P value Model 2 SNP ($\beta_{G2}$) | P value Model 3 SNP ($\beta_{G3}$) | Analysis |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | rs17370852 | 9 | 35510178 | a | 0.91 | 1800 | -1.45 | 18.71 | -?- | +?+ | 2.41E-12 | 7.65E-13 | 3.79E-01 | 5.79E-01 | 4.47E-01 | EA_ALL_SBP |
| 2 | rs113300617 | 9 | 37544221 | a | 0.07 | 1650 | -0.69 | -6.75 | -- | -- | 1.12E-10 | 4.90E-05 | 5.80E-01 | 5.65E-03 | 6.25E-03 | AA_ALL_MAP |
| 3 | rs6953359 | 7 | 114188174 | a | 0.93 | 1650 | -1.49 | -8.55 | -- | -- | 2.50E-10 | 4.30E-06 | 1.93E-01 | 2.79E-02 | 1.53E-02 | AA_ALL_MAP |
| 4 | rs868549 | 6 | 125027163 | t | 0.07 | 1650 | 0.89 | -8.65 | ++ | -- | 1.09E-09 | 3.03E-06 | 5.21E-01 | 1.85E-01 | 1.95E-01 | AA_ALL_PP |
| 5 | rs17370852 | 9 | 35510178 | a | 0.91 | 1800 | -0.31 | 9.76 | +?- | +?+ | 1.98E-09 | 7.17E-08 | 8.02E-01 | 8.18E-01 | 7.00E-01 | EA_ALL_PP |
| 6 | rs6953359 | 7 | 114188174 | a | 0.93 | 1650 | -1.19 | -7.67 | -- | -- | 5.20E-09 | 3.55E-06 | 2.12E-01 | 2.24E-02 | 1.28E-02 | AA_ALL_DBP |
| 7 | rs17370852 | 9 | 35510178 | a | 0.91 | 1800 | -1.29 | 11.60 | -?- | +?+ | 5.89E-09 | 2.45E-10 | 1.94E-01 | 5.33E-01 | 4.21E-01 | EA_ALL_MAP |
| 8 | rs7179425 | 15 | 61595293 | t | 0.90 | 1800 | -1.83 | 6.71 | -?- | +?+ | 9.40E-09 | 3.21E-10 | 7.33E-03 | 5.38E-01 | 5.12E-01 | EA_ALL_DBP |
| 9 | rs7179308 | 15 | 61595355 | a | 0.10 | 1800 | 1.84 | -6.70 | +?+ | -?- | 9.92E-09 | 3.33E-10 | 6.91E-03 | 5.27E-01 | 5.01E-01 | EA_ALL_DBP |
| 10 | rs6922858 | 6 | 888734 | a | 0.97 | 1816 | -1.17 | -8.90 | - | - | 1.19E-08 | 3.61E-04 | 5.30E-01 | 1.99E-06 | 1.70E-06 | AS_WOD_DBP |
| 11 | rs11185517 | 3 | 195931583 | t | 0.20 | 916 | -0.40 | -11.38 | --? | --? | 1.36E-08 | 1.73E-06 | 6.52E-01 | 2.06E-01 | 2.84E-01 | EA_WOD_PP |
| 12 | rs115038395 | 12 | 11757330 | a | 0.08 | 1650 | -2.62 | -7.94 | -- | -- | 1.36E-08 | 3.42E-03 | 1.82E-01 | 1.00E-02 | 1.46E-02 | AA_ALL_SBP |
| 13 | rs75149358 | 12 | 11757243 | a | 0.92 | 1650 | 2.59 | 7.96 | ++ | ++ | 1.42E-08 | 3.41E-03 | 1.89E-01 | 1.08E-02 | 1.57E-02 | AA_ALL_SBP |
| 14 | rs4324488 | 3 | 195931868 | t | 0.20 | 916 | -0.41 | -11.32 | --? | --? | 1.44E-08 | 1.83E-06 | 6.39E-01 | 2.01E-01 | 2.77E-01 | EA_WOD_PP |
| 15 | rs74652398 | 12 | 11754748 | c | 0.93 | 1650 | 1.95 | 8.55 | ++ | ++ | 1.65E-08 | 1.60E-03 | 3.24E-01 | 2.13E-02 | 2.98E-02 | AA_ALL_SBP |
| 16 | rs6922858 | 6 | 888734 | a | 0.97 | 1823 | -1.07 | -8.95 | - | - | 2.18E-08 | 3.94E-04 | 5.70E-01 | 3.08E-06 | 2.74E-06 | AS_ALL_DBP |
| 17 | rs17753104 | 10 | 28700861 | a | 0.14 | 1372 | -0.87 | -12.47 | +-? | --? | 2.49E-08 | 5.20E-06 | 4.71E-01 | 9.46E-02 | 1.11E-01 | EA_ALL_SBP |
| 18 | rs189689705 | 12 | 39316220 | a | 0.93 | 1650 | 0.58 | 6.78 | -+ | ++ | 2.57E-08 | 6.90E-03 | 6.93E-01 | 2.18E-03 | 1.90E-03 | AA_ALL_MAP |
| 19 | rs7243864 | 18 | 50713748 | t | 0.10 | 2547 | -2.34 | -2.42 | --- | -+- | 2.71E-08 | 4.88E-02 | 4.98E-05 | 1.90E-06 | 3.02E-06 | EA_ALL_MAP |
| 20 | rs6788070 | 3 | 195932512 | t | 0.20 | 916 | -0.40 | -11.09 | --? | --? | 2.91E-08 | 2.66E-06 | 6.49E-01 | 2.10E-01 | 2.88E-01 | EA_WOD_PP |
| 21 | rs6922858 | 6 | 888734 | a | 0.97 | 1816 | -2.44 | -7.43 | - | - | 3.05E-08 | 3.67E-03 | 2.04E-01 | 5.25E-07 | 4.45E-07 | AS_WOD_MAP |
| 22 | rs6778521 | 3 | 195932613 | a | 0.21 | 916 | -0.39 | -11.04 | --? | --? | 3.58E-08 | 2.96E-06 | 6.61E-01 | 2.14E-01 | 2.93E-01 | EA_WOD_PP |
| 23 | rs7678931 | 4 | 177545534 | t | 0.06 | 1650 | 1.27 | -8.49 | +- | -- | 4.82E-08 | 6.33E-06 | 3.87E-01 | 4.12E-02 | 3.64E-02 | AA_ALL_PP |
| 24 | rs114796468 | 6 | 480849 | c | 0.93 | 1650 | 1.20 | 6.65 | ++ | ++ | 5.00E-08 | 1.75E-03 | 4.62E-01 | 1.11E-03 | 1.13E-03 | AA_ALL_MAP |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 25 | rs11721985 | 4 | 177542233 | a | 0.94 | 1650 | -1.10 | 8.35 | -+ | ++ | 5.40E-08 | 8.82E-06 | 4.51E-01 | 3.25E-02 | 2.79E-02 | AA_ALL_PP |
| 26 | rs6922858 | 6 | 888734 | a | 0.97 | 1823 | -2.34 | -7.45 | - | - | 5.57E-08 | 4.01E-03 | 2.28E-01 | 8.06E-07 | 7.16E-07 | AS_ALL_MAP |
| 27 | rs7622198 | 3 | 159962614 | a | 0.93 | 1800 | 0.97 | 5.22 | -?+ | +?+ | 6.65E-08 | 2.82E-04 | 2.05E-01 | 1.59E-02 | 1.94E-02 | EA_ALL_DBP |
| 28 | rs58242808 | 4 | 177552843 | d | 0.07 | 1650 | 1.31 | -8.34 | +- | -- | 7.07E-08 | 8.59E-06 | 3.67E-01 | 4.96E-02 | 4.41E-02 | AA_ALL_PP |
| 29 | rs116587610 | 6 | 31243389 | a | 0.45 | 916 | -0.64 | -3.84 | --? | -+? | 7.29E-08 | 1.15E-02 | 3.60E-01 | 3.95E-01 | 3.92E-01 | EA_WOD_PP |
| 30 | rs115987494 | 6 | 31243410 | t | 0.45 | 916 | -0.64 | -3.84 | --? | -+? | 7.39E-08 | 1.16E-02 | 3.59E-01 | 3.93E-01 | 3.90E-01 | EA_WOD_PP |
| 31 | rs17037007 | 3 | 37845418 | t | 0.07 | 1650 | -2.56 | -8.05 | -+ | -- | 7.58E-08 | 2.16E-04 | 4.71E-02 | 7.05E-04 | 9.39E-04 | AA_ALL_PP |
| 32 | rs480935 | 9 | 124382470 | t | 0.08 | 1650 | 4.71 | -8.34 | ++ | -- | 7.67E-08 | 5.31E-07 | 9.26E-08 | 2.00E-03 | 2.65E-03 | AA_ALL_DBP |
| 33 | rs55900682 | 6 | 888396 | a | 0.98 | 1816 | -1.31 | -9.18 | - | - | 7.68E-08 | 8.16E-04 | 5.21E-01 | 5.38E-06 | 5.19E-06 | AS_WOD_DBP |
| 34 | rs75269061 | 6 | 888821 | a | 0.02 | 1816 | 1.34 | 9.19 | + | + | 7.79E-08 | 8.58E-04 | 5.13E-01 | 5.10E-06 | 5.00E-06 | AS_WOD_DBP |
| 35 | rs9834427 | 3 | 165772627 | a | 0.11 | 1000 | 6.89 | -10.71 | ++ | -- | 8.90E-08 | 1.09E-04 | 1.56E-07 | 4.50E-03 | 5.12E-03 | AA_WOD_PP |
| 36 | rs12508778 | 4 | 177548451 | a | 0.06 | 1650 | 1.42 | -8.42 | +- | -- | 9.78E-08 | 8.42E-06 | 3.33E-01 | 6.40E-02 | 5.67E-02 | AA_ALL_PP |
| 37 | rs17078700 | 13 | 33747458 | a | 0.12 | 1650 | -4.71 | 8.75 | -- | ++ | 1.11E-07 | 7.40E-06 | 2.14E-07 | 2.60E-02 | 2.78E-02 | AA_ALL_PP |
| 38 | rs114796468 | 6 | 480849 | c | 0.93 | 1650 | 0.22 | 11.38 | -+ | ++ | 1.17E-07 | 4.08E-04 | 9.29E-01 | 5.74E-03 | 5.81E-03 | AA_ALL_SBP |
| 39 | rs55900682 | 6 | 888396 | a | 0.98 | 1823 | -1.23 | -9.24 | - | - | 1.20E-07 | 8.76E-04 | 5.53E-01 | 7.33E-06 | 7.31E-06 | AS_ALL_DBP |
| 40 | rs17753104 | 10 | 28700861 | a | 0.14 | 1372 | -0.20 | -7.06 | +-? | --? | 1.21E-07 | 8.49E-06 | 7.73E-01 | 1.99E-01 | 2.19E-01 | EA_ALL_MAP |
| 41 | rs75269061 | 6 | 888821 | a | 0.02 | 1823 | 1.26 | 9.25 | + | + | 1.22E-07 | 9.18E-04 | 5.45E-01 | 7.07E-06 | 7.14E-06 | AS_ALL_DBP |
| 42 | rs75269061 | 6 | 888821 | a | 0.02 | 1816 | 2.76 | 7.67 | + | + | 1.23E-07 | 6.63E-03 | 1.93E-01 | 1.10E-06 | 1.07E-06 | AS_WOD_MAP |
| 43 | rs4439939 | 2 | 34988474 | t | 0.66 | 1815 | 2.09 | 0.24 | +++ | +-- | 1.24E-07 | 7.98E-01 | 1.51E-06 | 4.57E-08 | 5.88E-08 | EA_WOD_MAP |
| 44 | rs55900682 | 6 | 888396 | a | 0.98 | 1816 | -2.70 | -7.68 | - | - | 1.25E-07 | 6.24E-03 | 2.01E-01 | 1.20E-06 | 1.16E-06 | AS_WOD_MAP |
| 45 | rs1947534 | 18 | 41905790 | a | 0.96 | 1823 | -2.12 | -3.99 | - | - | 1.26E-07 | 2.53E-02 | 1.25E-01 | 3.48E-07 | 4.08E-07 | AS_ALL_DBP |
| 46 | rs111983094 | 1 | 19847611 | d | 0.18 | 1000 | -4.83 | 11.49 | -- | ++ | 1.34E-07 | 2.04E-09 | 6.87E-06 | 1.73E-01 | 1.79E-01 | AA_WOD_MAP |
| 47 | rs17773338 | 7 | 5878333 | a | 0.88 | 1502 | 1.96 | 4.37 | ?++ | ?++ | 1.40E-07 | 2.60E-03 | 2.47E-02 | 9.89E-05 | 1.07E-04 | EA_WOD_PP |
| 48 | rs75800997 | 11 | 79797734 | t | 0.06 | 1650 | -3.19 | -8.98 | -- | -- | 1.41E-07 | 1.26E-03 | 8.39E-02 | 2.26E-04 | 2.74E-04 | AA_ALL_SBP |
| 49 | rs926555 | 6 | 1039373 | a | 0.34 | 2547 | -0.81 | 3.75 | --- | +++ | 1.51E-07 | 1.24E-07 | 2.50E-02 | 9.23E-01 | 9.27E-01 | EA_ALL_DBP |
| 50 | rs78476095 | 11 | 79777103 | c | 0.94 | 1650 | 1.72 | 10.98 | +- | ++ | 1.57E-07 | 8.53E-05 | 3.63E-01 | 3.29E-03 | 3.91E-03 | AA_ALL_SBP |
| 51 | rs200938184 | 13 | 92688020 | d | 0.94 | 1650 | 0.11 | 14.63 | -+ | ++ | 1.62E-07 | 1.84E-06 | 9.54E-01 | 8.60E-02 | 1.08E-01 | AA_ALL_SBP |
| 52 | rs4344598 | 13 | 89419933 | a | 0.11 | 1000 | 1.21 | -8.71 | +- | -- | 1.64E-07 | 2.14E-04 | 3.61E-01 | 4.99E-02 | 6.72E-02 | AA_WOD_PP |
| 53 | rs9588408 | 13 | 89420896 | a | 0.89 | 1000 | -1.21 | 8.67 | -+ | ++ | 1.67E-07 | 2.25E-04 | 3.61E-01 | 4.97E-02 | 6.68E-02 | AA_WOD_PP |
| 54 | rs7243864 | 18 | 50713748 | t | 0.10 | 2547 | -2.14 | -2.08 | --- | -+- | 1.73E-07 | 6.42E-02 | 6.26E-05 | 1.67E-06 | 2.50E-06 | EA_ALL_DBP |
| 55 | rs9406244 | 6 | 1041616 | t | 0.66 | 2547 | 0.80 | -3.73 | +++ | --- | 1.77E-07 | 1.38E-07 | 2.71E-02 | 9.03E-01 | 9.07E-01 | EA_ALL_DBP |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 56 | rs77071256 | 12 | 131921244 | a | 0.09 | 1650 | -1.21 | -7.36 | -- | -- | 1.78E-07 | 7.19E-04 | 4.17E-01 | 1.46E-03 | 1.30E-03 | AA_ALL_SBP |
| 57 | rs4304213 | 6 | 1038795 | a | 0.34 | 2547 | -0.78 | 3.69 | --- | +++ | 1.81E-07 | 1.54E-07 | 2.89E-02 | 8.94E-01 | 8.97E-01 | EA_ALL_DBP |
| 58 | rs9964923 | 18 | 21828099 | a | 0.02 | 1816 | -5.30 | 14.60 | - | + | 1.88E-07 | 2.61E-07 | 1.30E-02 | 4.28E-02 | 3.82E-02 | AS_WOD_SBP |
| 59 | rs76774947 | 3 | 195933301 | a | 0.20 | 916 | -0.40 | -10.73 | --? | --? | 1.95E-07 | 6.75E-06 | 6.46E-01 | 2.13E-01 | 2.90E-01 | EA_WOD_PP |
| 60 | rs17097805 | 14 | 99262153 | a | 0.49 | 1823 | -1.10 | 0.27 | - | + | 1.95E-07 | 4.44E-01 | 3.24E-05 | 4.72E-08 | 5.00E-08 | AS_ALL_PP |
| 61 | rs75269061 | 6 | 888821 | a | 0.02 | 1823 | 2.68 | 7.69 | + | + | 1.96E-07 | 7.15E-03 | 2.12E-01 | 1.51E-06 | 1.52E-06 | AS_ALL_MAP |
| 62 | rs61981355 | 14 | 99257470 | a | 0.49 | 1823 | -1.08 | 0.23 | - | + | 1.96E-07 | 5.13E-01 | 4.49E-05 | 4.47E-08 | 4.74E-08 | AS_ALL_PP |
| 63 | rs55900682 | 6 | 888396 | a | 0.98 | 1823 | -2.62 | -7.71 | - | - | 1.97E-07 | 6.73E-03 | 2.20E-01 | 1.64E-06 | 1.61E-06 | AS_ALL_MAP |
| 64 | rs9949360 | 18 | 21833586 | a | 0.02 | 1816 | -5.58 | 15.04 | - | + | 2.05E-07 | 2.27E-07 | 1.05E-02 | 5.54E-02 | 4.94E-02 | AS_WOD_SBP |
| 65 | rs61981355 | 14 | 99257470 | a | 0.49 | 1816 | -1.08 | 0.23 | - | + | 2.06E-07 | 5.05E-01 | 4.54E-05 | 4.76E-08 | 5.09E-08 | AS_WOD_PP |
| 66 | rs56882310 | 18 | 41912072 | a | 0.96 | 1823 | -2.18 | -3.88 | - | - | 2.06E-07 | 3.02E-02 | 1.14E-01 | 5.22E-07 | 5.70E-07 | AS_ALL_DBP |
| 67 | rs9959834 | 18 | 21827805 | a | 0.98 | 1816 | 5.35 | -14.71 | + | - | 2.08E-07 | 2.70E-07 | 1.27E-02 | 4.63E-02 | 4.13E-02 | AS_WOD_SBP |
| 68 | rs1947534 | 18 | 41905790 | a | 0.96 | 1816 | -2.27 | -3.65 | - | - | 2.10E-07 | 3.82E-02 | 9.68E-02 | 4.73E-07 | 5.08E-07 | AS_WOD_DBP |
| 69 | rs76358082 | 4 | 177563281 | c | 0.93 | 1650 | -1.31 | 8.23 | -+ | ++ | 2.13E-07 | 1.18E-05 | 3.55E-01 | 5.63E-02 | 5.00E-02 | AA_ALL_PP |
| 70 | rs7149860 | 14 | 99264257 | a | 0.51 | 1823 | 1.09 | -0.26 | + | - | 2.18E-07 | 4.47E-01 | 3.48E-05 | 5.33E-08 | 5.64E-08 | AS_ALL_PP |
| 71 | rs79041712 | 15 | 94443760 | a | 0.90 | 1000 | -2.02 | 7.80 | -- | ++ | 2.18E-07 | 5.73E-04 | 8.60E-02 | 2.87E-01 | 3.17E-01 | AA_WOD_MAP |
| 72 | rs74355665 | 3 | 195933337 | t | 0.20 | 916 | -0.40 | -10.71 | --? | --? | 2.19E-07 | 7.15E-06 | 6.45E-01 | 2.13E-01 | 2.90E-01 | EA_WOD_PP |
| 73 | rs7150005 | 14 | 99264259 | a | 0.51 | 1823 | 1.09 | -0.26 | + | - | 2.20E-07 | 4.45E-01 | 3.48E-05 | 5.53E-08 | 5.85E-08 | AS_ALL_PP |
| 74 | rs4991185 | 12 | 119841693 | t | 0.89 | 1372 | -4.57 | 9.64 | --? | ++? | 2.21E-07 | 1.79E-04 | 6.10E-05 | 8.49E-04 | 8.97E-04 | EA_ALL_PP |
| 75 | rs4300442 | 12 | 119840132 | a | 0.89 | 1372 | -4.57 | 9.61 | --? | ++? | 2.23E-07 | 1.85E-04 | 5.86E-05 | 8.08E-04 | 8.53E-04 | EA_ALL_PP |
| 76 | rs11650288 | 17 | 10018145 | a | 0.20 | 1815 | 2.46 | -6.89 | +++ | --- | 2.24E-07 | 3.33E-07 | 1.45E-03 | 9.90E-02 | 1.09E-01 | EA_WOD_PP |
| 77 | rs12715418 | 3 | 4720118 | c | 0.90 | 1000 | 1.63 | 4.29 | ++ | -+ | 2.26E-07 | 6.58E-02 | 2.07E-01 | 8.36E-04 | 1.20E-03 | AA_WOD_PP |
| 78 | rs12523737 | 6 | 120595996 | a | 0.94 | 1650 | -2.56 | 12.84 | -- | ++ | 2.28E-07 | 9.36E-06 | 2.28E-01 | 1.52E-01 | 1.49E-01 | AA_ALL_SBP |
| 79 | rs71176194 | 19 | 33571006 | d | 0.07 | 1650 | -2.75 | -4.81 | -- | -- | 2.31E-07 | 1.49E-02 | 9.74E-03 | 3.95E-06 | 4.90E-06 | AA_ALL_PP |
| 80 | rs8101144 | 19 | 18715121 | a | 0.14 | 1650 | -7.37 | 5.84 | -- | ++ | 2.33E-07 | 1.20E-02 | 1.91E-08 | 4.95E-06 | 3.89E-06 | AA_ALL_SBP |
| 81 | rs17097805 | 14 | 99262153 | a | 0.49 | 1816 | -1.09 | 0.28 | - | + | 2.35E-07 | 4.19E-01 | 3.23E-05 | 6.19E-08 | 6.53E-08 | AS_WOD_PP |
| 82 | rs9964923 | 18 | 21828099 | a | 0.02 | 1823 | -5.40 | 14.60 | - | + | 2.41E-07 | 2.71E-07 | 1.15E-02 | 5.06E-02 | 4.58E-02 | AS_ALL_SBP |
| 83 | rs74491996 | 3 | 195933371 | a | 0.20 | 916 | -0.40 | -10.70 | --? | --? | 2.42E-07 | 7.50E-06 | 6.45E-01 | 2.13E-01 | 2.90E-01 | EA_WOD_PP |
| 84 | rs72995446 | 19 | 18716141 | a | 0.14 | 1650 | -7.41 | 6.13 | -- | ++ | 2.52E-07 | 8.88E-03 | 1.99E-08 | 7.73E-06 | 5.98E-06 | AA_ALL_SBP |
| 85 | rs79041712 | 15 | 94443760 | a | 0.90 | 1000 | -0.64 | 6.14 | -- | ++ | 2.52E-07 | 9.92E-04 | 5.30E-01 | 2.58E-02 | 2.80E-02 | AA_WOD_DBP |
| 86 | rs75809135 | 19 | 46790972 | t | 0.06 | 1650 | -6.56 | 3.05 | -- | ++ | 2.52E-07 | 2.72E-01 | 3.45E-08 | 1.62E-07 | 2.68E-07 | AA_ALL_PP |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 87 | rs114264676 | 19 | 46790358 | a | 0.06 | 1650 | -6.54 | 3.03 | -- | ++ | 2.54E-07 | 2.74E-01 | 3.50E-08 | 1.65E-07 | 2.80E-07 | AA_ALL_PP |
| 88 | rs115905395 | 5 | 63473312 | t | 0.97 | 1816 | -10.28 | 15.58 | - | + | 2.55E-07 | 2.59E-08 | 2.14E-06 | 4.82E-01 | 5.15E-01 | AS_WOD_MAP |
| 89 | rs71358291 | 17 | 10189273 | a | 0.06 | 1650 | 9.55 | -9.85 | ++ | +- | 2.60E-07 | 5.31E-04 | 3.53E-08 | 2.13E-05 | 1.73E-05 | AA_ALL_PP |
| 90 | rs7149860 | 14 | 99264257 | a | 0.51 | 1816 | 1.09 | -0.28 | + | - | 2.61E-07 | 4.22E-01 | 3.46E-05 | 6.98E-08 | 7.35E-08 | AS_WOD_PP |
| 91 | rs1598669 | 18 | 41914949 | a | 0.96 | 1823 | -2.16 | -3.89 | - | - | 2.62E-07 | 3.01E-02 | 1.18E-01 | 6.51E-07 | 6.99E-07 | AS_ALL_DBP |
| 92 | rs28594175 | 4 | 109264778 | a | 0.84 | 1000 | -0.58 | 9.40 | -- | ++ | 2.62E-07 | 2.96E-04 | 6.69E-01 | 1.73E-02 | 2.77E-02 | AA_WOD_SBP |
| 93 | rs772563 | 12 | 63305545 | t | 0.45 | 1815 | -3.44 | -0.34 | --- | ++- | 2.63E-07 | 7.97E-01 | 1.30E-06 | 5.71E-08 | 5.20E-08 | EA_WOD_SBP |
| 94 | rs7097658 | 10 | 3709316 | t | 0.62 | 1650 | 3.16 | -0.73 | ++ | +- | 2.65E-07 | 5.47E-01 | 7.64E-06 | 4.09E-08 | 3.43E-08 | AA_ALL_PP |
| 95 | rs1666872 | 12 | 63305152 | a | 0.55 | 1815 | 3.44 | 0.34 | +++ | --+ | 2.67E-07 | 7.96E-01 | 1.32E-06 | 5.71E-08 | 5.18E-08 | EA_WOD_SBP |
| 96 | rs9964923 | 18 | 21828099 | a | 0.02 | 1816 | -3.51 | 11.81 | - | + | 2.69E-07 | 8.61E-07 | 5.16E-02 | 1.25E-02 | 1.05E-02 | AS_WOD_MAP |
| 97 | rs9959834 | 18 | 21827805 | a | 0.98 | 1823 | 5.45 | -14.70 | + | - | 2.72E-07 | 2.86E-07 | 1.13E-02 | 5.46E-02 | 4.94E-02 | AS_ALL_SBP |
| 98 | rs926555 | 6 | 1039373 | a | 0.34 | 2547 | -0.90 | 3.87 | --- | +++ | 2.73E-07 | 7.58E-07 | 2.15E-02 | 9.00E-01 | 8.90E-01 | EA_ALL_MAP |
| 99 | rs9949360 | 18 | 21833586 | a | 0.02 | 1823 | -5.68 | 15.02 | - | + | 2.74E-07 | 2.45E-07 | 9.29E-03 | 6.51E-02 | 5.88E-02 | AS_ALL_SBP |
| 100 | rs2906924 | 17 | 27609209 | a | 0.84 | 1650 | -0.48 | 6.91 | +- | ++ | 2.75E-07 | 3.34E-05 | 6.49E-01 | 2.64E-02 | 2.75E-02 | AA_ALL_PP |
| 101 | rs28884496 | 18 | 21837697 | a | 0.98 | 1816 | 5.68 | -15.23 | + | - | 2.77E-07 | 2.82E-07 | 1.07E-02 | 6.18E-02 | 5.50E-02 | AS_WOD_SBP |
| 102 | rs7150005 | 14 | 99264259 | a | 0.51 | 1816 | 1.09 | -0.28 | + | - | 2.79E-07 | 4.21E-01 | 3.55E-05 | 7.11E-08 | 7.63E-08 | AS_WOD_PP |
| 103 | rs11898121 | 2 | 203088731 | a | 0.41 | 1650 | -0.09 | 4.05 | +- | ++ | 2.82E-07 | 1.26E-05 | 8.60E-01 | 1.15E-02 | 1.18E-02 | AA_ALL_DBP |
| 104 | rs772560 | 12 | 63304807 | a | 0.55 | 1815 | 3.43 | 0.32 | +++ | --+ | 2.85E-07 | 8.08E-01 | 1.32E-06 | 6.16E-08 | 5.61E-08 | EA_WOD_SBP |
| 105 | rs11938527 | 4 | 109270817 | a | 0.16 | 1000 | 0.63 | -9.52 | ++ | -- | 2.86E-07 | 2.40E-04 | 6.37E-01 | 2.30E-02 | 3.65E-02 | AA_WOD_SBP |
| 106 | rs772561 | 12 | 63304963 | a | 0.45 | 1815 | -3.44 | -0.32 | --- | ++- | 2.86E-07 | 8.08E-01 | 1.33E-06 | 6.14E-08 | 5.56E-08 | EA_WOD_SBP |
| 107 | rs888586 | 7 | 5878648 | t | 0.86 | 1502 | 1.99 | 3.39 | ?++ | ?++ | 2.88E-07 | 9.82E-03 | 1.30E-02 | 4.53E-05 | 4.81E-05 | EA_WOD_PP |
| 108 | rs772555 | 12 | 63304283 | a | 0.45 | 1815 | -3.44 | -0.32 | --- | ++- | 2.90E-07 | 8.09E-01 | 1.34E-06 | 6.21E-08 | 5.62E-08 | EA_WOD_SBP |
| 109 | rs772557 | 12 | 63304584 | a | 0.55 | 1815 | 3.43 | 0.32 | +++ | --+ | 2.91E-07 | 8.08E-01 | 1.34E-06 | 6.17E-08 | 5.59E-08 | EA_WOD_SBP |
| 110 | rs9959834 | 18 | 21827805 | a | 0.98 | 1816 | 3.56 | -11.91 | + | - | 2.94E-07 | 8.68E-07 | 5.00E-02 | 1.37E-02 | 1.14E-02 | AS_WOD_MAP |
| 111 | rs59078432 | 8 | 22697576 | t | 0.86 | 1650 | 4.48 | -0.46 | ++ | -+ | 2.95E-07 | 7.79E-01 | 3.32E-07 | 1.11E-07 | 1.31E-07 | AA_ALL_MAP |
| 112 | rs116741667 | 6 | 31243170 | a | 0.50 | 916 | -0.18 | -3.70 | -+? | -+? | 2.97E-07 | 1.31E-02 | 7.90E-01 | 8.56E-01 | 8.62E-01 | EA_WOD_PP |
| 113 | rs772559 | 12 | 63304757 | a | 0.55 | 1815 | 3.47 | 0.26 | +++ | --+ | 2.98E-07 | 8.46E-01 | 1.23E-06 | 6.61E-08 | 5.97E-08 | EA_WOD_SBP |
| 114 | rs8004974 | 14 | 99257911 | t | 0.51 | 1823 | 1.07 | -0.23 | + | - | 3.00E-07 | 5.11E-01 | 5.68E-05 | 6.97E-08 | 7.50E-08 | AS_ALL_PP |
| 115 | rs28478722 | 4 | 109269457 | a | 0.16 | 1000 | 0.62 | -9.50 | ++ | -- | 3.04E-07 | 2.53E-04 | 6.43E-01 | 2.29E-02 | 3.61E-02 | AA_WOD_SBP |
| 116 | rs2246214 | 12 | 63304868 | a | 0.55 | 1815 | 3.42 | 0.34 | +++ | --+ | 3.07E-07 | 8.01E-01 | 1.45E-06 | 6.88E-08 | 6.06E-08 | EA_WOD_SBP |
| 117 | rs141541522 | 14 | 99257953 | d | 0.51 | 1823 | 1.07 | -0.23 | + | - | 3.11E-07 | 5.14E-01 | 5.87E-05 | 7.13E-08 | 7.54E-08 | AS_ALL_PP |

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 118 | rs28526354 | 4 | 109263616 | a | 0.16 | 1000 | 0.56 | -9.33 | ++ | -- | 3.12E-07 | 3.38E-04 | 6.79E-01 | 1.70E-02 | 2.70E-02 | AA_WOD_SBP |
| 119 | rs4304213 | 6 | 1038795 | a | 0.34 | 2547 | -0.89 | 3.83 | --- | +++ | 3.14E-07 | 9.28E-07 | 2.20E-02 | 8.96E-01 | 8.87E-01 | EA_ALL_MAP |
| 120 | rs73212121 | 3 | 195933424 | t | 0.79 | 916 | 0.39 | 10.62 | ++? | ++? | 3.14E-07 | 9.04E-06 | 6.55E-01 | 2.21E-01 | 2.99E-01 | EA_WOD_PP |
| 121 | rs17033685 | 1 | 115867742 | a | 0.92 | 1650 | 2.01 | 8.52 | ++ | ++ | 3.15E-07 | 9.16E-04 | 1.93E-01 | 3.51E-04 | 4.07E-04 | AA_ALL_SBP |
| 122 | rs772568 | 12 | 63307346 | c | 0.55 | 1815 | 3.48 | 0.17 | +++ | --+ | 3.28E-07 | 8.99E-01 | 1.14E-06 | 6.89E-08 | 6.37E-08 | EA_WOD_SBP |
| 123 | rs699586 | 12 | 63306382 | t | 0.55 | 1815 | 3.47 | 0.18 | +++ | --+ | 3.30E-07 | 8.92E-01 | 1.18E-06 | 7.01E-08 | 6.43E-08 | EA_WOD_SBP |
| 124 | rs772567 | 12 | 63307326 | t | 0.55 | 1815 | 3.48 | 0.17 | +++ | --+ | 3.30E-07 | 8.99E-01 | 1.15E-06 | 6.89E-08 | 6.35E-08 | EA_WOD_SBP |
| 125 | rs772566 | 12 | 63307248 | t | 0.55 | 1815 | 3.48 | 0.17 | +++ | --+ | 3.31E-07 | 9.00E-01 | 1.14E-06 | 6.94E-08 | 6.39E-08 | EA_WOD_SBP |
| 126 | rs148910075 | 11 | 79798963 | a | 0.06 | 1650 | -3.17 | -9.05 | -- | -- | 3.31E-07 | 1.62E-03 | 9.18E-02 | 3.12E-04 | 3.79E-04 | AA_ALL_SBP |
| 127 | rs28482267 | 15 | 94352467 | a | 0.14 | 1000 | 4.62 | -15.79 | ++ | -- | 3.32E-07 | 2.33E-06 | 1.28E-02 | 9.95E-01 | 9.79E-01 | AA_WOD_SBP |
| 128 | rs115905395 | 5 | 63473312 | t | 0.97 | 1823 | -10.19 | 15.59 | - | + | 3.32E-07 | 3.74E-08 | 3.31E-06 | 5.29E-01 | 5.64E-01 | AS_ALL_MAP |
| 129 | rs28380415 | 4 | 109266821 | t | 0.16 | 1000 | 0.58 | -9.50 | ++ | -- | 3.32E-07 | 2.68E-04 | 6.65E-01 | 2.13E-02 | 3.34E-02 | AA_WOD_SBP |
| 130 | rs772565 | 12 | 63306853 | t | 0.55 | 1815 | 3.47 | 0.17 | +++ | --+ | 3.33E-07 | 8.97E-01 | 1.17E-06 | 7.04E-08 | 6.51E-08 | EA_WOD_SBP |
| 131 | rs9406244 | 6 | 1041616 | t | 0.66 | 2547 | 0.89 | -3.83 | +++ | --- | 3.35E-07 | 8.94E-07 | 2.29E-02 | 9.05E-01 | 8.95E-01 | EA_ALL_MAP |
| 132 | rs699585 | 12 | 63306132 | t | 0.55 | 1815 | 3.47 | 0.17 | +++ | --+ | 3.36E-07 | 8.98E-01 | 1.17E-06 | 7.01E-08 | 6.49E-08 | EA_WOD_SBP |
| 133 | rs9949360 | 18 | 21833586 | a | 0.02 | 1816 | -3.73 | 12.14 | - | + | 3.40E-07 | 8.02E-07 | 4.34E-02 | 1.72E-02 | 1.43E-02 | AS_WOD_MAP |
| 134 | rs772569 | 12 | 63307760 | a | 0.45 | 1815 | -3.48 | -0.18 | --- | ++- | 3.49E-07 | 8.93E-01 | 1.19E-06 | 7.27E-08 | 6.71E-08 | EA_WOD_SBP |
| 135 | rs772556 | 12 | 63304447 | t | 0.45 | 1815 | -3.47 | -0.14 | --- | ++- | 3.52E-07 | 9.17E-01 | 1.17E-06 | 6.85E-08 | 6.32E-08 | EA_WOD_SBP |
| 136 | rs56882310 | 18 | 41912072 | a | 0.96 | 1816 | -2.32 | -3.55 | - | - | 3.54E-07 | 4.50E-02 | 8.84E-02 | 6.94E-07 | 6.93E-07 | AS_WOD_DBP |
| 137 | rs79474826 | 4 | 177571411 | a | 0.07 | 1650 | 1.45 | -8.45 | +- | -- | 3.57E-07 | 1.05E-05 | 3.13E-01 | 7.39E-02 | 6.66E-02 | AA_ALL_PP |
| 138 | rs1729531 | 13 | 72893992 | t | 0.40 | 1212 | -0.04 | 5.06 | +?- | +?+ | 3.59E-07 | 1.06E-06 | 9.53E-01 | 9.26E-03 | 1.19E-02 | EA_WOD_DBP |
| 139 | rs1860132 | 4 | 109262095 | c | 0.16 | 1000 | 0.54 | -9.22 | ++ | -- | 3.62E-07 | 4.06E-04 | 6.88E-01 | 1.69E-02 | 2.66E-02 | AA_WOD_SBP |
| 140 | rs258097 | 16 | 55765906 | a | 0.09 | 1650 | -4.70 | -2.75 | -- | -- | 3.64E-07 | 2.58E-01 | 7.63E-04 | 5.44E-07 | 7.36E-07 | AA_ALL_SBP |
| 141 | rs115100192 | 18 | 41929553 | c | 0.04 | 1823 | 2.11 | 3.94 | + | + | 3.67E-07 | 2.88E-02 | 1.29E-01 | 9.68E-07 | 1.01E-06 | AS_ALL_DBP |
| 142 | rs28668769 | 4 | 109264793 | a | 0.16 | 1000 | 0.94 | -10.03 | ++ | -- | 3.70E-07 | 1.22E-04 | 4.87E-01 | 4.25E-02 | 6.52E-02 | AA_WOD_SBP |
| 143 | rs2200226 | 4 | 53738359 | t | 0.42 | 1000 | -3.67 | 0.73 | -- | ++ | 3.71E-07 | 5.51E-01 | 1.12E-07 | 7.81E-07 | 5.81E-07 | AA_WOD_MAP |
| 144 | rs28884496 | 18 | 21837697 | a | 0.98 | 1823 | 5.78 | -15.21 | + | - | 3.71E-07 | 3.06E-07 | 9.46E-03 | 7.23E-02 | 6.51E-02 | AS_ALL_SBP |
| 145 | rs1537905 | 1 | 88672066 | a | 0.05 | 1650 | -5.20 | 0.80 | -- | +- | 3.71E-07 | 6.98E-01 | 1.83E-07 | 4.29E-06 | 3.54E-06 | AA_ALL_MAP |
| 146 | rs9964923 | 18 | 21828099 | a | 0.02 | 1823 | -3.63 | 11.86 | - | + | 3.74E-07 | 1.06E-06 | 4.64E-02 | 1.56E-02 | 1.32E-02 | AS_ALL_MAP |
| 147 | rs8004974 | 14 | 99257911 | t | 0.51 | 1816 | 1.06 | -0.24 | + | - | 3.76E-07 | 4.85E-01 | 5.75E-05 | 9.17E-08 | 9.62E-08 | AS_WOD_PP |
| 148 | rs10163977 | 18 | 41935966 | a | 0.04 | 1823 | 2.11 | 3.93 | + | + | 3.81E-07 | 2.96E-02 | 1.27E-01 | 1.02E-06 | 1.06E-06 | AS_ALL_DBP |

| 149 | rs10600624 | 3 | 144108989 | d | 0.88 | 1000 | -3.75 | 11.52 | -- | ++ | 3.82E-07 | 1.14E-07 | 1.36E-02 | 8.92E-01 | 8.53E-01 | AA_WOD_PP |
| 150 | rs148258828 | 18 | 41909525 | a | 0.96 | 1823 | -2.04 | -4.16 | - | - | 3.86E-07 | 2.42E-02 | 1.51E-01 | 1.30E-06 | 1.31E-06 | AS_ALL_DBP |
| 151 | rs17097800 | 14 | 99257740 | t | 0.49 | 1823 | -1.06 | 0.22 | - | + | 3.89E-07 | 5.22E-01 | 6.84E-05 | 8.85E-08 | 9.36E-08 | AS_ALL_PP |
| 152 | rs141541522 | 14 | 99257953 | d | 0.51 | 1816 | 1.06 | -0.24 | + | - | 3.90E-07 | 4.88E-01 | 5.94E-05 | 9.37E-08 | 9.87E-08 | AS_WOD_PP |
| 153 | rs16861081 | 1 | 168592866 | a | 0.87 | 1000 | -4.18 | 5.70 | -- | ++ | 3.93E-07 | 1.61E-04 | 1.65E-06 | 3.91E-02 | 4.59E-02 | AA_WOD_DBP |
| 154 | rs76905458 | 10 | 28695807 | t | 0.14 | 1372 | -1.01 | -11.55 | +-? | --? | 3.94E-07 | 3.94E-05 | 4.07E-01 | 8.93E-02 | 1.05E-01 | EA_ALL_SBP |
| 155 | rs73132694 | 5 | 93926680 | t | 0.18 | 1650 | -3.73 | 5.93 | -- | ++ | 3.94E-07 | 6.73E-06 | 3.18E-07 | 4.61E-03 | 3.10E-03 | AA_ALL_MAP |
| 156 | rs7711380 | 5 | 93928945 | t | 0.82 | 1650 | 3.73 | -5.94 | ++ | -- | 3.95E-07 | 6.71E-06 | 3.22E-07 | 4.65E-03 | 3.12E-03 | AA_ALL_MAP |
| 157 | rs7725462 | 5 | 93928868 | t | 0.18 | 1650 | -3.73 | 5.94 | -- | ++ | 3.95E-07 | 6.72E-06 | 3.22E-07 | 4.65E-03 | 3.12E-03 | AA_ALL_MAP |
| 158 | rs59078432 | 8 | 22697576 | t | 0.86 | 1650 | 7.17 | -1.50 | ++ | -+ | 3.97E-07 | 5.44E-01 | 2.36E-07 | 2.86E-07 | 3.28E-07 | AA_ALL_SBP |
| 159 | rs77979528 | 1 | 115869092 | a | 0.08 | 1650 | -2.21 | -8.33 | -- | -- | 3.98E-07 | 1.19E-03 | 1.55E-01 | 2.55E-04 | 2.78E-04 | AA_ALL_SBP |
| 160 | rs138824325 | 10 | 28702905 | a | 0.14 | 1372 | -1.02 | -11.38 | +-? | --? | 4.00E-07 | 4.39E-05 | 4.02E-01 | 8.76E-02 | 1.03E-01 | EA_ALL_SBP |
| 161 | rs79465916 | 16 | 73454000 | t | 0.82 | 1000 | -1.09 | 10.62 | -- | ++ | 4.00E-07 | 1.57E-05 | 4.99E-01 | 2.10E-02 | 2.49E-02 | AA_WOD_SBP |
| 162 | rs200700876 | 2 | 67436058 | d | 0.06 | 1650 | -1.40 | -5.11 | -- | -- | 4.02E-07 | 3.07E-03 | 2.06E-01 | 1.81E-04 | 1.03E-04 | AA_ALL_DBP |
| 163 | rs151312462 | 2 | 67436059 | d | 0.06 | 1650 | -1.40 | -5.11 | -- | -- | 4.04E-07 | 3.07E-03 | 2.06E-01 | 1.82E-04 | 1.03E-04 | AA_ALL_DBP |
| 164 | rs8287 | 4 | 53732586 | t | 0.53 | 1000 | 5.63 | -2.18 | ++ | -- | 4.06E-07 | 2.36E-01 | 7.27E-08 | 1.22E-06 | 1.03E-06 | AA_WOD_SBP |
| 165 | rs112520268 | 7 | 5880020 | t | 0.15 | 1815 | -2.09 | -2.74 | --- | +-- | 4.06E-07 | 3.49E-02 | 3.59E-03 | 2.96E-05 | 3.15E-05 | EA_WOD_PP |
| 166 | rs9959834 | 18 | 21827805 | a | 0.98 | 1823 | 3.68 | -11.96 | + | - | 4.12E-07 | 1.07E-06 | 4.52E-02 | 1.71E-02 | 1.44E-02 | AS_ALL_MAP |
| 167 | rs1598669 | 18 | 41914949 | a | 0.96 | 1816 | -2.30 | -3.57 | - | - | 4.14E-07 | 4.48E-02 | 9.14E-02 | 8.68E-07 | 8.59E-07 | AS_WOD_DBP |
| 168 | rs28482267 | 15 | 94352467 | a | 0.14 | 1000 | 1.39 | -9.24 | ++ | -- | 4.16E-07 | 7.40E-06 | 2.34E-01 | 1.63E-01 | 1.55E-01 | AA_WOD_MAP |
| 169 | rs7030417 | 9 | 134502556 | a | 0.13 | 1650 | -7.35 | 3.98 | -- | ++ | 4.20E-07 | 1.37E-01 | 3.78E-08 | 6.11E-06 | 8.33E-06 | AA_ALL_SBP |
| 170 | rs4968882 | 17 | 66310599 | a | 0.73 | 1815 | 0.18 | 4.07 | -++ | +++ | 4.25E-07 | 1.66E-04 | 7.71E-01 | 1.95E-02 | 2.12E-02 | EA_WOD_PP |
| 171 | rs9997202 | 4 | 109260797 | a | 0.16 | 1000 | 0.56 | -9.12 | ++ | -- | 4.30E-07 | 4.85E-04 | 6.82E-01 | 1.87E-02 | 2.90E-02 | AA_WOD_SBP |
| 172 | rs12603759 | 17 | 10022257 | t | 0.20 | 1815 | 2.21 | -6.42 | +++ | --- | 4.31E-07 | 7.63E-07 | 3.29E-03 | 1.75E-01 | 1.95E-01 | EA_WOD_PP |
| 173 | rs1331485 | 6 | 1045462 | a | 0.35 | 2547 | -0.83 | 3.67 | --- | +++ | 4.41E-07 | 2.96E-07 | 2.18E-02 | 9.97E-01 | 1.00E+00 | EA_ALL_DBP |
| 174 | rs115905395 | 5 | 63473312 | t | 0.97 | 1816 | -12.18 | 17.58 | - | + | 4.42E-07 | 1.06E-07 | 2.07E-06 | 3.03E-01 | 3.24E-01 | AS_WOD_SBP |
| 175 | rs114194661 | 6 | 476348 | t | 0.06 | 1650 | -1.64 | -6.11 | -- | -- | 4.43E-07 | 4.71E-03 | 3.10E-01 | 1.06E-03 | 1.14E-03 | AA_ALL_MAP |
| 176 | rs189689705 | 12 | 39316220 | a | 0.93 | 1650 | 0.39 | 5.68 | -+ | ++ | 4.46E-07 | 6.93E-03 | 7.48E-01 | 3.40E-03 | 3.09E-03 | AA_ALL_DBP |
| 177 | rs112142223 | 7 | 5883137 | t | 0.15 | 1815 | -2.30 | -2.47 | --- | +-- | 4.53E-07 | 5.73E-02 | 1.35E-03 | 1.22E-05 | 1.31E-05 | EA_WOD_PP |
| 178 | rs11220332 | 11 | 125940800 | a | 0.88 | 1650 | 1.66 | 7.83 | ++ | ++ | 4.60E-07 | 1.96E-03 | 2.86E-01 | 1.45E-04 | 1.89E-04 | AA_ALL_SBP |
| 179 | rs2240405 | 7 | 5880392 | c | 0.14 | 1815 | -2.08 | -2.71 | --- | +-- | 4.63E-07 | 3.62E-02 | 3.73E-03 | 3.22E-05 | 3.47E-05 | EA_WOD_PP |

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 180 | rs9949360 | 18 | 21833586 | a | 0.02 | 1823 | -3.84 | 12.19 | - | + | 4.66E-07 | 9.86E-07 | 3.92E-02 | 2.12E-02 | 1.79E-02 | AS_ALL_MAP |
| 181 | rs28884496 | 18 | 21837697 | a | 0.98 | 1816 | 3.81 | -12.30 | + | - | 4.70E-07 | 9.76E-07 | 4.29E-02 | 2.03E-02 | 1.68E-02 | AS_WOD_MAP |
| 182 | rs72884862 | 18 | 21843356 | a | 0.02 | 1816 | -6.03 | 15.70 | - | + | 4.74E-07 | 3.44E-07 | 8.73E-03 | 9.34E-02 | 8.23E-02 | AS_WOD_SBP |
| 183 | rs17097800 | 14 | 99257740 | t | 0.49 | 1816 | -1.05 | 0.24 | - | + | 4.79E-07 | 4.96E-01 | 6.93E-05 | 1.14E-07 | 1.22E-07 | AS_WOD_PP |
| 184 | rs17033692 | 1 | 115869850 | t | 0.92 | 1650 | 2.13 | 8.38 | ++ | ++ | 4.83E-07 | 1.15E-03 | 1.70E-01 | 3.13E-04 | 3.38E-04 | AA_ALL_SBP |
| 185 | rs113300617 | 9 | 37544221 | a | 0.07 | 1650 | -1.63 | -8.58 | -- | -- | 4.86E-07 | 1.17E-03 | 3.99E-01 | 7.15E-03 | 8.14E-03 | AA_ALL_SBP |
| 186 | rs11931137 | 4 | 109259817 | a | 0.16 | 1000 | 0.57 | -9.03 | ++ | -- | 4.88E-07 | 5.74E-04 | 6.76E-01 | 2.03E-02 | 3.13E-02 | AA_WOD_SBP |
| 187 | rs75620742 | 1 | 162117393 | a | 0.07 | 1650 | -0.32 | 7.45 | +- | ++ | 4.91E-07 | 1.52E-06 | 7.07E-01 | 1.38E-02 | 1.47E-02 | AA_ALL_DBP |
| 188 | rs73196659 | 3 | 107082584 | a | 0.90 | 1800 | -3.15 | 10.43 | -?- | +?+ | 4.95E-07 | 1.11E-07 | 6.23E-03 | 4.30E-01 | 4.29E-01 | EA_ALL_PP |
| 189 | rs500945 | 13 | 72912370 | a | 0.36 | 1815 | -1.01 | -3.29 | --- | --- | 5.00E-07 | 8.98E-04 | 4.73E-02 | 3.13E-04 | 4.04E-04 | EA_WOD_MAP |
| 190 | rs885581 | 1 | 62445706 | a | 0.47 | 1650 | -1.21 | -2.23 | -- | -- | 5.13E-07 | 7.44E-03 | 1.83E-02 | 8.58E-06 | 9.78E-06 | AA_ALL_DBP |
| 191 | rs80315633 | 5 | 93955316 | d | 0.29 | 1000 | -3.69 | 4.35 | -- | ++ | 5.15E-07 | 3.65E-04 | 8.92E-08 | 4.88E-04 | 3.89E-04 | AA_WOD_DBP |
| 192 | rs1331486 | 6 | 1045382 | t | 0.65 | 2547 | 0.80 | -3.65 | +++ | --- | 5.22E-07 | 3.37E-07 | 2.70E-02 | 9.35E-01 | 9.40E-01 | EA_ALL_DBP |
| 193 | rs138939593 | 18 | 41930279 | c | 0.04 | 1823 | 2.15 | 3.93 | + | + | 5.32E-07 | 3.12E-02 | 1.23E-01 | 1.42E-06 | 1.38E-06 | AS_ALL_DBP |
| 194 | rs72646023 | 13 | 85079520 | t | 0.06 | 1650 | -0.05 | -9.95 | -+ | -- | 5.44E-07 | 5.82E-04 | 9.80E-01 | 7.20E-02 | 5.68E-02 | AA_ALL_SBP |
| 195 | rs843605 | 4 | 121426884 | t | 0.93 | 1650 | 3.29 | 6.95 | ++ | ++ | 5.50E-07 | 1.75E-02 | 4.91E-02 | 1.37E-05 | 1.35E-05 | AA_ALL_SBP |
| 196 | rs72646022 | 13 | 85079280 | t | 0.94 | 1650 | 0.04 | 9.93 | +- | ++ | 5.56E-07 | 5.95E-04 | 9.81E-01 | 7.23E-02 | 5.71E-02 | AA_ALL_SBP |
| 197 | rs2643205 | 15 | 39007170 | t | 0.57 | 2547 | 0.92 | -5.06 | +++ | --- | 5.62E-07 | 3.70E-08 | 6.32E-02 | 8.53E-01 | 8.24E-01 | EA_ALL_PP |
| 198 | rs4960486 | 6 | 1044908 | t | 0.65 | 2547 | 0.79 | -3.64 | +++ | --- | 5.65E-07 | 3.68E-07 | 2.90E-02 | 9.22E-01 | 9.27E-01 | EA_ALL_DBP |
| 199 | rs115905395 | 5 | 63473312 | t | 0.97 | 1823 | -12.04 | 17.53 | - | + | 5.65E-07 | 1.20E-07 | 2.78E-06 | 3.37E-01 | 3.60E-01 | AS_ALL_SBP |
| 200 | rs2250624 | 12 | 47355587 | a | 0.29 | 1000 | 0.37 | -6.08 | -+ | -- | 5.70E-07 | 3.46E-06 | 6.72E-01 | 9.41E-03 | 9.74E-03 | AA_WOD_DBP |
| 201 | rs1331485 | 6 | 1045462 | a | 0.35 | 2547 | -0.94 | 3.78 | --- | +++ | 5.76E-07 | 1.35E-06 | 1.60E-02 | 7.76E-01 | 7.67E-01 | EA_ALL_MAP |
| 202 | rs147344979 | 8 | 83509698 | t | 0.93 | 1650 | 5.29 | 4.96 | ++ | ++ | 5.77E-07 | 7.64E-02 | 1.36E-03 | 2.56E-06 | 2.96E-06 | AA_ALL_SBP |
| 203 | rs9392251 | 6 | 1045864 | a | 0.66 | 2547 | 0.79 | -3.66 | +++ | --- | 5.80E-07 | 3.72E-07 | 2.97E-02 | 9.13E-01 | 9.16E-01 | EA_ALL_DBP |
| 204 | rs1537905 | 1 | 88672066 | a | 0.05 | 1650 | -8.30 | 3.80 | -- | +- | 5.89E-07 | 2.81E-01 | 1.01E-07 | 1.22E-04 | 1.03E-04 | AA_ALL_SBP |
| 205 | rs115100192 | 18 | 41929553 | c | 0.04 | 1816 | 2.24 | 3.62 | + | + | 5.91E-07 | 4.28E-02 | 1.02E-01 | 1.30E-06 | 1.26E-06 | AS_WOD_DBP |
| 206 | rs114194661 | 6 | 476348 | t | 0.06 | 1650 | -0.86 | -10.45 | +- | -- | 5.94E-07 | 1.22E-03 | 7.26E-01 | 5.84E-03 | 6.18E-03 | AA_ALL_SBP |
| 207 | rs111769553 | 1 | 168590413 | a | 0.87 | 1000 | -4.18 | 5.56 | -- | ++ | 5.98E-07 | 2.49E-04 | 2.03E-06 | 3.63E-02 | 4.22E-02 | AA_WOD_DBP |
| 208 | rs3800570 | 7 | 138411332 | c | 0.92 | 1800 | 1.06 | 3.98 | +?+ | +?+ | 6.14E-07 | 1.21E-03 | 1.74E-01 | 2.01E-02 | 2.33E-02 | EA_ALL_DBP |
| 209 | rs72884862 | 18 | 21843356 | a | 0.02 | 1823 | -6.12 | 15.68 | - | + | 6.15E-07 | 3.72E-07 | 7.80E-03 | 1.07E-01 | 9.58E-02 | AS_ALL_SBP |
| 210 | rs10849654 | 12 | 119838146 | a | 0.10 | 1372 | 4.35 | -9.30 | ++? | --? | 6.16E-07 | 3.14E-04 | 1.21E-04 | 1.24E-03 | 1.32E-03 | EA_ALL_PP |

| 211 | rs112991830 | 2 | 203025238 | a | 0.54 | 1000 | -0.59 | 5.10 | -- | -+ | 6.28E-07 | 1.07E-04 | 4.50E-01 | 6.45E-02 | 6.20E-02 | AA_WOD_MAP |
|-----|-------------|---|-----------|---|------|------|-------|-------|-----|-----|----------|----------|----------|----------|----------|------------|
| 212 | rs138824325 | 10 | 28702905 | a | 0.14 | 1372 | -0.28 | -6.67 | +-? | --? | 6.34E-07 | 3.24E-05 | 6.82E-01 | 1.75E-01 | 1.95E-01 | EA_ALL_MAP |
| 213 | rs534618 | 13 | 72913721 | a | 0.63 | 1815 | 1.01 | 3.27 | +++ | +++ | 6.36E-07 | 9.76E-04 | 4.76E-02 | 3.29E-04 | 4.26E-04 | EA_WOD_MAP |
| 214 | rs10163977 | 18 | 41935966 | a | 0.04 | 1816 | 2.25 | 3.60 | + | + | 6.36E-07 | 4.40E-02 | 1.00E-01 | 1.38E-06 | 1.32E-06 | AS_WOD_DBP |
| 215 | rs13020769 | 2 | 152153552 | a | 0.52 | 1000 | -1.86 | -2.38 | -- | -- | 6.37E-07 | 4.45E-02 | 6.50E-03 | 9.82E-07 | 1.24E-06 | AA_WOD_DBP |
| 216 | rs74135423 | 10 | 43429610 | t | 0.92 | 1650 | 0.66 | 4.79 | ++ | ++ | 6.45E-07 | 7.79E-04 | 4.84E-01 | 1.22E-03 | 1.21E-03 | AA_ALL_DBP |
| 217 | rs72219928 | 13 | 72935136 | d | 0.32 | 1815 | -1.00 | -2.86 | --- | --- | 6.54E-07 | 4.84E-03 | 4.69E-02 | 2.78E-04 | 3.21E-04 | EA_WOD_MAP |
| 218 | rs7580215 | 2 | 214045537 | a | 0.82 | 1000 | 3.11 | -6.73 | ++ | -- | 6.57E-07 | 2.40E-06 | 4.79E-05 | 3.05E-01 | 3.09E-01 | AA_WOD_DBP |
| 219 | rs28884496 | 18 | 21837697 | a | 0.98 | 1823 | 3.93 | -12.34 | + | - | 6.59E-07 | 1.22E-06 | 3.89E-02 | 2.49E-02 | 2.09E-02 | AS_ALL_MAP |
| 220 | rs55947090 | 13 | 85080173 | a | 0.94 | 1650 | 0.03 | 9.95 | +- | ++ | 6.63E-07 | 6.04E-04 | 9.89E-01 | 7.44E-02 | 5.87E-02 | AA_ALL_SBP |
| 221 | rs73137851 | 7 | 64403345 | t | 0.10 | 1372 | -1.80 | -12.29 | --? | --? | 6.65E-07 | 5.60E-04 | 2.45E-01 | 4.83E-02 | 4.89E-02 | EA_ALL_SBP |
| 222 | rs1332182 | 9 | 21507082 | t | 0.59 | 1000 | 0.66 | -4.56 | +- | -- | 6.82E-07 | 1.75E-03 | 4.57E-01 | 2.01E-02 | 2.22E-02 | AA_WOD_PP |
| 223 | rs343084 | 7 | 35572165 | a | 0.10 | 1000 | -3.89 | -3.91 | -- | -+ | 6.85E-07 | 5.52E-02 | 2.97E-03 | 7.01E-05 | 1.03E-04 | AA_WOD_PP |
| 224 | rs62012629 | 15 | 79070351 | a | 0.25 | 916 | 3.32 | 6.67 | ++? | ++? | 6.89E-07 | 3.71E-02 | 1.15E-02 | 1.50E-03 | 1.29E-03 | EA_WOD_SBP |
| 225 | rs111397655 | 7 | 38658037 | t | 0.09 | 1823 | -2.97 | -0.89 | - | - | 6.91E-07 | 5.14E-01 | 5.88E-03 | 2.48E-07 | 1.63E-07 | AS_ALL_SBP |
| 226 | rs116552539 | 15 | 50465911 | a | 0.19 | 1000 | -2.93 | -1.28 | -- | -- | 6.94E-07 | 3.47E-01 | 7.80E-04 | 4.72E-07 | 4.11E-07 | AA_WOD_DBP |
| 227 | rs9387798 | 6 | 120803246 | a | 0.06 | 1650 | 1.96 | -12.16 | ++ | -- | 6.94E-07 | 7.79E-06 | 3.08E-01 | 9.50E-02 | 8.91E-02 | AA_ALL_SBP |
| 228 | rs148258828 | 18 | 41909525 | a | 0.96 | 1816 | -2.18 | -3.83 | - | - | 6.95E-07 | 3.65E-02 | 1.21E-01 | 1.80E-06 | 1.66E-06 | AS_WOD_DBP |
| 229 | rs138740080 | 20 | 20904948 | d | 0.25 | 1650 | -0.21 | -3.66 | +- | -- | 6.95E-07 | 2.36E-04 | 7.06E-01 | 1.02E-03 | 7.36E-04 | AA_ALL_DBP |
| 230 | rs2777315 | 9 | 124383214 | a | 0.10 | 1650 | 3.44 | -6.85 | ++ | -- | 6.97E-07 | 1.63E-06 | 2.91E-06 | 2.36E-02 | 2.97E-02 | AA_ALL_DBP |
| 231 | rs58774946 | 1 | 168589420 | t | 0.13 | 1000 | 4.18 | -5.50 | ++ | -- | 6.99E-07 | 2.90E-04 | 2.16E-06 | 3.55E-02 | 4.12E-02 | AA_WOD_DBP |
| 232 | rs4238352 | 15 | 61593303 | t | 0.08 | 1800 | 1.90 | -6.24 | +?+ | -?- | 7.00E-07 | 1.59E-08 | 7.76E-03 | 3.20E-01 | 3.03E-01 | EA_ALL_DBP |
| 233 | rs138100114 | 7 | 5881839 | d | 0.84 | 1815 | 2.30 | 2.63 | +++ | --+ | 7.02E-07 | 5.13E-02 | 2.32E-03 | 2.18E-05 | 2.17E-05 | EA_WOD_PP |
| 234 | rs9834427 | 3 | 165772627 | a | 0.11 | 1000 | 8.90 | -14.41 | ++ | -- | 7.04E-07 | 8.61E-05 | 5.42E-06 | 2.09E-02 | 2.27E-02 | AA_WOD_SBP |
| 235 | rs2777314 | 9 | 124383844 | t | 0.10 | 1650 | 3.44 | -6.85 | ++ | -- | 7.06E-07 | 1.63E-06 | 2.96E-06 | 2.37E-02 | 3.00E-02 | AA_ALL_DBP |
| 236 | rs76905458 | 10 | 28695807 | t | 0.14 | 1372 | -0.27 | -6.75 | +-? | --? | 7.10E-07 | 3.13E-05 | 6.96E-01 | 1.81E-01 | 2.01E-01 | EA_ALL_MAP |
| 237 | rs2200226 | 4 | 53738359 | t | 0.42 | 1000 | -5.58 | 1.24 | -- | ++ | 7.32E-07 | 5.12E-01 | 1.47E-07 | 1.70E-06 | 1.28E-06 | AA_WOD_SBP |
| 238 | rs151312462 | 2 | 67436059 | d | 0.06 | 1650 | -1.45 | -5.85 | -- | -- | 7.33E-07 | 3.33E-03 | 2.65E-01 | 4.01E-04 | 2.13E-04 | AA_ALL_MAP |
| 239 | rs1331486 | 6 | 1045382 | t | 0.65 | 2547 | 0.90 | -3.76 | +++ | --- | 7.34E-07 | 1.57E-06 | 2.10E-02 | 8.47E-01 | 8.37E-01 | EA_ALL_MAP |
| 240 | rs200700876 | 2 | 67436058 | d | 0.06 | 1650 | -1.45 | -5.85 | -- | -- | 7.34E-07 | 3.33E-03 | 2.65E-01 | 3.99E-04 | 2.13E-04 | AA_ALL_MAP |
| 241 | rs2469761 | 8 | 22367274 | a | 0.41 | 1650 | 2.55 | -3.74 | ++ | -- | 7.44E-07 | 3.02E-05 | 1.59E-07 | 1.86E-03 | 2.02E-03 | AA_ALL_DBP |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 242 | rs67064413 | 1 | 238171619 | d | 0.18 | 1815 | 0.97 | -5.73 | -++ | --- | 7.50E-07 | 8.29E-06 | 1.83E-01 | 9.17E-01 | 8.73E-01 | EA_WOD_PP |
| 243 | rs560076 | 13 | 72935038 | a | 0.32 | 1815 | -1.02 | -2.81 | --- | --- | 7.51E-07 | 5.27E-03 | 4.23E-02 | 2.48E-04 | 2.86E-04 | EA_WOD_MAP |
| 244 | rs74640988 | 13 | 72934978 | a | 0.67 | 1815 | 1.10 | 2.75 | +++ | +++ | 7.56E-07 | 7.10E-03 | 2.93E-02 | 1.68E-04 | 1.95E-04 | EA_WOD_MAP |
| 245 | rs9392251 | 6 | 1045864 | a | 0.66 | 2547 | 0.90 | -3.78 | +++ | --- | 7.56E-07 | 1.61E-06 | 2.22E-02 | 8.61E-01 | 8.52E-01 | EA_ALL_MAP |
| 246 | rs6940225 | 6 | 120799255 | a | 0.94 | 1650 | -1.75 | 11.89 | -- | ++ | 7.59E-07 | 1.24E-05 | 3.63E-01 | 8.05E-02 | 7.47E-02 | AA_ALL_SBP |
| 247 | rs9401265 | 6 | 120798508 | a | 0.94 | 1650 | -1.75 | 11.89 | -- | ++ | 7.61E-07 | 1.24E-05 | 3.63E-01 | 8.05E-02 | 7.47E-02 | AA_ALL_SBP |
| 248 | rs111983094 | 1 | 19847611 | d | 0.18 | 1000 | -4.04 | 9.15 | -- | ++ | 7.61E-07 | 1.09E-08 | 2.17E-05 | 1.86E-01 | 1.91E-01 | AA_WOD_DBP |
| 249 | rs113876113 | 3 | 53719994 | a | 0.07 | 1650 | -0.79 | -7.50 | -- | -- | 7.66E-07 | 1.22E-04 | 5.21E-01 | 1.45E-02 | 1.63E-02 | AA_ALL_PP |
| 250 | rs6050422 | 20 | 25177920 | a | 0.33 | 1000 | 2.23 | -5.61 | ++ | -- | 7.75E-07 | 2.03E-06 | 1.70E-03 | 6.97E-01 | 7.26E-01 | AA_WOD_DBP |
| 251 | rs79322622 | 14 | 78381284 | t | 0.07 | 1650 | 0.55 | -8.14 | -+ | -- | 7.79E-07 | 1.68E-04 | 6.99E-01 | 2.19E-01 | 2.22E-01 | AA_ALL_MAP |
| 252 | rs35867523 | 2 | 203095575 | d | 0.41 | 1650 | -0.10 | 3.98 | +- | ++ | 7.79E-07 | 1.95E-05 | 8.49E-01 | 1.40E-02 | 1.45E-02 | AA_ALL_DBP |
| 253 | rs12523737 | 6 | 120595996 | a | 0.94 | 1650 | -2.39 | 8.33 | -- | ++ | 7.85E-07 | 2.25E-06 | 6.23E-02 | 3.87E-01 | 3.67E-01 | AA_ALL_MAP |
| 254 | rs4960486 | 6 | 1044908 | t | 0.65 | 2547 | 0.89 | -3.75 | +++ | --- | 7.86E-07 | 1.68E-06 | 2.28E-02 | 8.66E-01 | 8.54E-01 | EA_ALL_MAP |
| 255 | rs13219862 | 6 | 120793223 | t | 0.06 | 1650 | 1.74 | -11.87 | ++ | -- | 8.08E-07 | 1.32E-05 | 3.66E-01 | 8.07E-02 | 7.49E-02 | AA_ALL_SBP |
| 256 | rs537143 | 9 | 124387137 | a | 0.10 | 1650 | 3.42 | -6.90 | ++ | -- | 8.17E-07 | 1.55E-06 | 3.93E-06 | 2.72E-02 | 3.42E-02 | AA_ALL_DBP |
| 257 | rs144597722 | 7 | 21473268 | d | 0.88 | 1000 | -2.16 | 8.16 | -- | ++ | 8.36E-07 | 5.24E-07 | 3.94E-02 | 5.26E-01 | 4.98E-01 | AA_WOD_DBP |
| 258 | rs10123663 | 9 | 132763543 | a | 0.83 | 2547 | -0.17 | -4.28 | -+- | --- | 8.37E-07 | 2.19E-05 | 7.32E-01 | 3.94E-02 | 3.63E-02 | EA_ALL_MAP |
| 259 | rs10789860 | 11 | 111969965 | t | 0.09 | 1650 | -3.24 | -2.59 | -- | -- | 8.57E-07 | 1.21E-01 | 1.31E-04 | 5.77E-08 | 1.41E-07 | AA_ALL_DBP |
| 260 | rs10006594 | 4 | 36652453 | t | 0.80 | 1815 | 1.20 | 4.70 | +++ | +++ | 8.59E-07 | 9.34E-04 | 9.46E-02 | 2.11E-03 | 1.66E-03 | EA_WOD_PP |
| 261 | rs9895990 | 17 | 66712506 | a | 0.87 | 1800 | 2.98 | 2.56 | +?+ | +?+ | 8.60E-07 | 1.09E-01 | 6.93E-04 | 3.73E-04 | 3.96E-04 | EA_ALL_MAP |
| 262 | rs78373079 | 3 | 21687409 | t | 0.94 | 1650 | -0.52 | 7.99 | -- | ++ | 8.68E-07 | 1.40E-04 | 7.30E-01 | 4.12E-02 | 3.70E-02 | AA_ALL_PP |
| 263 | rs7649309 | 3 | 55217829 | a | 0.34 | 1650 | 0.22 | -2.87 | +- | -- | 8.71E-07 | 3.23E-03 | 6.90E-01 | 1.16E-02 | 1.54E-02 | AA_ALL_DBP |
| 264 | rs114642658 | 19 | 46792651 | t | 0.06 | 1650 | -6.63 | 3.70 | -- | ++ | 8.72E-07 | 1.92E-01 | 1.08E-07 | 6.16E-07 | 1.04E-06 | AA_ALL_PP |
| 265 | rs258096 | 16 | 55762882 | a | 0.10 | 1650 | -4.46 | -2.68 | -- | -- | 8.75E-07 | 2.70E-01 | 1.25E-03 | 1.13E-06 | 1.68E-06 | AA_ALL_SBP |
| 266 | rs9307319 | 4 | 109274125 | t | 0.15 | 1000 | 0.81 | -9.62 | ++ | -- | 8.77E-07 | 3.96E-04 | 5.56E-01 | 5.22E-02 | 8.05E-02 | AA_WOD_SBP |
| 267 | rs6494255 | 15 | 61595365 | a | 0.08 | 1800 | 1.94 | -6.23 | +?+ | -?- | 8.81E-07 | 1.84E-08 | 6.82E-03 | 3.02E-01 | 2.87E-01 | EA_ALL_DBP |
| 268 | rs5857499 | 4 | 36666783 | d | 0.20 | 1815 | -1.30 | -4.82 | --- | --- | 8.82E-07 | 1.07E-03 | 8.11E-02 | 1.65E-03 | 1.28E-03 | EA_WOD_PP |
| 269 | rs111397655 | 7 | 38658037 | t | 0.09 | 1816 | -2.87 | -0.97 | - | - | 8.84E-07 | 4.77E-01 | 7.64E-03 | 3.62E-07 | 2.29E-07 | AS_WOD_SBP |
| 270 | rs513891 | 13 | 72946718 | c | 0.66 | 1815 | 1.03 | 3.06 | +++ | +++ | 8.90E-07 | 2.21E-03 | 3.38E-02 | 2.15E-04 | 2.67E-04 | EA_WOD_MAP |
| 271 | rs75458041 | 16 | 76851070 | a | 0.93 | 1650 | -2.62 | 10.61 | -- | ++ | 8.93E-07 | 5.73E-05 | 7.63E-02 | 5.13E-01 | 5.68E-01 | AA_ALL_MAP |
| 272 | rs2176167 | 2 | 203100918 | t | 0.59 | 1650 | 0.09 | -3.97 | -+ | -- | 8.96E-07 | 2.11E-05 | 8.64E-01 | 1.36E-02 | 1.41E-02 | AA_ALL_DBP |

| 273 | rs74847356 | 1 | 247998148 | a | 0.10 | 1650 | -2.10 | -2.49 | -- | -- | 8.98E-07 | 1.03E-01 | 3.39E-02 | 2.89E-05 | 1.89E-05 | AA_ALL_MAP |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 274 | rs1149048 | 1 | 31198733 | a | 0.18 | 1650 | -3.04 | 1.01 | -- | ++ | 9.02E-07 | 3.87E-01 | 2.58E-06 | 2.42E-07 | 1.64E-07 | AA_ALL_DBP |
| 275 | rs1486201 | 6 | 120791750 | a | 0.06 | 1650 | 1.72 | -11.82 | ++ | -- | 9.06E-07 | 1.45E-05 | 3.71E-01 | 8.07E-02 | 7.46E-02 | AA_ALL_SBP |
| 276 | rs519377 | 13 | 72947336 | a | 0.66 | 1815 | 1.02 | 3.05 | +++ | +++ | 9.10E-07 | 2.22E-03 | 3.50E-02 | 2.32E-04 | 2.89E-04 | EA_WOD_MAP |
| 277 | rs138939593 | 18 | 41930279 | c | 0.04 | 1816 | 2.28 | 3.60 | + | + | 9.16E-07 | 4.63E-02 | 9.67E-02 | 1.95E-06 | 1.75E-06 | AS_WOD_DBP |
| 278 | rs4954158 | 2 | 135426618 | t | 0.22 | 1000 | -4.24 | 5.67 | -- | ++ | 9.22E-07 | 1.19E-03 | 4.95E-07 | 5.99E-03 | 2.51E-03 | AA_WOD_PP |
| 279 | rs16861034 | 1 | 168587942 | t | 0.87 | 1000 | -4.20 | 5.44 | -- | ++ | 9.25E-07 | 3.72E-04 | 2.21E-06 | 3.17E-02 | 3.66E-02 | AA_WOD_DBP |
| 280 | rs78428774 | 11 | 79790957 | t | 0.94 | 1650 | 1.91 | 10.04 | ++ | ++ | 9.30E-07 | 4.72E-04 | 3.32E-01 | 3.70E-03 | 4.14E-03 | AA_ALL_SBP |
| 281 | rs6531476 | 4 | 36653541 | t | 0.80 | 1815 | 1.22 | 4.63 | +++ | +++ | 9.40E-07 | 1.03E-03 | 8.79E-02 | 1.83E-03 | 1.42E-03 | EA_WOD_PP |
| 282 | rs2443496 | 8 | 22365788 | a | 0.59 | 1650 | -2.49 | 3.79 | -- | ++ | 9.41E-07 | 2.35E-05 | 2.61E-07 | 3.15E-03 | 3.50E-03 | AA_ALL_DBP |
| 283 | rs74045701 | 13 | 33749052 | t | 0.11 | 1650 | -4.64 | 8.79 | -- | ++ | 9.48E-07 | 2.64E-05 | 1.07E-06 | 3.68E-02 | 3.85E-02 | AA_ALL_PP |
| 284 | rs147340264 | 15 | 32318437 | d | 0.09 | 1650 | 0.09 | 6.50 | +- | ++ | 9.55E-07 | 1.11E-05 | 9.17E-01 | 2.40E-02 | 2.24E-02 | AA_ALL_DBP |
| 285 | rs562136 | 13 | 72935310 | a | 0.68 | 1815 | 0.96 | 2.84 | +++ | +++ | 9.60E-07 | 4.85E-03 | 5.39E-02 | 3.59E-04 | 4.08E-04 | EA_WOD_MAP |
| 286 | rs2000523 | 11 | 105632364 | c | 0.80 | 1000 | 1.00 | 4.08 | -+ | ++ | 9.70E-07 | 9.47E-03 | 2.72E-01 | 9.36E-05 | 1.20E-04 | AA_WOD_MAP |
| 287 | rs57955811 | 9 | 37535368 | d | 0.92 | 1650 | 0.40 | 6.11 | -+ | ++ | 9.72E-07 | 2.88E-04 | 7.28E-01 | 2.16E-02 | 2.24E-02 | AA_ALL_MAP |
| 288 | rs10791773 | 11 | 105631278 | a | 0.80 | 1000 | 1.01 | 4.06 | -+ | ++ | 9.79E-07 | 9.83E-03 | 2.67E-01 | 9.13E-05 | 1.18E-04 | AA_WOD_MAP |
| 289 | rs1467194 | 2 | 135430621 | a | 0.20 | 1000 | -4.36 | 5.82 | -- | ++ | 9.81E-07 | 1.09E-03 | 8.99E-07 | 2.05E-03 | 1.48E-03 | AA_WOD_PP |
| 290 | rs61948170 | 13 | 34797815 | a | 0.03 | 1816 | 6.94 | -2.21 | + | - | 9.85E-07 | 3.18E-01 | 6.38E-05 | 2.23E-07 | 3.37E-07 | AS_WOD_SBP |

[1]SNPs are duplicate if found from multiple analyses

[2]Effect is in mmHg unit

[3]Direction of effect in GENOA, FHS, and HyperGEN EA in European ancestry, respectively; Direction of effect in JHA and HyperGEN AA in African American ancestry, respectively; Question mark if cohort was not included in a meta-analysis

Abbreviations: BP: blood pressure; SBP: systolic BP; DBP: diastolic BP; EA: effect allele; EAF: effect allele frequency; 1 DF Interaction P: P-value of the interaction test with 1 degree of freedom; 2 DF Joint P: P-value of the joint test with 2 degrees of freedom of genetic main and interaction effects; Model 2: P-value of SNP only model; Model 3: P-value of SNP in a model with SNP and E; EA: European ancestry; AA: African American ancestry; AS: Asian ancestry; G: Genetic Main; GxE: Interaction; ALL: All participants; WOD: Subject without diuretic use

**Table 17** Replication of novel loci from Li et al. in European and African ancestry in Aim 3

**European ancestry**

| rs ID | CHR | POS | P Value | | | | | | | |
|-------|-----|-----|---------|---|---|---|---|---|---|---|
| | | | ALL | | | | WOD | | | |
| | | | SBP | DBP | MAP | PP | SBP | DBP | MAP | PP |
| rs11104632 | 12 | 86747816 | 0.69 | 0.44 | 0.55 | 0.49 | 0.58 | 0.28 | 0.36 | 0.93 |
| rs13211840 | 6 | 149153883 | 0.75 | 0.14 | 0.36 | 0.27 | 0.71 | 0.27 | 0.38 | 0.55 |
| rs2567241 | 4 | 141542612 | 0.87 | 0.27 | 0.50 | 0.94 | 0.70 | 0.29 | 0.42 | 0.76 |

**African ancestry**

| rs ID | CHR | POS | P Value | | | | | | | |
|-------|-----|-----|---------|---|---|---|---|---|---|---|
| | | | ALL | | | | WOD | | | |
| | | | SBP | DBP | MAP | PP | SBP | DBP | MAP | PP |
| rs11104632 | 12 | 86747816 | 0.55 | 0.90 | 0.87 | 0.30 | 0.26 | 1.00 | 0.60 | 0.19 |
| rs13211840 | 6 | 149153883 | 0.20 | 0.15 | 0.17 | 0.25 | 0.21 | 0.32 | 0.32 | 0.19 |
| rs2567241 | 4 | 141542612 | 0.40 | 0.10 | 0.20 | 0.75 | 0.65 | 0.35 | 0.59 | 0.27 |

P-value < 0.1 bolded
Abbreviations: P Value: P-value for the joint test with 2 degrees of freedom, testing genetic main and interaction effects; ALL: All participants; WOD: Participants without diuretic use

**Table 18** Replication of known blood pressure loci using 2DF joint test in Aim 3

Known blood pressure loci until June 2017 (M=239)
FDR adjusted P-value < 0.1 bolded
ALL: All participants; WOD: Participants without diuretic use
"-" if a SNP did not exist in genotyping data

## European Americans

| rs ID | CHR | POS | Gene / Locus | Reference | FDR adjusted P-value | | | | | | | |
|-------|-----|-----|--------------|-----------|------|------|------|------|------|------|------|------|
| | | | | | ALL | | | | WOD | | | |
| | | | | | SBP | DBP | MAP | PP | SBP | DBP | MAP | PP |
| rs10059921 | 5 | 87514515 | TMEM161B | Warren, ture Genetics 2017 | 0.982 | 0.918 | 0.992 | 0.971 | 0.871 | 0.885 | 0.893 | 0.938 |
| rs10077885 | 5 | 114390121 | TRIM36 | Ehret, ture Genetics 2016 | 0.737 | 0.969 | 0.992 | 0.902 | 0.738 | 0.912 | 0.918 | 0.869 |
| rs10078021 | 5 | 75038431 | POC5 | Warren, ture Genetics 2017 | 0.991 | 0.922 | 0.992 | 0.902 | 0.871 | 0.914 | 0.962 | 0.869 |
| rs1008058 | 5 | 122435627 | PRDM6 | Surendran, ture Genetics 2016 | 0.730 | 0.953 | 0.659 | 0.902 | 0.731 | 0.888 | 0.836 | 0.869 |
| rs1011018 | 7 | 139463264 | HIPK2 | Warren, ture Genetics 2017 | 0.737 | 0.712 | 0.898 | 0.929 | 0.598 | 0.719 | 0.676 | 0.869 |
| rs10224002 | 7 | 151415041 | PRKAG2 | Tragante, AJHG 2014 | 0.991 | 0.999 | 0.992 | 0.983 | 0.950 | 0.940 | 0.962 | 0.973 |
| rs10260816 | 7 | 46010100 | IGFBP3 | Kato, ture Genetics 2015 | 0.884 | 0.712 | 0.659 | 0.950 | 0.783 | 0.843 | 0.585 | 0.925 |
| rs1036477 | 15 | 48914926 | FBN1 | Tragante, AJHG 2014 | 0.737 | 0.598 | 0.659 | 0.917 | 0.710 | 0.682 | 0.585 | 0.869 |
| rs10407022 | 19 | 2249477 | AMH | Surendran, ture Genetics 2016 | 0.991 | 0.970 | 0.992 | 0.971 | 0.856 | 0.711 | 0.676 | 0.938 |
| rs1060105 | 12 | 123806219 | SBNO1 | Surendran, ture Genetics 2016 | 0.884 | 0.910 | 0.982 | 0.969 | 0.738 | 0.811 | 0.676 | 0.925 |
| rs10760117 | 9 | 123586737 | PSMD5 | Ehret, ture Genetics 2016 | 0.737 | 0.983 | 0.982 | 0.902 | 0.858 | 0.940 | 0.918 | 0.869 |
| rs10826995 | 10 | 32082658 | ARHGAP12 | Warren, ture Genetics 2017 | 0.974 | 0.953 | 0.992 | 0.994 | 0.710 | 0.885 | 0.676 | 0.869 |
| rs10850411 | 12 | 115387796 | TBX5-TBX3 | Ehret, ture 2011 | 0.737 | 0.589 | 0.552 | 0.917 | 0.598 | 0.711 | 0.585 | 0.869 |
| rs10916082 | 1 | 227252626 | CDC42BPA | Warren, ture Genetics 2017 | 0.991 | 0.922 | 0.992 | 0.971 | 0.925 | 0.885 | 0.893 | 0.945 |
| rs10922502 | 1 | 89360158 | GTF2B | Warren, ture Genetics 2017 | 0.737 | 0.983 | 0.992 | 0.902 | 0.738 | 0.940 | 0.988 | 0.869 |
| rs10943605 | 6 | 79655477 | PHIP | Liu, ture Genetics 2016 | 0.940 | 0.970 | 0.992 | 0.902 | 0.925 | 0.922 | 0.962 | 0.869 |
| rs10948071 | 6 | 43280713 | CRIP3 | Ganesh, AJHG 2014 | 0.991 | 0.983 | 0.992 | 0.962 | 0.927 | 0.885 | 0.879 | 0.951 |
| rs10995311 | 10 | 64564934 | ADO | Surendran, ture Genetics 2016 | 0.737 | 0.848 | 0.659 | 0.902 | 0.710 | 0.711 | 0.585 | 0.869 |
| rs110419 | 11 | 8252853 | LMO1 | Surendran, ture Genetics 2016 | 0.991 | 0.791 | 0.992 | 0.971 | 0.925 | 0.876 | 0.960 | 0.979 |
| rs11066280 | 12 | 112817783 | RPL6-ALDH1 | Kato, ture Genetics 2011 | - | - | - | - | - | - | - | - |
| rs111245230 | 9 | 113169775 | SVEP1 | Liu, ture Genetics 2016 | 0.619 | 0.918 | 0.630 | 0.902 | 0.710 | 0.888 | 0.809 | 0.869 |
| rs11128722 | 3 | 14958126 | FGD5 | Ehret, ture Genetics 2016 | 0.974 | 0.970 | 0.992 | 0.920 | 0.738 | 0.968 | 0.918 | 0.869 |
| rs11154027 | 6 | 121781390 | GJA1 | Warren, ture Genetics 2017 | 0.737 | 0.983 | 0.992 | 0.902 | 0.925 | 0.940 | 0.992 | 0.869 |
| rs11191548 | 10 | 104846178 | CYP17A1-NT5C2 | Newton-Cheh, ture Genetics 2009 | 0.884 | 0.983 | 0.992 | 0.950 | 0.842 | 0.942 | 0.960 | 0.869 |

| rs112184198 | 10 | 102604514 | PAX2 | Warren, ture Genetics 2017 | 0.991 | 0.970 | 0.992 | 0.971 | 0.871 | 0.887 | 0.918 | 0.869 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs11222084 | 11 | 130273230 | ADAMTS8 | Wain, ture Genetics 2011 | 0.940 | 0.910 | 0.992 | 0.902 | 0.836 | 0.711 | 0.962 | 0.417 |
| rs11229457 | 11 | 58207203 | OR5B12 | Surendran, ture Genetics 2016 | 0.892 | 0.970 | 0.982 | 0.917 | 0.925 | 0.913 | 0.988 | 0.869 |
| rs112557609 | 1 | 56576924 | RP4-710M16.1-PPAP2B | Warren, ture Genetics 2017 | 0.997 | 0.953 | 0.992 | 0.959 | 0.998 | 0.888 | 0.962 | 0.869 |
| rs1126464 | 16 | 89704365 | DPEP1 | Surendran, ture Genetics 2016 | 0.991 | 0.937 | 0.992 | 0.971 | 0.871 | 0.843 | 0.838 | 0.938 |
| rs11442819 | 11 | 45208141 | PRDM11 | Warren, ture Genetics 2017 | 0.730 | 0.514 | 0.530 | 0.917 | 0.925 | 0.843 | 0.893 | 0.966 |
| rs11537751 | 11 | 47587452 | PTPMT1 | Liu, ture Genetics 2016 | 0.954 | 0.970 | 0.992 | 0.902 | 0.925 | 0.968 | 0.992 | 0.930 |
| rs11556924 | 7 | 129663496 | ZC3HC1 | Ehret, ture Genetics 2016 | 0.737 | 0.970 | 0.982 | 0.902 | 0.710 | 0.930 | 0.893 | 0.869 |
| rs115795127 | 9 | 85993901 | FRMD3 | Liang, PLoS Genetics 2017 | - | - | - | - | - | - | - | - |
| rs11639856 | 16 | 24788645 | TNRC6A | Liu, ture Genetics 2016 | 0.954 | 0.983 | 0.992 | 0.950 | 0.925 | 0.986 | 0.960 | 0.869 |
| rs11643209 | 16 | 75331044 | CFDP1 | Warren, ture Genetics 2017 | 0.619 | 0.953 | 0.630 | 0.902 | 0.396 | 0.843 | 0.585 | 0.732 |
| rs11689667 | 2 | 85491365 | TCF7L1 | Warren, ture Genetics 2017 | 0.929 | 0.918 | 0.992 | 0.902 | 0.921 | 0.703 | 0.913 | 0.869 |
| rs1173771 | 5 | 32815028 | NPR3-C5orf23 | Ehret, ture 2011 | 0.884 | 0.712 | 0.859 | 0.929 | 0.925 | 0.849 | 0.943 | 0.938 |
| rs11953630 | 5 | 157845402 | EBF1 | Ehret, ture 2011 | 0.884 | 0.922 | 0.992 | 0.902 | 0.783 | 0.828 | 0.879 | 0.938 |
| rs11977526 | 7 | 46008110 | IGFBP1-IGFBP3 | Zhu, AJHG 2015 | 0.737 | 0.605 | 0.552 | 0.929 | 0.710 | 0.843 | 0.585 | 0.869 |
| rs12374077 | 3 | 185317674 | SENP2 | Warren, ture Genetics 2017 | 0.846 | 0.970 | 0.992 | 0.920 | 0.921 | 0.914 | 0.940 | 0.938 |
| rs12408022 | 1 | 217718789 | GPATCH2 | Warren, ture Genetics 2017 | 0.974 | 0.943 | 0.992 | 0.902 | 0.871 | 0.888 | 0.960 | 0.869 |
| rs1250259 | 2 | 216300482 | FN1 | Warren, ture Genetics 2017 | 0.991 | 0.953 | 0.992 | 0.902 | 0.925 | 0.888 | 0.918 | 0.869 |
| rs12521868 | 5 | 131784393 | C5orf56 | Surendran, ture Genetics 2016 | 0.991 | 0.999 | 0.992 | 0.971 | 0.871 | 0.968 | 0.962 | 0.869 |
| rs12579720 | 12 | 20173764 | PDE3A | Kato, ture Genetics 2015 | 0.737 | 0.483 | 0.549 | 0.962 | 0.598 | 0.569 | 0.585 | 0.869 |
| rs12627651 | 21 | 44760603 | CRYAA-SIK1 | Ehret, ture Genetics 2016 | 0.974 | 0.978 | 0.992 | 0.927 | 0.842 | 0.888 | 0.960 | 0.789 |
| rs12628032 | 22 | 19967980 | ARVCF | Warren, ture Genetics 2017 | 0.730 | 0.712 | 0.552 | 0.902 | 0.871 | 0.888 | 0.893 | 0.938 |
| rs12731740 | 1 | 208024820 | CD34 | Warren, ture Genetics 2017 | 0.884 | 0.970 | 0.992 | 0.929 | 0.167 | 0.569 | 0.186 | 0.732 |
| rs1275988 | 2 | 26914364 | KCNK3 | Ganesh, AJHG 2014 | 0.737 | 0.598 | 0.552 | 0.902 | 0.710 | 0.777 | 0.585 | 0.732 |
| rs12921187 | 16 | 4943019 | PPL | Warren, ture Genetics 2017 | 0.991 | 0.910 | 0.992 | 0.971 | 0.925 | 0.888 | 0.960 | 0.872 |
| rs12940887 | 17 | 47402807 | ZNF652 | Ehret, ture 2011 | 0.999 | 0.970 | 0.992 | 0.971 | 0.871 | 0.888 | 0.918 | 0.869 |
| rs12941318 | 17 | 1333598 | CRK | Warren, ture Genetics 2017 | 0.991 | 0.999 | 0.992 | 0.971 | 0.871 | 0.942 | 0.940 | 0.869 |
| rs12946454 | 17 | 43208121 | PLCD3 | Newton-Cheh, ture Genetics 2009 | 0.759 | 0.970 | 0.992 | 0.902 | 0.836 | 0.843 | 0.838 | 0.925 |
| rs12958173 | 18 | 42141977 | SETBP1 | Ehret, ture Genetics 2016 | 0.972 | 0.983 | 0.992 | 0.962 | 0.710 | 0.843 | 0.785 | 0.869 |
| rs13002573 | 2 | 164915208 | FIGN-GRB14 | Wain, ture Genetics 2011 | 0.757 | 0.712 | 0.773 | 0.950 | 0.738 | 0.777 | 0.722 | 0.869 |
| rs13082711 | 3 | 27537909 | SLC4A7 | Ehret, ture 2011 | 0.884 | 0.969 | 0.992 | 0.929 | 0.871 | 0.885 | 0.893 | 0.938 |
| rs13107325 | 4 | 103188709 | SLC39A8 | Ehret, ture 2011 | 0.991 | 0.712 | 0.982 | 0.962 | 0.871 | 0.828 | 0.879 | 0.869 |
| rs13139571 | 4 | 156645513 | GUCY1A3-GUCY1B3 | Ehret, ture 2011 | 0.991 | 0.983 | 0.992 | 0.977 | 0.871 | 0.885 | 0.893 | 0.938 |
| rs13209747 | 6 | 127115454 | RSPO3 | Francescini, AJHG 2013 | 0.884 | 0.953 | 0.982 | 0.959 | 0.752 | 0.843 | 0.879 | 0.869 |
| rs13238550 | 7 | 131059056 | MKLN1 | Warren, ture Genetics 2017 | 0.646 | 0.623 | 0.552 | 0.902 | 0.738 | 0.711 | 0.676 | 0.938 |
| rs1327235 | 20 | 10969030 | JAG1 | Ehret, ture 2011 | 0.892 | 0.377 | 0.530 | 0.929 | 0.871 | 0.569 | 0.585 | 0.938 |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs13333226 | 16 | 20365654 | UMOD | Padmabhan, PloS Genetics 2010 | 0.991 | 0.970 | 0.992 | 0.971 | 0.710 | 0.912 | 0.676 | 0.869 |
| rs13359291 | 5 | 122476457 | PRDM6 | Kato, ture Genetics 2015 | 0.730 | 0.794 | 0.659 | 0.902 | 0.710 | 0.912 | 0.879 | 0.869 |
| rs1344653 | 2 | 19730845 | OSR1 | Kato, ture Genetics 2015 | 0.619 | 0.377 | 0.468 | 0.902 | 0.598 | 0.569 | 0.585 | 0.732 |
| rs1378942 | 15 | 75077367 | CYP1A1-ULK3 | Newton-Cheh, ture Genetics 2009 | 0.737 | 0.712 | 0.552 | 0.902 | 0.738 | 0.682 | 0.676 | 0.869 |
| rs139236208 | 12 | 94880742 | CCDC41 | Warren, ture Genetics 2017 | 0.757 | 0.970 | 0.992 | 0.917 | 0.598 | 0.912 | 0.785 | 0.869 |
| rs139385870 | 1 | 1685921 | DK-CPSF3L | Warren, ture Genetics 2017 | 0.974 | 0.605 | 0.552 | 0.969 | 0.950 | 0.711 | 0.676 | 0.869 |
| rs1401454 | 11 | 16250183 | SOX6 | Francescini, AJHG 2013 | 0.759 | 0.910 | 0.992 | 0.929 | 0.783 | 0.885 | 0.918 | 0.938 |
| rs1421811 | 5 | 32714270 | NPR3-C5orf23 | Johnson, AJHG 2011 | 0.991 | 0.712 | 0.982 | 0.969 | 0.871 | 0.843 | 0.879 | 0.945 |
| rs143112823 | 3 | 154707967 | RP11-439C8.2 | Warren, ture Genetics 2017 | 0.991 | 0.970 | 0.992 | 0.977 | 0.858 | 0.967 | 0.957 | 0.869 |
| rs1438896 | 2 | 145646072 | TEX41 | Warren, ture Genetics 2017 | 0.991 | 0.953 | 0.992 | 0.971 | 0.975 | 0.888 | 0.918 | 0.938 |
| rs1446468 | 2 | 164963486 | FIGN-GRB14 | Wain, ture Genetics 2011 | 0.991 | 0.910 | 0.926 | 0.996 | 0.998 | 0.892 | 0.893 | 0.938 |
| rs1458038 | 4 | 81164723 | FGF5 | Ehret, ture 2011 | 0.884 | 0.712 | 0.982 | 0.983 | 0.710 | 0.719 | 0.676 | 0.869 |
| rs147212971 | 6 | 166178451 | PDE10A | Warren, ture Genetics 2017 | - | - | - | - | - | - | - | - |
| rs1530440 | 10 | 63524591 | C10orf107 | Newton-Cheh, ture Genetics 2009 | 0.737 | 0.618 | 0.785 | 0.950 | 0.738 | 0.888 | 0.893 | 0.869 |
| rs1563788 | 6 | 43308363 | TTBK1, SLC22A7, ZNF318 | Kato, ture Genetics 2015 | 0.991 | 0.970 | 0.992 | 0.969 | 0.925 | 0.914 | 0.962 | 0.938 |
| rs1566497 | 4 | 169717148 | PALLD | Warren, ture Genetics 2017 | 0.990 | 0.839 | 0.982 | 0.971 | 0.998 | 0.940 | 0.960 | 0.951 |
| rs167479 | 19 | 11526765 | RGL3 | Surendran, ture Genetics 2016 | - | - | - | - | - | - | - | - |
| rs16823124 | 2 | 183224127 | PDE1A | Tragante, AJHG 2014 | 0.972 | 0.918 | 0.982 | 0.990 | 0.925 | 0.888 | 0.918 | 0.938 |
| rs16833934 | 3 | 163737250 | MIR1263 | Simino, AJHG 2014 | 0.884 | 0.837 | 0.659 | 0.969 | 0.925 | 0.888 | 0.879 | 0.938 |
| rs16849225 | 2 | 164906820 | FIGN-GRB14 | Kato, ture Genetics 2011 | 0.737 | 0.598 | 0.630 | 0.950 | 0.710 | 0.682 | 0.585 | 0.869 |
| rs16851397 | 3 | 141134818 | ZBTB38 | Surendran, ture Genetics 2016 | - | - | - | - | - | - | - | - |
| rs17030613 | 1 | 113190807 | ST7L-CAPZA1-MOV10 | Kato, ture Genetics 2011 | 0.991 | 0.970 | 0.992 | 0.971 | 0.871 | 0.942 | 0.893 | 0.869 |
| rs17059668 | 4 | 174584663 | chr4mb174 | Warren, ture Genetics 2017 | - | - | - | - | - | - | - | - |
| rs17080102 | 6 | 151004770 | PLEKHG1 | Francescini, AJHG 2013 | 0.999 | 0.910 | 0.992 | 0.971 | 0.925 | 0.914 | 0.988 | 0.869 |
| rs17249754 | 12 | 90060586 | ATP2B1 | Levy, ture Genetics 2009 | 0.737 | 0.377 | 0.552 | 0.971 | 0.752 | 0.569 | 0.722 | 0.966 |
| rs17367504 | 1 | 11862778 | MTHFR-NPPB | Newton-Cheh, ture Genetics 2009 | 0.737 | 0.910 | 0.982 | 0.929 | 0.871 | 0.888 | 0.918 | 0.869 |
| rs17428471 | 7 | 27337867 | EVX1-HOXA | Francescini, AJHG 2013 | 0.884 | 0.970 | 0.992 | 0.902 | 0.710 | 0.970 | 0.906 | 0.732 |
| rs17477177 | 7 | 106411858 | PIK3CG | Wain, ture Genetics 2011 | 0.737 | 0.910 | 0.864 | 0.902 | 0.710 | 0.843 | 0.838 | 0.869 |
| rs17608766 | 17 | 45013271 | GOSR2 | Ehret, ture 2011 | 0.814 | 0.999 | 0.992 | 0.902 | 0.871 | 0.942 | 0.962 | 0.869 |
| rs17638167 | 19 | 11584818 | ELAVL3 | Ehret, ture Genetics 2016 | 0.991 | 0.970 | 0.992 | 0.969 | 0.871 | 0.968 | 0.962 | 0.869 |
| rs1799945 | 6 | 26091179 | HFE | Ehret, ture 2011 | 0.619 | 0.712 | 0.530 | 0.902 | 0.710 | 0.887 | 0.585 | 0.869 |
| rs1801253 | 10 | 115805056 | ADRB1 | Johnson, Hypertension 2011 | 0.737 | 0.970 | 0.992 | 0.902 | 0.925 | 0.935 | 0.962 | 0.869 |
| rs1813353 | 10 | 18707448 | CACNB2 | Ehret, ture 2011 | 0.974 | 0.999 | 0.992 | 0.950 | 0.783 | 0.885 | 0.676 | 0.938 |
| rs1925153 | 6 | 56102780 | COL21A1 | Liu, ture Genetics 2016 | 0.991 | 0.969 | 0.992 | 0.920 | 0.925 | 0.888 | 0.940 | 0.925 |
| rs1953126 | 9 | 123640500 | PHF19 | Liu, ture Genetics 2016 | 0.991 | 0.953 | 0.992 | 0.902 | 0.856 | 0.885 | 0.893 | 0.869 |
| rs1975487 | 2 | 55809054 | PNPT1 | Ehret, ture Genetics 2016 | 0.991 | 0.953 | 0.992 | 0.920 | 0.998 | 0.888 | 0.960 | 0.938 |

| rs2004776 | 1 | 230848702 | AGT | Johnson, AJHG 2011 | 0.999 | 0.922 | 0.992 | 0.917 | 0.925 | 0.912 | 0.918 | 0.869 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs2014408 | 11 | 16365282 | SOX6 | Johnson, AJHG 2011 | 0.619 | 0.589 | 0.552 | 0.902 | 0.598 | 0.711 | 0.676 | 0.930 |
| rs2014912 | 4 | 86715670 | ARHGAP24 | Kato, ture Genetics 2015 | 0.672 | 0.423 | 0.530 | 0.962 | 0.598 | 0.571 | 0.585 | 0.925 |
| rs2071518 | 8 | 120435812 | NOV | Wain, ture Genetics 2011 | 0.853 | 0.970 | 0.992 | 0.920 | 0.998 | 0.942 | 0.962 | 0.950 |
| rs2107595 | 7 | 19049388 | HDAC9 | Kato, ture Genetics 2015 | 0.884 | 0.589 | 0.992 | 0.589 | 0.925 | 0.733 | 0.918 | 0.869 |
| rs217727 | 11 | 2016908 | H19 | Tragante, AJHG 2014 | 0.759 | 0.970 | 0.992 | 0.902 | 0.710 | 0.682 | 0.585 | 0.869 |
| rs2188962 | 5 | 131770805 | C5orf56 | Liu, ture Genetics 2016 | 0.991 | 0.983 | 0.992 | 0.971 | 0.871 | 0.968 | 0.962 | 0.869 |
| rs2240736 | 17 | 59485393 | C17orf82,TBX2 | Kato, ture Genetics 2015 | 0.991 | 0.899 | 0.828 | 0.982 | 0.998 | 0.912 | 0.918 | 0.938 |
| rs2270860 | 6 | 43270151 | SLC22A7 | Liu, ture Genetics 2016 | 0.991 | 0.970 | 0.992 | 0.962 | 0.925 | 0.888 | 0.960 | 0.938 |
| rs2282978 | 7 | 92264410 | CDK6 | Tragante, AJHG 2014 | 0.771 | 0.969 | 0.992 | 0.902 | 0.871 | 0.968 | 0.988 | 0.869 |
| rs2289081 | 2 | 20881840 | C2orf43 | Warren, ture Genetics 2017 | 0.840 | 0.918 | 0.727 | 0.917 | 0.738 | 0.785 | 0.585 | 0.869 |
| rs2291435 | 4 | 38387395 | TBC1D1-FLJ13197 | Ehret, ture Genetics 2016 | 0.884 | 0.943 | 0.992 | 0.971 | 0.871 | 0.888 | 0.928 | 0.938 |
| rs2302061 | 19 | 2226772 | DOT1L | Liu, ture Genetics 2016 | 0.991 | 0.999 | 0.992 | 0.962 | - | - | - | - |
| rs2304130 | 19 | 19789528 | ZNF101 | Surendran, ture Genetics 2016 | - | - | - | - | - | - | - | - |
| rs2306374 | 3 | 138119952 | MRAS | Warren, ture Genetics 2017 | 0.619 | 0.598 | 0.552 | 0.902 | 0.222 | 0.682 | 0.585 | 0.732 |
| rs2384550 | 12 | 115352731 | TBX5-TBX3 | Levy, ture Genetics 2009 | 0.913 | 0.970 | 0.992 | 0.929 | 0.738 | 0.885 | 0.879 | 0.869 |
| rs2467099 | 17 | 73949045 | ACOX1 | Warren, ture Genetics 2017 | 0.999 | 0.943 | 0.992 | 0.962 | 0.966 | 0.711 | 0.879 | 0.869 |
| rs2493292 | 1 | 3328659 | PRDM16 | Liu, ture Genetics 2016 | 0.999 | 0.970 | 0.992 | 0.971 | - | - | - | - |
| rs2521501 | 15 | 91437388 | FURIN-FES | Ehret, ture 2011 | 0.901 | 0.953 | 0.992 | 0.902 | 0.958 | 0.914 | 0.962 | 0.938 |
| rs2579519 | 2 | 96675166 | GPAT2-FAHD2CP | Warren, ture Genetics 2017 | 0.991 | 0.910 | 0.992 | 0.971 | 0.871 | 0.888 | 0.893 | 0.938 |
| rs2760061 | 1 | 228191075 | WNT3A | Warren, ture Genetics 2017 | 0.901 | 0.655 | 0.630 | 0.971 | 0.925 | 0.843 | 0.879 | 0.869 |
| rs2782980 | 10 | 115781527 | ADRB1 | Wain, ture Genetics 2011 | 0.957 | 0.910 | 0.992 | 0.929 | 0.858 | 0.746 | 0.893 | 0.938 |
| rs2854275 | 6 | 32628428 | HLA-DQB1 | Tragante, AJHG 2014 | 0.991 | 0.943 | 0.992 | 0.971 | - | - | - | - |
| rs2898290 | 8 | 11433909 | BLK-GATA4 | Ho, Jourl of Hypertension 2011 | 0.974 | 0.970 | 0.992 | 0.990 | 0.989 | 0.922 | 0.962 | 0.938 |
| rs2932538 | 1 | 113216543 | ST7L-CAPZA1-MOV10 | Ehret, ture 2011 | 0.884 | 0.918 | 0.630 | 0.929 | 0.871 | 0.912 | 0.893 | 0.869 |
| rs2969070 | 7 | 2512545 | CHST12-LFNG | Ehret, ture Genetics 2016 | 0.884 | 0.508 | 0.552 | 0.962 | 0.710 | 0.571 | 0.585 | 0.869 |
| rs2972146 | 2 | 227100698 | 2q36.3 | Surendran, ture Genetics 2016 | 0.619 | 0.910 | 0.828 | 0.902 | 0.598 | 0.885 | 0.785 | 0.734 |
| rs2978098 | 8 | 101676675 | SNX31 | Warren, ture Genetics 2017 | 0.991 | 0.943 | 0.992 | 0.996 | 0.950 | 0.940 | 0.962 | 0.938 |
| rs2978456 | 8 | 42324765 | SLC20A2 | Warren, ture Genetics 2017 | 0.737 | 0.712 | 0.571 | 0.920 | 0.784 | 0.888 | 0.879 | 0.925 |
| rs3184504 | 12 | 111884608 | SH2B3 | Levy, ture Genetics 2009 | 0.759 | 0.712 | 0.659 | 0.917 | 0.710 | 0.571 | 0.585 | 0.869 |
| rs319690 | 3 | 47927484 | MAP4 | Wain, ture Genetics 2011 | 0.737 | 0.970 | 0.992 | 0.902 | 0.783 | 0.912 | 0.893 | 0.869 |
| rs33063 | 16 | 69640217 | NFAT5 | Tragante, AJHG 2014 | 0.737 | 0.714 | 0.915 | 0.902 | 0.710 | 0.843 | 0.676 | 0.869 |
| rs34591516 | 8 | 142367087 | GPR20 | Surendran, ture Genetics 2016 | 0.940 | 0.703 | 0.773 | 0.971 | 0.871 | 0.711 | 0.676 | 0.997 |
| rs347591 | 3 | 11290122 | HRH1-ATG7 | Ganesh, Human Molecular Genetics 2013 | 0.991 | 0.970 | 0.992 | 0.920 | 0.842 | 0.885 | 0.869 | 0.869 |
| rs35199222 | 15 | 81013037 | ABHD17C | Warren, ture Genetics 2017 | 0.888 | 0.953 | 0.992 | 0.950 | 0.925 | 0.887 | 0.940 | 0.938 |
| rs35444 | 12 | 115552437 | TBX5-TBX3 | Kato, ture Genetics 2011 | 0.737 | 0.910 | 0.992 | 0.917 | 0.710 | 0.942 | 0.975 | 0.841 |

| rs36022378 | 3 | 49913705 | CAMKV-ACTBP13 | Warren, ture Genetics 2017 | 0.999 | 0.970 | 0.997 | 0.962 | 0.776 | 0.295 | 0.675 | 0.938 |
| rs36083386 | 6 | 152397912 | ESR1 | Warren, ture Genetics 2017 | 0.759 | 0.910 | 0.859 | 0.962 | 0.925 | 0.733 | 0.893 | 0.938 |
| rs3741378 | 11 | 65408937 | SIPA1 | Tragante, AJHG 2014 | 0.913 | 0.712 | 0.982 | 0.983 | 0.925 | 0.914 | 0.957 | 0.938 |
| rs3771371 | 2 | 71627539 | ZNF638 | Warren, ture Genetics 2017 | 0.737 | 0.983 | 0.992 | 0.902 | 0.738 | 0.888 | 0.960 | 0.732 |
| rs3774372 | 3 | 41877414 | ULK4 | Ehret, ture 2011 | 0.737 | 0.686 | 0.530 | 0.929 | 0.776 | 0.719 | 0.585 | 0.869 |
| rs381815 | 11 | 16902268 | PLEKHA7 | Levy, ture Genetics 2009 | 0.759 | 0.910 | 0.769 | 0.902 | 0.752 | 0.711 | 0.676 | 0.869 |
| rs3889199 | 1 | 59653742 | FGGY | Warren, ture Genetics 2017 | 0.913 | 0.970 | 0.992 | 0.902 | 0.858 | 0.968 | 0.998 | 0.869 |
| rs3918226 | 7 | 150690176 | NOS3 | Johnson, AJHG 2011 | 0.737 | 0.953 | 0.982 | 0.902 | - | - | - | - |
| rs409558 | 6 | 31708147 | MSH5-SAPCD1 | Liu, ture Genetics 2016 | 0.884 | 0.759 | 0.659 | 0.929 | 0.871 | 0.780 | 0.676 | 0.869 |
| rs419076 | 3 | 169100886 | MECOM | Ehret, ture 2011 | 0.940 | 0.598 | 0.982 | 0.920 | 0.940 | 0.711 | 0.960 | 0.869 |
| rs4245739 | 1 | 204518842 | MDM4 | Ganesh, Human Molecular Genetics 2013 | 0.884 | 0.508 | 0.552 | 0.962 | 0.925 | 0.843 | 0.893 | 0.938 |
| rs4247374 | 19 | 7252756 | INSR | Ehret, ture Genetics 2016 | - | - | - | - | - | - | - | - |
| rs4308 | 17 | 61559625 | ACE | Warren, ture Genetics 2017 | 0.884 | 0.970 | 0.992 | 0.920 | 0.783 | 0.888 | 0.943 | 0.869 |
| rs4360494 | 1 | 38455891 | SF3A3 | Warren, ture Genetics 2017 | 0.991 | 0.999 | 0.992 | 0.971 | 0.925 | 0.888 | 0.936 | 0.869 |
| rs4364717 | 9 | 21801530 | MTAP | Warren, ture Genetics 2017 | 0.619 | 0.508 | 0.530 | 0.902 | 0.434 | 0.280 | 0.384 | 0.869 |
| rs4373814 | 10 | 18419972 | CACNB2 | Ehret, ture 2011 | 0.960 | 0.969 | 0.992 | 0.969 | 0.871 | 0.888 | 0.893 | 0.869 |
| rs4387287 | 10 | 105677897 | OBFC1 | Surendran, ture Genetics 2016 | 0.814 | 0.712 | 0.982 | 0.917 | 0.871 | 0.912 | 0.962 | 0.869 |
| rs4454254 | 8 | 141060027 | TRAPPC9 | Warren, ture Genetics 2017 | 0.913 | 0.983 | 0.992 | 0.950 | 0.752 | 0.885 | 0.879 | 0.938 |
| rs4494250 | 10 | 96563757 | CYP2C19 | Liu, ture Genetics 2016 | 0.997 | 0.983 | 0.992 | 0.969 | 0.925 | 0.888 | 0.962 | 0.938 |
| rs449789 | 6 | 159699125 | FNDC1 | Warren, ture Genetics 2017 | 0.737 | 0.910 | 0.659 | 0.902 | 0.925 | 0.912 | 0.918 | 0.938 |
| rs452036 | 14 | 23865885 | MYH6 | Surendran, ture Genetics 2016 | 0.999 | 0.970 | 0.992 | 0.971 | 0.921 | 0.912 | 0.940 | 0.938 |
| rs4530754 | 5 | 122855416 | CSNK1G3 | Liu, ture Genetics 2016 | 0.974 | 0.918 | 0.982 | 0.971 | 0.783 | 0.840 | 0.838 | 0.973 |
| rs4590817 | 10 | 63467553 | C10orf107 | Ehret, ture 2011 | 0.782 | 0.618 | 0.982 | 0.971 | 0.871 | 0.843 | 0.879 | 0.951 |
| rs4601790 | 11 | 65353906 | EHBP1L1 | Simino, AJHG 2014 | 0.991 | 0.943 | 0.992 | 0.950 | 0.925 | 0.899 | 0.893 | 0.869 |
| rs4660293 | 1 | 40028180 | PABPC4 | Liu, ture Genetics 2016 | 0.884 | 0.970 | 0.992 | 0.929 | 0.925 | 0.888 | 0.960 | 0.938 |
| rs470113 | 22 | 40729614 | TNRC6B | Surendran, ture Genetics 2016 | 0.737 | 0.377 | 0.487 | 0.950 | 0.598 | 0.569 | 0.585 | 0.869 |
| rs4728142 | 7 | 128573967 | 7q32.1 | Surendran, ture Genetics 2016 | 0.991 | 0.910 | 0.992 | 0.927 | 0.925 | 0.827 | 0.893 | 0.870 |
| rs4746172 | 10 | 75855842 | VCL | Tragante, AJHG 2014 | 0.619 | 0.427 | 0.530 | 0.902 | 0.710 | 0.623 | 0.676 | 0.869 |
| rs4823006 | 22 | 29451671 | ZNRF3 | Liu, ture Genetics 2016 | 0.884 | 0.717 | 0.982 | 0.969 | 0.598 | 0.569 | 0.675 | 0.869 |
| rs4841569 | 8 | 11452177 | BLK-GATA4 | Simino, AJHG 2014 | 0.884 | 0.970 | 0.992 | 0.927 | 0.856 | 0.968 | 0.962 | 0.869 |
| rs4846049 | 1 | 11850365 | MTHFR-NPPB | Johnson, AJHG 2011 | 0.737 | 0.910 | 0.982 | 0.950 | 0.710 | 0.711 | 0.676 | 0.925 |
| rs4952611 | 2 | 40567743 | SLC8A1 | Warren, ture Genetics 2017 | 0.884 | 0.956 | 0.982 | 0.917 | 0.598 | 0.746 | 0.585 | 0.869 |
| rs5068 | 1 | 11905974 | MTHFR-NPPB | Newton-Cheh, ture Genetics 2009 | 0.954 | 0.922 | 0.992 | 0.969 | 0.783 | 0.843 | 0.811 | 0.938 |
| rs5219 | 11 | 17409572 | KCNJ11 | Liu, ture Genetics 2016 | 0.991 | 0.970 | 0.992 | 0.929 | 0.783 | 0.892 | 0.893 | 0.869 |
| rs55701159 | 2 | 25139596 | ADCY3 | Warren, ture Genetics 2017 | 0.991 | 0.970 | 0.992 | 0.998 | 0.925 | 0.885 | 0.893 | 0.986 |
| rs55780018 | 2 | 208526140 | METTL21A-AC079767.3 | Warren, ture Genetics 2017 | 0.954 | 0.953 | 0.992 | 0.971 | 0.989 | 0.914 | 0.962 | 0.952 |

| rs6015450 | 20 | 57751117 | GS-EDN3 | Ehret, ture 2011 | 0.737 | 0.712 | 0.552 | 0.929 | 0.760 | 0.569 | 0.585 | 0.938 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs6081613 | 20 | 19465907 | SLC24A3 | Warren, ture Genetics 2017 | 0.954 | 0.922 | 0.992 | 0.902 | 0.738 | 0.914 | 0.960 | 0.869 |
| rs6095241 | 20 | 47308798 | PREX1 | Surendran, ture Genetics 2016 | 0.759 | 0.970 | 0.992 | 0.902 | 0.856 | 0.843 | 0.893 | 0.938 |
| rs6108168 | 20 | 8626271 | PLCB1 | Warren, ture Genetics 2017 | 0.991 | 0.970 | 0.992 | 0.969 | 0.856 | 0.711 | 0.585 | 0.938 |
| rs62012628 | 15 | 79070000 | ADAMTS7 | Warren, ture Genetics 2017 | 0.840 | 0.918 | 0.945 | 0.920 | **0.037** | 0.295 | 0.102 | 0.417 |
| rs62080325 | 17 | 42060631 | PYY | Warren, ture Genetics 2017 | 0.954 | 0.970 | 0.992 | 0.962 | 0.925 | 0.912 | 0.962 | 0.938 |
| rs62104477 | 19 | 30294991 | CCNE1 | Warren, ture Genetics 2017 | 0.913 | 0.983 | 0.992 | 0.917 | 0.921 | 0.738 | 0.676 | 0.938 |
| rs6271 | 9 | 136522274 | DBH | Ehret, ture Genetics 2016 | 0.737 | 0.712 | 0.630 | 0.929 | 0.388 | 0.569 | 0.290 | 0.869 |
| rs633185 | 11 | 100593538 | FLJ32810-TMEM133 | Ehret, ture 2011 | 0.737 | 0.969 | 0.659 | 0.902 | 0.731 | 0.888 | 0.601 | 0.869 |
| rs6487543 | 12 | 26438189 | SSPN | Warren, ture Genetics 2017 | 0.737 | 0.970 | 0.930 | 0.902 | 0.925 | 0.940 | 0.962 | 0.941 |
| rs661348 | 11 | 1905292 | LSP1-TNNT3 | Johnson, AJHG 2011 | 0.884 | 0.943 | 0.992 | 0.902 | 0.925 | 0.968 | 0.992 | 0.869 |
| rs6686889 | 1 | 25030470 | chr1mb25 | Warren, ture Genetics 2017 | 0.974 | 0.970 | 0.992 | 0.962 | 0.958 | 0.914 | 0.895 | 0.938 |
| rs6712094 | 2 | 165043460 | FIGN-GRB14 | Ganesh, AJHG 2014 | 0.814 | 0.953 | 0.982 | 0.917 | 0.856 | 0.922 | 0.957 | 0.869 |
| rs6722745 | 2 | 108875244 | SULT1C3 | Liu, ture Genetics 2016 | 0.991 | 0.970 | 0.992 | 0.971 | 0.738 | 0.843 | 0.893 | 0.732 |
| rs67330701 | 11 | 69079707 | MYEOV | Warren, ture Genetics 2017 | - | - | - | - | - | - | - | - |
| rs6797587 | 3 | 48197614 | CDC25A | Simino, AJHG 2014 | 0.954 | 0.953 | 0.992 | 0.902 | 0.776 | 0.887 | 0.918 | 0.869 |
| rs6825911 | 4 | 111381638 | ENPEP | Kato, ture Genetics 2011 | 0.991 | 0.918 | 0.992 | 0.977 | 0.921 | 0.843 | 0.943 | 0.869 |
| rs687621 | 9 | 136137065 | ABO | Surendran, ture Genetics 2016 | 0.913 | 0.508 | 0.630 | 0.902 | 0.925 | 0.623 | 0.676 | 0.869 |
| rs6891344 | 5 | 123136656 | CSNK1G3 | Ehret, ture Genetics 2016 | 0.884 | 0.970 | 0.992 | 0.917 | 0.921 | 0.914 | 0.940 | 0.938 |
| rs6911827 | 6 | 22130601 | CASC15 | Warren, ture Genetics 2017 | 0.730 | 0.377 | 0.530 | 0.950 | 0.598 | 0.569 | 0.585 | 0.925 |
| rs6969780 | 7 | 27159136 | HOXA3 | Liu, ture Genetics 2016 | 0.991 | 0.859 | 0.926 | 0.929 | 0.871 | 0.682 | 0.676 | 0.938 |
| rs709209 | 1 | 6278414 | RNF207 | Surendran, ture Genetics 2016 | 0.991 | 0.970 | 0.992 | 0.917 | 0.710 | 0.295 | 0.548 | 0.869 |
| rs7103648 | 11 | 47461783 | RAPSN, PSMC3, SLC39A13 | Ehret, ture Genetics 2016 | 0.940 | 0.978 | 0.992 | 0.902 | 0.871 | 0.922 | 0.992 | 0.869 |
| rs7126805 | 11 | 828916 | CRACR2B | Warren, ture Genetics 2017 | 0.913 | 0.970 | 0.992 | 0.929 | 0.921 | 0.998 | 0.962 | 0.869 |
| rs7129220 | 11 | 10350538 | ADM | Ehret, ture 2011 | 0.935 | 0.970 | 0.992 | 0.902 | 0.710 | 0.888 | 0.838 | 0.869 |
| rs7178615 | 15 | 66869072 | RP11-321F6.1 | Warren, ture Genetics 2017 | 0.884 | 0.970 | 0.982 | 0.920 | 0.949 | 0.914 | 0.962 | 0.869 |
| rs7236548 | 18 | 43097750 | SLC14A2 | Warren, ture Genetics 2017 | 0.974 | 0.970 | 0.992 | 0.950 | 0.871 | 0.885 | 0.893 | 0.872 |
| rs7248104 | 19 | 7224431 | INSR | Liu, ture Genetics 2016 | 0.619 | 0.598 | 0.487 | 0.902 | 0.378 | 0.280 | 0.171 | 0.869 |
| rs72765298 | 9 | 127900996 | SCAI | Warren, ture Genetics 2017 | 0.737 | 0.983 | 0.992 | 0.902 | 0.925 | 0.940 | 0.992 | 0.869 |
| rs7297416 | 12 | 54443090 | HOXC4 | Tragante, AJHG 2014 | 0.913 | 0.999 | 0.992 | 0.920 | 0.598 | 0.888 | 0.838 | 0.789 |
| rs7302981 | 12 | 50537815 | CERS5 | Surendran, ture Genetics 2016 | 0.757 | 0.712 | 0.773 | 0.971 | 0.710 | 0.711 | 0.676 | 0.925 |
| rs740406 | 19 | 2232221 | AMH | Kato, ture Genetics 2015 | - | - | - | - | - | - | - | - |
| rs7406910 | 17 | 46688256 | HOXB7 | Surendran, ture Genetics 2016 | 0.884 | 0.983 | 0.992 | 0.902 | 0.921 | 0.885 | 0.893 | 0.869 |
| rs740698 | 17 | 60767151 | MRC2 | Warren, ture Genetics 2017 | 0.999 | 0.863 | 0.992 | 0.969 | 0.949 | 0.968 | 0.962 | 0.870 |
| rs74181299 | 2 | 65283972 | CEP68 | Warren, ture Genetics 2017 | 0.737 | 0.717 | 0.659 | 0.902 | 0.738 | 0.885 | 0.820 | 0.869 |
| rs743757 | 3 | 50476378 | CAC2D2 | Warren, ture Genetics 2017 | 0.737 | 0.423 | 0.571 | 0.902 | 0.913 | **0.077** | 0.676 | 0.732 |

| rs745821 | 18 | 48142854 | MAPK4 | Warren, ture Genetics 2017 | 0.991 | 0.943 | 0.992 | 0.917 | 0.937 | 0.885 | 0.893 | 0.869 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs7515635 | 1 | 42408070 | HIVEP3 | Ehret, ture Genetics 2016 | 0.991 | 0.970 | 0.992 | 0.929 | 0.925 | 0.968 | 0.960 | 0.925 |
| rs751984 | 11 | 61278246 | LRRC10B | Kato, ture Genetics 2015 | 0.737 | 0.918 | 0.630 | 0.902 | 0.776 | 0.915 | 0.893 | 0.869 |
| rs7562 | 2 | 28635740 | FOSL2 | Warren, ture Genetics 2017 | 0.974 | 0.655 | 0.992 | 0.971 | 0.925 | 0.682 | 0.879 | 0.870 |
| rs757081 | 11 | 17351683 | NUCB2 | Tragante, AJHG 2014 | 0.888 | 0.970 | 0.992 | 0.917 | 0.871 | 0.922 | 0.957 | 0.925 |
| rs7592578 | 2 | 191439591 | TMEM194B | Warren, ture Genetics 2017 | 0.737 | 0.918 | 0.982 | 0.902 | 0.731 | 0.914 | 0.893 | 0.869 |
| rs76206723 | 7 | 40447971 | SUGCT | Warren, ture Genetics 2017 | 0.646 | 0.953 | 0.859 | 0.589 | 0.738 | 0.912 | 0.960 | 0.417 |
| rs76326501 | 2 | 43167878 | AC016735.1 | Warren, ture Genetics 2017 | 0.737 | 0.423 | 0.542 | 0.929 | 0.776 | 0.569 | 0.585 | 0.938 |
| rs76452347 | 9 | 35906471 | HRCT1 | Liu, ture Genetics 2016 | 0.730 | 0.970 | 0.859 | 0.902 | 0.921 | 0.942 | 0.947 | 0.938 |
| rs76987554 | 6 | 134080855 | TARID/TCF21 | Liang, PLoS Genetics 2017 | - | - | - | - | - | - | - | - |
| rs78648104 | 6 | 50683009 | TFAP2D | Warren, ture Genetics 2017 | 0.997 | 0.970 | 0.992 | 0.989 | 0.925 | 0.888 | 0.940 | 0.870 |
| rs79089478 | 17 | 40317241 | KCNH4-HSD17B1 | Warren, ture Genetics 2017 | 0.958 | 0.623 | 0.769 | 0.989 | 0.925 | 0.682 | 0.814 | 0.789 |
| rs79146658 | 2 | 179786068 | CCDC141 | Warren, ture Genetics 2017 | 0.999 | 0.970 | 0.992 | 0.971 | 0.598 | 0.827 | 0.585 | 0.869 |
| rs8016306 | 14 | 63928546 | PPP2R5E | Warren, ture Genetics 2017 | 0.888 | 0.953 | 0.992 | 0.930 | 0.921 | 0.930 | 0.960 | 0.869 |
| rs8059962 | 16 | 81574197 | CMIP | Warren, ture Genetics 2017 | 0.913 | 0.983 | 0.992 | 0.902 | 0.783 | 0.843 | 0.838 | 0.938 |
| rs8068318 | 17 | 59483766 | TBX2 | Surendran, ture Genetics 2016 | 0.991 | 0.910 | 0.864 | 0.989 | 0.998 | 0.914 | 0.918 | 0.938 |
| rs8258 | 11 | 117283676 | CEP164 | Warren, ture Genetics 2017 | 0.737 | 0.729 | 0.926 | 0.962 | 0.784 | 0.843 | 0.879 | 0.938 |
| rs867186 | 20 | 33764554 | PROCR | Surendran, ture Genetics 2016 | 0.884 | 0.970 | 0.992 | 0.920 | 0.925 | 0.682 | 0.809 | 0.938 |
| rs871606 | 4 | 54799245 | CHIC2 | Wain, ture Genetics 2011 | 0.737 | 0.969 | 0.992 | 0.902 | 0.598 | 0.711 | 0.585 | 0.869 |
| rs880315 | 1 | 10796866 | CASZ1 | Takeuchi, Circulation 2010 | 0.730 | 0.712 | 0.552 | 0.902 | 0.598 | 0.719 | 0.585 | 0.869 |
| rs891511 | 7 | 150704843 | NOS3 | Liu, ture Genetics 2016 | 0.814 | 0.970 | 0.992 | 0.902 | 0.871 | 0.843 | 0.879 | 0.941 |
| rs894344 | 8 | 135612745 | ZFAT | Warren, ture Genetics 2017 | 0.730 | 0.589 | 0.659 | 0.929 | 0.738 | 0.885 | 0.879 | 0.869 |
| rs900145 | 11 | 13293905 | ARNTL | Liu, ture Genetics 2016 | 0.991 | 0.983 | 0.992 | 0.917 | 0.925 | 0.914 | 0.985 | 0.869 |
| rs918466 | 3 | 64710253 | ADAMTS9 | Ehret, ture Genetics 2016 | 0.884 | 0.943 | 0.992 | 0.950 | 0.598 | 0.914 | 0.676 | 0.732 |
| rs9306160 | 21 | 45107562 | RRP1B | Surendran, ture Genetics 2016 | 0.884 | 0.686 | 0.992 | 0.929 | 0.921 | 0.952 | 0.992 | 0.869 |
| rs9323988 | 14 | 98587630 | RP11-61O1.1 | Warren, ture Genetics 2017 | 0.730 | 0.712 | 0.785 | 0.902 | 0.858 | 0.914 | 0.960 | 0.869 |
| rs932764 | 10 | 95895940 | PLCE1 | Ehret, ture 2011 | 0.619 | 0.377 | 0.487 | 0.902 | 0.598 | 0.711 | 0.585 | 0.851 |
| rs9349379 | 6 | 12903957 | PHACTR1 | Surendran, ture Genetics 2016 | 0.991 | 0.970 | 0.992 | 0.977 | 0.925 | 0.914 | 0.918 | 0.938 |
| rs9372498 | 6 | 118572486 | SLC35F1 | Warren, ture Genetics 2017 | 0.737 | 0.970 | 0.859 | 0.902 | 0.738 | 0.888 | 0.838 | 0.869 |
| rs953492 | 1 | 243471192 | SDCCAG8 | Warren, ture Genetics 2017 | 0.892 | 0.970 | 0.992 | 0.902 | 0.598 | 0.885 | 0.676 | 0.732 |
| rs9549328 | 13 | 113636156 | MCF2L | Warren, ture Genetics 2017 | 0.884 | 0.970 | 0.997 | 0.902 | 0.958 | 0.888 | 0.893 | 0.938 |
| rs9687065 | 5 | 148391140 | ABLIM3,SH3TC2 | Kato, ture Genetics 2015 | 0.730 | 0.423 | 0.487 | 0.917 | 0.388 | 0.275 | 0.186 | 0.869 |
| rs9827472 | 3 | 56726646 | FAM208A | Warren, ture Genetics 2017 | 0.737 | 0.759 | 0.659 | 0.902 | 0.783 | 0.828 | 0.809 | 0.869 |
| rs9859176 | 3 | 134000025 | RYK | Warren, ture Genetics 2017 | 0.935 | 0.970 | 0.982 | 0.962 | 0.921 | 0.912 | 0.838 | 0.938 |
| rs9888615 | 14 | 53377540 | FERMT2 | Warren, ture Genetics 2017 | 0.737 | 0.943 | 0.992 | 0.902 | 0.752 | 0.843 | 0.879 | 0.869 |

## African Americans

| rs ID | CHR | POS | Gene / Locus | Reference | FDR adjusted P-value | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | ALL | | | | WOD | | | |
| | | | | | SBP | DBP | MAP | PP | SBP | DBP | MAP | PP |
| rs10059921 | 5 | 87514515 | TMEM161B | Warren, ture Genetics 2017 | 0.984 | 0.964 | 0.980 | 0.977 | - | - | - | - |
| rs10077885 | 5 | 114390121 | TRIM36 | Ehret, ture Genetics 2016 | 0.984 | 0.987 | 0.980 | 0.977 | 0.958 | 0.959 | 0.946 | 0.979 |
| rs10078021 | 5 | 75038431 | POC5 | Warren, ture Genetics 2017 | 0.984 | 0.964 | 0.959 | 0.977 | 0.958 | 0.959 | 0.972 | 0.979 |
| rs1008058 | 5 | 122435627 | PRDM6 | Surendran, ture Genetics 2016 | 0.984 | 0.964 | 0.980 | 0.977 | 0.966 | 0.956 | 0.975 | 0.979 |
| rs1011018 | 7 | 139463264 | HIPK2 | Warren, ture Genetics 2017 | 0.984 | 0.964 | 0.922 | 0.947 | 0.958 | 0.871 | 0.901 | 0.979 |
| rs10224002 | 7 | 151415041 | PRKAG2 | Tragante, AJHG 2014 | 0.984 | 0.767 | 0.922 | 0.977 | 0.958 | 0.700 | 0.784 | 0.979 |
| rs10260816 | 7 | 46010100 | IGFBP3 | Kato, ture Genetics 2015 | 0.996 | 0.998 | 0.993 | 0.977 | 0.958 | 0.833 | 0.901 | 0.979 |
| rs1036477 | 15 | 48914926 | FBN1 | Tragante, AJHG 2014 | 0.761 | 0.604 | 0.559 | 0.947 | 0.958 | 0.959 | 0.962 | 0.979 |
| rs10407022 | 19 | 2249477 | AMH | Surendran, ture Genetics 2016 | 0.984 | 0.964 | 0.980 | 0.977 | 0.958 | 0.959 | 0.946 | 0.979 |
| rs1060105 | 12 | 123806219 | SBNO1 | Surendran, ture Genetics 2016 | 0.727 | 0.499 | 0.559 | 0.947 | 0.958 | 0.717 | 0.866 | 0.979 |
| rs10760117 | 9 | 123586737 | PSMD5 | Ehret, ture Genetics 2016 | 0.996 | 0.987 | 0.993 | 0.977 | 0.958 | 0.952 | 0.962 | 0.979 |
| rs10826995 | 10 | 32082658 | ARHGAP12 | Warren, ture Genetics 2017 | 0.984 | 0.871 | 0.922 | 0.977 | 0.958 | 0.795 | 0.866 | 0.979 |
| rs10850411 | 12 | 115387796 | TBX5-TBX3 | Ehret, ture 2011 | 0.984 | 0.964 | 0.922 | 0.947 | 0.958 | 0.959 | 0.972 | 0.979 |
| rs10916082 | 1 | 227252626 | CDC42BPA | Warren, ture Genetics 2017 | 0.984 | 0.871 | 0.980 | 0.947 | 0.966 | 0.795 | 0.901 | 0.979 |
| rs10922502 | 1 | 89360158 | GTF2B | Warren, ture Genetics 2017 | 0.984 | 0.964 | 0.980 | 0.985 | 0.958 | 0.959 | 0.988 | 0.979 |
| rs10943605 | 6 | 79655477 | PHIP | Liu, ture Genetics 2016 | 0.984 | 0.770 | 0.922 | 0.977 | 0.958 | 0.717 | 0.843 | 0.979 |
| rs10948071 | 6 | 43280713 | CRIP3 | Ganesh, AJHG 2014 | 0.984 | 0.943 | 0.988 | 0.948 | 0.958 | 0.753 | 0.866 | 0.979 |
| rs10995311 | 10 | 64564934 | ADO | Surendran, ture Genetics 2016 | 0.984 | 0.918 | 0.958 | 0.977 | 0.958 | 0.867 | 0.946 | 0.979 |
| rs110419 | 11 | 8252853 | LMO1 | Surendran, ture Genetics 2016 | 0.984 | 0.871 | 0.922 | 0.977 | 0.958 | 0.959 | 0.996 | 0.979 |
| rs11066280 | 12 | 112817783 | RPL6-ALDH1 | Kato, ture Genetics 2011 | - | - | - | - | - | - | - | - |
| rs111245230 | 9 | 113169775 | SVEP1 | Liu, ture Genetics 2016 | - | - | - | - | - | - | - | - |
| rs11128722 | 3 | 14958126 | FGD5 | Ehret, ture Genetics 2016 | 0.984 | 0.964 | 0.980 | 0.977 | 0.958 | 0.959 | 0.972 | 0.979 |
| rs11154027 | 6 | 121781390 | GJA1 | Warren, ture Genetics 2017 | 0.996 | 0.943 | 0.980 | 0.977 | 0.958 | 0.952 | 0.946 | 0.979 |
| rs11191548 | 10 | 104846178 | CYP17A1-NT5C2 | Newton-Cheh, ture Genetics 2009 | 0.984 | 0.964 | 0.980 | 0.977 | 0.958 | 0.859 | 0.901 | 0.979 |
| rs112184198 | 10 | 102604514 | PAX2 | Warren, ture Genetics 2017 | 0.985 | 0.943 | 0.980 | 0.977 | 0.968 | 0.959 | 0.989 | 0.983 |
| rs11222084 | 11 | 130273230 | ADAMTS8 | Wain, ture Genetics 2011 | 0.984 | 0.964 | 0.980 | 0.977 | 0.958 | 0.959 | 0.975 | 0.979 |
| rs11229457 | 11 | 58207203 | OR5B12 | Surendran, ture Genetics 2016 | 0.984 | 0.767 | 0.914 | 0.977 | 0.958 | 0.867 | 0.901 | 0.979 |
| rs112557609 | 1 | 56576924 | RP4-710M16.1-PPAP2B | Warren, ture Genetics 2017 | 0.996 | 0.964 | 0.980 | 0.977 | 0.958 | 0.817 | 0.866 | 0.979 |
| rs1126464 | 16 | 89704365 | DPEP1 | Surendran, ture Genetics 2016 | 0.984 | 0.767 | 0.922 | 0.977 | 0.966 | 0.771 | 0.901 | 0.979 |
| rs11442819 | 11 | 45208141 | PRDM11 | Warren, ture Genetics 2017 | 0.984 | 0.987 | 0.980 | 0.977 | 0.958 | 0.899 | 0.901 | 0.979 |

| rs11537751 | 11 | 47587452 | PTPMT1 | Liu, ture Genetics 2016 | 0.984 | 0.964 | 0.993 | 0.977 | - | - | - | - |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs11556924 | 7 | 129663496 | ZC3HC1 | Ehret, ture Genetics 2016 | 0.984 | 0.499 | 0.588 | 0.977 | 0.958 | 0.447 | 0.858 | 0.979 |
| rs115795127 | 9 | 85993901 | FRMD3 | Liang, PLoS Genetics 2017 | 0.984 | 0.868 | 0.980 | 0.977 | 0.958 | 0.959 | 0.975 | 0.979 |
| rs11639856 | 16 | 24788645 | TNRC6A | Liu, ture Genetics 2016 | 0.984 | 0.918 | 0.980 | 0.977 | 0.958 | 0.959 | 0.946 | 0.979 |
| rs11643209 | 16 | 75331044 | CFDP1 | Warren, ture Genetics 2017 | 0.984 | 0.964 | 0.980 | 0.977 | 0.958 | 0.959 | 0.913 | 0.979 |
| rs11689667 | 2 | 85491365 | TCF7L1 | Warren, ture Genetics 2017 | 0.984 | 0.767 | 0.922 | 0.977 | 0.958 | 0.817 | 0.901 | 0.979 |
| rs1173771 | 5 | 32815028 | NPR3-C5orf23 | Ehret, ture 2011 | 0.984 | 0.499 | 0.914 | 0.977 | 0.958 | 0.717 | 0.866 | 0.979 |
| rs11953630 | 5 | 157845402 | EBF1 | Ehret, ture 2011 | 0.984 | 0.943 | 0.922 | 0.977 | 0.958 | 0.840 | 0.901 | 0.979 |
| rs11977526 | 7 | 46008110 | IGFBP1-IGFBP3 | Zhu, AJHG 2015 | 0.984 | 0.964 | 0.980 | 0.977 | 0.958 | 0.867 | 0.901 | 0.979 |
| rs12374077 | 3 | 185317674 | SENP2 | Warren, ture Genetics 2017 | 0.984 | 0.918 | 0.980 | 0.977 | 0.958 | 0.867 | 0.901 | 0.992 |
| rs12408022 | 1 | 217718789 | GPATCH2 | Warren, ture Genetics 2017 | 0.996 | 0.964 | 0.980 | 0.977 | 0.958 | 0.795 | 0.901 | 0.979 |
| rs1250259 | 2 | 216300482 | FN1 | Warren, ture Genetics 2017 | 0.984 | 0.943 | 0.980 | 0.977 | 0.958 | 0.952 | 0.946 | 0.979 |
| rs12521868 | 5 | 131784393 | C5orf56 | Surendran, ture Genetics 2016 | 0.984 | 0.987 | 0.980 | 0.977 | 0.958 | 0.833 | 0.946 | 0.979 |
| rs12579720 | 12 | 20173764 | PDE3A | Kato, ture Genetics 2015 | 0.984 | 0.943 | 0.980 | 0.977 | 0.958 | 0.700 | 0.858 | 0.983 |
| rs12627651 | 21 | 44760603 | CRYAA-SIK1 | Ehret, ture Genetics 2016 | 0.984 | 0.499 | 0.559 | 0.977 | 0.949 | 0.447 | 0.759 | 0.979 |
| rs12628032 | 22 | 19967980 | ARVCF | Warren, ture Genetics 2017 | 0.665 | 0.515 | 0.559 | 0.845 | 0.958 | 0.700 | 0.784 | 0.979 |
| rs12731740 | 1 | 208024820 | CD34 | Warren, ture Genetics 2017 | 0.984 | 0.114 | 0.771 | 0.977 | - | - | - | - |
| rs1275988 | 2 | 26914364 | KCNK3 | Ganesh, AJHG 2014 | 0.984 | 0.964 | 0.980 | 0.977 | 0.993 | 0.959 | 0.972 | 0.979 |
| rs12921187 | 16 | 4943019 | PPL | Warren, ture Genetics 2017 | 0.984 | 0.964 | 0.980 | 0.977 | 0.993 | 0.959 | 0.975 | 0.983 |
| rs12940887 | 17 | 47402807 | ZNF652 | Ehret, ture 2011 | 0.984 | 0.987 | 0.980 | 0.977 | 0.958 | 0.959 | 0.972 | 0.979 |
| rs12941318 | 17 | 1333598 | CRK | Warren, ture Genetics 2017 | 0.984 | 0.443 | 0.559 | 0.977 | 0.958 | 0.447 | 0.759 | 0.983 |
| rs12946454 | 17 | 43208121 | PLCD3 | Newton-Cheh, ture Genetics 2009 | 0.984 | 0.987 | 0.980 | 0.977 | 0.949 | 0.700 | 0.784 | 0.979 |
| rs12958173 | 18 | 42141977 | SETBP1 | Ehret, ture Genetics 2016 | 0.984 | 0.919 | 0.980 | 0.977 | 0.958 | 0.859 | 0.913 | 0.983 |
| rs13002573 | 2 | 164915208 | FIGN-GRB14 | Wain, ture Genetics 2011 | 0.984 | 0.767 | 0.914 | 0.977 | 0.958 | 0.959 | 0.989 | 0.979 |
| rs13082711 | 3 | 27537909 | SLC4A7 | Ehret, ture 2011 | 0.984 | 0.767 | 0.922 | 0.977 | 0.966 | 0.899 | 0.972 | 0.979 |
| rs13107325 | 4 | 103188709 | SLC39A8 | Ehret, ture 2011 | - | - | - | - | - | - | - | - |
| rs13139571 | 4 | 156645513 | GUCY1A3-GUCY1B3 | Ehret, ture 2011 | **0.069** | 0.830 | 0.559 | **0.059** | 0.394 | 0.959 | 0.866 | **0.021** |
| rs13209747 | 6 | 127115454 | RSPO3 | Francescini, AJHG 2013 | 0.966 | 0.499 | 0.559 | 0.977 | 0.958 | 0.795 | 0.866 | 0.979 |
| rs13238550 | 7 | 131059056 | MKLN1 | Warren, ture Genetics 2017 | 0.984 | 0.964 | 0.980 | 0.977 | 0.958 | 0.959 | 0.962 | 0.979 |
| rs1327235 | 20 | 10969030 | JAG1 | Ehret, ture 2011 | 0.996 | 0.964 | 0.980 | 0.977 | 0.958 | 0.975 | 0.975 | 0.979 |
| rs13333226 | 16 | 20365654 | UMOD | Padmabhan, PloS Genetics 2010 | 0.984 | 0.871 | 0.914 | 0.977 | 0.958 | 0.717 | 0.866 | 0.979 |
| rs13359291 | 5 | 122476457 | PRDM6 | Kato, ture Genetics 2015 | 0.984 | 0.987 | 0.980 | 0.947 | 0.966 | 0.959 | 0.972 | 0.979 |
| rs1344653 | 2 | 19730845 | OSR1 | Kato, ture Genetics 2015 | 0.984 | 0.964 | 0.980 | 0.977 | 0.966 | 0.959 | 0.974 | 1.000 |
| rs1378942 | 15 | 75077367 | CYP1A1-ULK3 | Newton-Cheh, ture Genetics 2009 | 0.984 | 0.964 | 0.980 | 0.977 | 0.966 | 0.931 | 0.962 | 0.979 |
| rs139236208 | 12 | 94880742 | CCDC41 | Warren, ture Genetics 2017 | 0.984 | 1.000 | 0.988 | 0.977 | - | - | - | - |
| rs139385870 | 1 | 1685921 | DK-CPSF3L | Warren, ture Genetics 2017 | 0.984 | 0.964 | 0.980 | 0.977 | 0.949 | 0.795 | 0.843 | 0.979 |

| rs1401454 | 11 | 16250183 | SOX6 | Francescini, AJHG 2013 | 0.984 | 0.499 | 0.559 | 0.977 | 0.958 | 0.700 | 0.866 | 0.979 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs1421811 | 5 | 32714270 | NPR3-C5orf23 | Johnson, AJHG 2011 | 0.984 | 0.987 | 0.980 | 0.977 | 0.993 | 0.952 | 0.972 | 0.979 |
| rs143112823 | 3 | 154707967 | RP11-439C8.2 | Warren, ture Genetics 2017 | 0.416 | 0.499 | 0.559 | 0.845 | 0.886 | 0.717 | 0.784 | 0.893 |
| rs1438896 | 2 | 145646072 | TEX41 | Warren, ture Genetics 2017 | 0.985 | 0.964 | 0.980 | 0.977 | 0.958 | 0.952 | 0.946 | 0.979 |
| rs1446468 | 2 | 164963486 | FIGN-GRB14 | Wain, ture Genetics 2011 | 0.996 | 0.964 | 0.980 | 0.977 | 0.958 | 0.867 | 0.972 | 0.979 |
| rs1458038 | 4 | 81164723 | FGF5 | Ehret, ture 2011 | 0.984 | 0.964 | 0.988 | 0.977 | 0.958 | 0.959 | 0.946 | 0.979 |
| rs147212971 | 6 | 166178451 | PDE10A | Warren, ture Genetics 2017 | 0.984 | 0.604 | 0.922 | 0.977 | 0.958 | 0.717 | 0.866 | 0.979 |
| rs1530440 | 10 | 63524591 | C10orf107 | Newton-Cheh, ture Genetics 2009 | 0.984 | 0.964 | 0.980 | 0.977 | 0.958 | 0.901 | 0.972 | 0.979 |
| rs1563788 | 6 | 43308363 | TTBK1,SLC22A7,ZNF318 | Kato, ture Genetics 2015 | 0.984 | 0.767 | 0.922 | 0.977 | 0.958 | 0.795 | 0.866 | 0.979 |
| rs1566497 | 4 | 169717148 | PALLD | Warren, ture Genetics 2017 | 0.984 | 0.964 | 0.980 | 0.977 | 0.958 | 0.959 | 0.962 | 0.979 |
| rs167479 | 19 | 11526765 | RGL3 | Surendran, ture Genetics 2016 | 0.984 | 0.964 | 0.978 | 0.845 | 0.958 | 0.901 | 0.996 | 0.893 |
| rs16823124 | 2 | 183224127 | PDE1A | Tragante, AJHG 2014 | 0.984 | 0.772 | 0.914 | 0.977 | 0.949 | 0.700 | 0.759 | 0.979 |
| rs16833934 | 3 | 163737250 | MIR1263 | Simino, AJHG 2014 | 0.984 | 0.767 | 0.922 | 0.977 | 0.959 | 0.833 | 0.946 | 0.979 |
| rs16849225 | 2 | 164906820 | FIGN-GRB14 | Kato, ture Genetics 2011 | 0.984 | 0.767 | 0.914 | 0.977 | 0.966 | 0.859 | 0.946 | 0.979 |
| rs16851397 | 3 | 141134818 | ZBTB38 | Surendran, ture Genetics 2016 | 0.984 | 0.964 | 0.980 | 0.845 | 0.958 | 0.952 | 0.975 | 0.979 |
| rs17030613 | 1 | 113190807 | ST7L-CAPZA1-MOV10 | Kato, ture Genetics 2011 | 0.984 | 0.964 | 0.980 | 0.977 | 0.958 | 0.717 | 0.843 | 0.979 |
| rs17059668 | 4 | 174584663 | chr4mb174 | Warren, ture Genetics 2017 | 0.727 | 0.499 | 0.559 | 0.947 | 0.958 | 0.867 | 0.866 | 0.979 |
| rs17080102 | 6 | 151004770 | PLEKHG1 | Francescini, AJHG 2013 | 0.984 | 0.964 | 0.980 | 0.977 | 0.958 | 0.833 | 0.903 | 0.979 |
| rs17249754 | 12 | 90060586 | ATP2B1 | Levy, ture Genetics 2009 | 0.984 | 0.964 | 0.993 | 0.977 | 0.958 | 0.997 | 0.975 | 0.979 |
| rs17367504 | 1 | 11862778 | MTHFR-NPPB | Newton-Cheh, ture Genetics 2009 | 0.984 | 0.964 | 0.980 | 0.977 | 0.958 | 0.867 | 0.866 | 0.979 |
| rs17428471 | 7 | 27337867 | EVX1-HOXA | Francescini, AJHG 2013 | 0.984 | 0.987 | 0.980 | 0.977 | 0.958 | 0.931 | 0.901 | 0.979 |
| rs17477177 | 7 | 106411858 | PIK3CG | Wain, ture Genetics 2011 | 0.984 | 0.998 | 0.980 | 0.947 | 0.958 | 0.931 | 0.977 | 0.979 |
| rs17608766 | 17 | 45013271 | GOSR2 | Ehret, ture 2011 | 0.984 | 0.943 | 0.980 | 0.977 | 0.993 | 0.959 | 0.975 | 1.000 |
| rs17638167 | 19 | 11584818 | ELAVL3 | Ehret, ture Genetics 2016 | - | - | - | - | - | - | - | - |
| rs1799945 | 6 | 26091179 | HFE | Ehret, ture 2011 | 0.984 | 0.964 | 0.980 | 0.977 | 0.958 | 0.931 | 0.975 | 0.979 |
| rs1801253 | 10 | 115805056 | ADRB1 | Johnson, Hypertension 2011 | 0.727 | 0.499 | 0.559 | 0.947 | 0.958 | 0.952 | 0.920 | 0.979 |
| rs1813353 | 10 | 18707448 | CACNB2 | Ehret, ture 2011 | 0.984 | 1.000 | 0.993 | 0.977 | 0.958 | 0.871 | 0.901 | 0.979 |
| rs1925153 | 6 | 56102780 | COL21A1 | Liu, ture Genetics 2016 | 0.984 | 0.868 | 0.922 | 0.977 | 0.958 | 0.931 | 0.946 | 0.983 |
| rs1953126 | 9 | 123640500 | PHF19 | Liu, ture Genetics 2016 | 0.996 | 0.964 | 0.980 | 0.977 | 0.958 | 0.717 | 0.866 | 0.979 |
| rs1975487 | 2 | 55809054 | PNPT1 | Ehret, ture Genetics 2016 | 0.984 | 0.964 | 0.980 | 0.977 | 0.958 | 0.819 | 0.901 | 0.983 |
| rs2004776 | 1 | 230848702 | AGT | Johnson, AJHG 2011 | 0.996 | 0.964 | 0.980 | 0.977 | 0.958 | 0.956 | 0.962 | 0.979 |
| rs2014408 | 11 | 16365282 | SOX6 | Johnson, AJHG 2011 | 0.984 | 0.604 | 0.914 | 0.977 | 0.958 | 0.700 | 0.866 | 0.979 |
| rs2014912 | 4 | 86715670 | ARHGAP24 | Kato, ture Genetics 2015 | 0.996 | 0.964 | 0.980 | 0.977 | 0.958 | 0.931 | 0.901 | 0.979 |
| rs2071518 | 8 | 120435812 | NOV | Wain, ture Genetics 2011 | 0.984 | 0.745 | 0.922 | 0.977 | 0.958 | 0.714 | 0.901 | 0.979 |
| rs2107595 | 7 | 19049388 | HDAC9 | Kato, ture Genetics 2015 | 0.984 | 0.964 | 0.980 | 0.977 | 0.958 | 0.959 | 0.977 | 0.979 |
| rs217727 | 11 | 2016908 | H19 | Tragante, AJHG 2014 | 0.984 | 0.964 | 0.980 | 0.977 | 0.958 | 0.959 | 0.962 | 0.979 |

| rs2188962 | 5 | 131770805 | C5orf56 | Liu, ture Genetics 2016 | 0.984 | 0.964 | 0.980 | 0.977 | 0.958 | 0.901 | 0.962 | 0.979 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs2240736 | 17 | 59485393 | C17orf82,TBX2 | Kato, ture Genetics 2015 | 0.984 | 0.964 | 0.993 | 0.977 | 0.958 | 0.959 | 0.962 | 0.979 |
| rs2270860 | 6 | 43270151 | SLC22A7 | Liu, ture Genetics 2016 | 0.984 | 0.767 | 0.922 | 0.977 | 0.958 | 0.817 | 0.866 | 0.979 |
| rs2282978 | 7 | 92264410 | CDK6 | Tragante, AJHG 2014 | 0.984 | 0.964 | 0.980 | 0.845 | 0.958 | 0.959 | 0.946 | 0.893 |
| rs2289081 | 2 | 20881840 | C2orf43 | Warren, ture Genetics 2017 | 0.727 | 0.943 | 0.771 | 0.845 | 0.958 | 0.975 | 0.946 | 0.979 |
| rs2291435 | 4 | 38387395 | TBC1D1-FLJ13197 | Ehret, ture Genetics 2016 | 0.984 | 0.853 | 0.922 | 0.977 | 0.958 | 0.833 | 0.866 | 0.979 |
| rs2302061 | 19 | 2226772 | DOT1L | Liu, ture Genetics 2016 | 0.984 | 0.853 | 0.980 | 0.948 | 0.958 | 0.700 | 0.901 | 0.979 |
| rs2304130 | 19 | 19789528 | ZNF101 | Surendran, ture Genetics 2016 | 0.984 | 0.943 | 0.922 | 0.977 | 0.958 | 0.899 | 0.901 | 0.979 |
| rs2306374 | 3 | 138119952 | MRAS | Warren, ture Genetics 2017 | 0.984 | 0.964 | 0.980 | 0.977 | 0.966 | 0.959 | 0.977 | 0.979 |
| rs2384550 | 12 | 115352731 | TBX5-TBX3 | Levy, ture Genetics 2009 | 0.984 | 0.964 | 0.980 | 0.977 | 0.958 | 0.959 | 0.972 | 0.979 |
| rs2467099 | 17 | 73949045 | ACOX1 | Warren, ture Genetics 2017 | 0.985 | 0.964 | 0.980 | 0.977 | 0.958 | 0.960 | 0.972 | 0.979 |
| rs2493292 | 1 | 3328659 | PRDM16 | Liu, ture Genetics 2016 | 0.987 | 0.772 | 0.980 | 0.977 | 0.966 | 0.700 | 0.901 | 0.979 |
| rs2521501 | 15 | 91437388 | FURIN-FES | Ehret, ture 2011 | 0.984 | 0.964 | 0.980 | 0.977 | 0.958 | 0.871 | 0.901 | 0.979 |
| rs2579519 | 2 | 96675166 | GPAT2-FAHD2CP | Warren, ture Genetics 2017 | 0.984 | 0.964 | 0.980 | 0.977 | 0.958 | 0.959 | 0.962 | 0.979 |
| rs2760061 | 1 | 228191075 | WNT3A | Warren, ture Genetics 2017 | 0.984 | 0.964 | 0.980 | 0.977 | 0.958 | 0.931 | 0.913 | 0.979 |
| rs2782980 | 10 | 115781527 | ADRB1 | Wain, ture Genetics 2011 | 0.996 | 0.964 | 0.980 | 0.977 | 0.958 | 0.931 | 0.903 | 0.979 |
| rs2854275 | 6 | 32628428 | HLA-DQB1 | Tragante, AJHG 2014 | - | - | - | - | - | - | - | - |
| rs2898290 | 8 | 11433909 | BLK-GATA4 | Ho, Jourl of Hypertension 2011 | 0.984 | 0.918 | 0.980 | 0.845 | 0.958 | 0.952 | 0.975 | 0.979 |
| rs2932538 | 1 | 113216543 | ST7L-CAPZA1-MOV10 | Ehret, ture 2011 | 0.984 | 0.566 | 0.914 | 0.977 | 0.958 | 0.959 | 0.996 | 0.979 |
| rs2969070 | 7 | 2512545 | CHST12-LFNG | Ehret, ture Genetics 2016 | 0.984 | 0.964 | 0.993 | 0.977 | 0.966 | 0.887 | 0.972 | 0.979 |
| rs2972146 | 2 | 227100698 | 2q36.3 | Surendran, ture Genetics 2016 | 0.984 | 0.987 | 0.980 | 0.977 | 0.958 | 0.952 | 0.901 | 0.979 |
| rs2978098 | 8 | 101676675 | SNX31 | Warren, ture Genetics 2017 | 0.984 | 0.964 | 0.980 | 0.977 | 0.958 | 0.959 | 0.977 | 0.979 |
| rs2978456 | 8 | 42324765 | SLC20A2 | Warren, ture Genetics 2017 | 0.984 | 0.964 | 0.980 | 0.951 | 0.958 | 0.959 | 0.901 | 0.979 |
| rs3184504 | 12 | 111884608 | SH2B3 | Levy, ture Genetics 2009 | 0.984 | 0.964 | 0.980 | 0.948 | 0.958 | 0.771 | 0.901 | 0.979 |
| rs319690 | 3 | 47927484 | MAP4 | Wain, ture Genetics 2011 | 0.984 | 0.943 | 0.914 | 0.947 | 0.958 | 0.931 | 0.901 | 0.979 |
| rs33063 | 16 | 69640217 | NFAT5 | Tragante, AJHG 2014 | 0.984 | 0.964 | 0.980 | 0.977 | 0.958 | 0.952 | 0.962 | 0.979 |
| rs34591516 | 8 | 142367087 | GPR20 | Surendran, ture Genetics 2016 | 0.984 | 0.767 | 0.914 | 0.977 | 0.958 | 0.822 | 0.901 | 0.979 |
| rs347591 | 3 | 11290122 | HRH1-ATG7 | Ganesh, Human Molecular Genetics 2013 | 0.984 | 0.964 | 0.922 | 0.977 | 0.958 | 0.931 | 0.946 | 0.989 |
| rs35199222 | 15 | 81013037 | ABHD17C | Warren, ture Genetics 2017 | 0.984 | 0.964 | 0.993 | 0.977 | 0.976 | 0.959 | 0.977 | 0.979 |
| rs35444 | 12 | 115552437 | TBX5-TBX3 | Kato, ture Genetics 2011 | 0.984 | 0.964 | 0.980 | 0.977 | 0.958 | 0.960 | 0.975 | 0.979 |
| rs36022378 | 3 | 49913705 | CAMKV-ACTBP13 | Warren, ture Genetics 2017 | 0.984 | 0.987 | 0.980 | 0.977 | 0.958 | 0.819 | 0.866 | 0.979 |
| rs36083386 | 6 | 152397912 | ESR1 | Warren, ture Genetics 2017 | 0.966 | 0.767 | 0.725 | 0.947 | 0.958 | 0.959 | 0.903 | 0.979 |
| rs3741378 | 11 | 65408937 | SIPA1 | Tragante, AJHG 2014 | 0.984 | 0.566 | 0.559 | 0.977 | 0.958 | 0.840 | 0.901 | 0.983 |
| rs3771371 | 2 | 71627539 | ZNF638 | Warren, ture Genetics 2017 | 0.984 | 0.964 | 0.988 | 0.977 | 0.958 | 0.959 | 0.946 | 0.979 |
| rs3774372 | 3 | 41877414 | ULK4 | Ehret, ture 2011 | 0.984 | 0.964 | 0.980 | 0.947 | 0.958 | 0.977 | 0.946 | 0.979 |
| rs381815 | 11 | 16902268 | PLEKHA7 | Levy, ture Genetics 2009 | 0.727 | 0.395 | 0.559 | 0.977 | 0.958 | 0.700 | 0.866 | 0.979 |

| rs3889199 | 1 | 59653742 | FGGY | Warren, ture Genetics 2017 | 0.984 | 0.964 | 0.993 | 0.977 | 0.958 | 0.977 | 0.975 | 0.979 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs3918226 | 7 | 150690176 | NOS3 | Johnson, AJHG 2011 | - | - | - | - | - | - | - | - |
| rs409558 | 6 | 31708147 | MSH5-SAPCD1 | Liu, ture Genetics 2016 | 0.984 | 0.964 | 0.980 | 0.977 | 0.958 | 0.959 | 0.975 | 0.979 |
| rs419076 | 3 | 169100886 | MECOM | Ehret, ture 2011 | 0.984 | 0.987 | 0.980 | 0.947 | 0.949 | 0.959 | 0.866 | 0.462 |
| rs4245739 | 1 | 204518842 | MDM4 | Ganesh, Human Molecular Genetics 2013 | 0.984 | 1.000 | 0.980 | 0.977 | 0.965 | 0.959 | 0.975 | 0.979 |
| rs4247374 | 19 | 7252756 | INSR | Ehret, ture Genetics 2016 | 0.985 | 0.964 | 0.980 | 0.977 | - | - | - | - |
| rs4308 | 17 | 61559625 | ACE | Warren, ture Genetics 2017 | 0.984 | 0.964 | 0.922 | 0.947 | 0.993 | 0.959 | 0.975 | 0.984 |
| rs4360494 | 1 | 38455891 | SF3A3 | Warren, ture Genetics 2017 | 0.996 | 0.604 | 0.922 | 0.977 | 0.958 | 0.700 | 0.784 | 0.979 |
| rs4364717 | 9 | 21801530 | MTAP | Warren, ture Genetics 2017 | 0.984 | 0.499 | 0.707 | 0.977 | 0.958 | 0.700 | 0.787 | 0.979 |
| rs4373814 | 10 | 18419972 | CACNB2 | Ehret, ture 2011 | 0.727 | 0.747 | 0.559 | 0.947 | 0.394 | 0.700 | 0.759 | 0.893 |
| rs4387287 | 10 | 105677897 | OBFC1 | Surendran, ture Genetics 2016 | 0.984 | 0.853 | 0.980 | 0.977 | 0.958 | 0.840 | 0.946 | 0.979 |
| rs4454254 | 8 | 141060027 | TRAPPC9 | Warren, ture Genetics 2017 | 0.985 | 0.964 | 0.980 | 0.985 | 0.958 | 0.863 | 0.901 | 0.979 |
| rs4494250 | 10 | 96563757 | CYP2C19 | Liu, ture Genetics 2016 | 0.984 | 0.993 | 0.998 | 0.977 | 0.958 | 0.952 | 0.946 | 0.979 |
| rs449789 | 6 | 159699125 | FNDC1 | Warren, ture Genetics 2017 | 0.984 | 0.964 | 0.993 | 0.977 | 0.958 | 0.959 | 0.972 | 0.983 |
| rs452036 | 14 | 23865885 | MYH6 | Surendran, ture Genetics 2016 | 0.984 | 0.964 | 0.980 | 0.977 | 0.958 | 0.959 | 0.972 | 0.979 |
| rs4530754 | 5 | 122855416 | CSNK1G3 | Liu, ture Genetics 2016 | 0.984 | 0.998 | 0.980 | 0.947 | 0.958 | 0.867 | 0.901 | 0.979 |
| rs4590817 | 10 | 63467553 | C10orf107 | Ehret, ture 2011 | 0.966 | 0.566 | 0.559 | 0.977 | 0.949 | 0.447 | 0.759 | 0.979 |
| rs4601790 | 11 | 65353906 | EHBP1L1 | Simino, AJHG 2014 | 0.996 | 0.964 | 0.980 | 0.977 | 0.976 | 0.931 | 0.972 | 0.979 |
| rs4660293 | 1 | 40028180 | PABPC4 | Liu, ture Genetics 2016 | 0.984 | 0.964 | 0.980 | 0.845 | 0.958 | 0.959 | 0.962 | 0.979 |
| rs470113 | 22 | 40729614 | TNRC6B | Surendran, ture Genetics 2016 | 0.984 | 0.964 | 0.980 | 0.977 | 0.958 | 0.949 | 0.946 | 0.979 |
| rs4728142 | 7 | 128573967 | 7q32.1 | Surendran, ture Genetics 2016 | 0.984 | 0.964 | 0.922 | 0.947 | 0.958 | 0.840 | 0.866 | 0.979 |
| rs4746172 | 10 | 75855842 | VCL | Tragante, AJHG 2014 | 0.996 | 0.964 | 0.988 | 0.977 | 0.958 | 0.819 | 0.866 | 0.979 |
| rs4823006 | 22 | 29451671 | ZNRF3 | Liu, ture Genetics 2016 | 0.984 | 0.918 | 0.978 | 0.977 | 0.958 | 0.717 | 0.866 | 0.979 |
| rs4841569 | 8 | 11452177 | BLK-GATA4 | Simino, AJHG 2014 | 0.984 | 0.570 | 0.559 | 0.977 | 0.886 | 0.700 | 0.759 | 0.979 |
| rs4846049 | 1 | 11850365 | MTHFR-NPPB | Johnson, AJHG 2011 | 0.984 | 0.853 | 0.924 | 0.977 | 0.966 | 0.819 | 0.903 | 0.979 |
| rs4952611 | 2 | 40567743 | SLC8A1 | Warren, ture Genetics 2017 | 0.984 | 0.964 | 0.980 | 0.977 | 0.958 | 0.959 | 0.946 | 0.979 |
| rs5068 | 1 | 11905974 | MTHFR-NPPB | Newton-Cheh, ture Genetics 2009 | 0.984 | 0.565 | 0.559 | 0.977 | - | - | - | - |
| rs5219 | 11 | 17409572 | KCNJ11 | Liu, ture Genetics 2016 | 0.984 | 0.918 | 0.980 | 0.977 | 0.958 | 0.931 | 0.972 | 0.979 |
| rs55701159 | 2 | 25139596 | ADCY3 | Warren, ture Genetics 2017 | 0.984 | 0.964 | 0.980 | 0.977 | 0.958 | 0.833 | 0.901 | 0.983 |
| rs55780018 | 2 | 208526140 | METTL21A-AC079767.3 | Warren, ture Genetics 2017 | 0.984 | 0.767 | 0.922 | 0.977 | 0.966 | 0.819 | 0.946 | 0.979 |
| rs6015450 | 20 | 57751117 | GS-EDN3 | Ehret, ture 2011 | 0.984 | 0.499 | 0.593 | 0.977 | 0.958 | 0.833 | 0.901 | 0.979 |
| rs6081613 | 20 | 19465907 | SLC24A3 | Warren, ture Genetics 2017 | 0.984 | 0.499 | 0.559 | 0.977 | 0.993 | 0.959 | 0.975 | 0.979 |
| rs6095241 | 20 | 47308798 | PREX1 | Surendran, ture Genetics 2016 | 0.984 | 0.767 | 0.922 | 0.977 | 0.958 | 0.795 | 0.866 | 0.979 |
| rs6108168 | 20 | 8626271 | PLCB1 | Warren, ture Genetics 2017 | 0.984 | 0.964 | 0.993 | 0.977 | 0.958 | 0.817 | 0.901 | 0.979 |
| rs62012628 | 15 | 79070000 | ADAMTS7 | Warren, ture Genetics 2017 | 0.984 | 0.964 | 0.980 | 0.977 | 0.966 | 0.959 | 0.996 | 0.979 |
| rs62080325 | 17 | 42060631 | PYY | Warren, ture Genetics 2017 | 0.984 | 0.964 | 0.993 | 0.977 | 0.958 | 0.840 | 0.913 | 0.979 |

| rs62104477 | 19 | 30294991 | CCNE1 | Warren, ture Genetics 2017 | 0.984 | 0.964 | 0.980 | 0.977 | 0.958 | 0.931 | 0.901 | 0.983 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs6271 | 9 | 136522274 | DBH | Ehret, ture Genetics 2016 | - | - | - | - | - | - | - | - |
| rs633185 | 11 | 100593538 | FLJ32810-TMEM133 | Ehret, ture 2011 | 0.984 | 0.964 | 0.980 | 0.845 | 0.958 | 0.795 | 0.946 | 0.979 |
| rs6487543 | 12 | 26438189 | SSPN | Warren, ture Genetics 2017 | 0.984 | 0.871 | 0.980 | 0.977 | 0.958 | 0.959 | 0.946 | 0.979 |
| rs661348 | 11 | 1905292 | LSP1-TNNT3 | Johnson, AJHG 2011 | 0.984 | 0.767 | 0.922 | 0.985 | 0.958 | 0.867 | 0.946 | 0.979 |
| rs6686889 | 1 | 25030470 | chr1mb25 | Warren, ture Genetics 2017 | 0.984 | 0.918 | 0.980 | 0.977 | 0.958 | 0.959 | 0.972 | 0.979 |
| rs6712094 | 2 | 165043460 | FIGN-GRB14 | Ganesh, AJHG 2014 | 0.984 | 0.964 | 0.980 | 0.947 | 0.958 | 0.959 | 0.972 | 0.979 |
| rs6722745 | 2 | 108875244 | SULT1C3 | Liu, ture Genetics 2016 | 0.984 | 0.964 | 0.980 | 0.977 | 0.958 | 0.952 | 0.989 | 0.979 |
| rs67330701 | 11 | 69079707 | MYEOV | Warren, ture Genetics 2017 | - | - | - | - | - | - | - | - |
| rs6797587 | 3 | 48197614 | CDC25A | Simino, AJHG 2014 | 0.984 | 0.964 | 0.980 | 0.977 | 0.958 | 0.840 | 0.974 | 0.979 |
| rs6825911 | 4 | 111381638 | ENPEP | Kato, ture Genetics 2011 | 0.984 | 0.964 | 0.980 | 0.977 | 0.958 | 0.931 | 0.901 | 0.979 |
| rs687621 | 9 | 136137065 | ABO | Surendran, ture Genetics 2016 | 0.984 | 0.964 | 0.980 | 0.977 | 0.958 | 0.896 | 0.901 | 0.979 |
| rs6891344 | 5 | 123136656 | CSNK1G3 | Ehret, ture Genetics 2016 | 0.984 | 0.964 | 0.980 | 0.977 | 0.966 | 0.959 | 0.982 | 0.979 |
| rs6911827 | 6 | 22130601 | CASC15 | Warren, ture Genetics 2017 | 0.984 | 0.964 | 0.980 | 0.977 | 0.958 | 0.867 | 0.901 | 0.979 |
| rs6969780 | 7 | 27159136 | HOXA3 | Liu, ture Genetics 2016 | 0.984 | 0.767 | 0.922 | 0.977 | 0.949 | 0.700 | 0.759 | 0.979 |
| rs709209 | 1 | 6278414 | RNF207 | Surendran, ture Genetics 2016 | 0.984 | 0.964 | 0.980 | 0.977 | 0.958 | 0.959 | 0.946 | 0.979 |
| rs7103648 | 11 | 47461783 | RAPSN, PSMC3, SLC39A13 | Ehret, ture Genetics 2016 | 0.984 | 0.767 | 0.980 | 0.977 | 0.958 | 0.819 | 0.901 | 1.000 |
| rs7126805 | 11 | 828916 | CRACR2B | Warren, ture Genetics 2017 | 0.984 | 0.499 | 0.559 | 0.977 | 0.949 | 0.700 | 0.784 | 0.979 |
| rs7129220 | 11 | 10350538 | ADM | Ehret, ture 2011 | 0.984 | 0.964 | 0.980 | 0.977 | 0.958 | 0.959 | 0.946 | 0.979 |
| rs7178615 | 15 | 66869072 | RP11-321F6.1 | Warren, ture Genetics 2017 | 0.984 | 0.918 | 0.978 | 0.977 | 0.958 | 0.752 | 0.866 | 0.979 |
| rs7236548 | 18 | 43097750 | SLC14A2 | Warren, ture Genetics 2017 | 0.984 | 0.964 | 0.980 | 0.977 | 0.958 | 0.867 | 0.901 | 0.979 |
| rs7248104 | 19 | 7224431 | INSR | Liu, ture Genetics 2016 | 0.984 | 0.964 | 0.980 | 0.985 | 0.966 | 0.959 | 0.972 | 0.979 |
| rs72765298 | 9 | 127900996 | SCAI | Warren, ture Genetics 2017 | 0.984 | 0.871 | 0.938 | 0.977 | - | - | - | - |
| rs7297416 | 12 | 54443090 | HOXC4 | Tragante, AJHG 2014 | 0.984 | 0.964 | 0.980 | 0.977 | 0.958 | 0.899 | 0.901 | 0.979 |
| rs7302981 | 12 | 50537815 | CERS5 | Surendran, ture Genetics 2016 | 0.984 | 0.964 | 0.980 | 0.951 | 0.958 | 0.952 | 0.866 | 0.979 |
| rs740406 | 19 | 2232221 | AMH | Kato, ture Genetics 2015 | 0.984 | 0.871 | 0.980 | 0.947 | 0.958 | 0.753 | 0.946 | 0.893 |
| rs7406910 | 17 | 46688256 | HOXB7 | Surendran, ture Genetics 2016 | 0.984 | 0.767 | 0.922 | 0.977 | 0.958 | 0.795 | 0.901 | 0.979 |
| rs740698 | 17 | 60767151 | MRC2 | Warren, ture Genetics 2017 | 0.984 | 0.964 | 0.980 | 0.977 | 0.958 | 0.795 | 0.866 | 0.979 |
| rs74181299 | 2 | 65283972 | CEP68 | Warren, ture Genetics 2017 | 0.984 | 0.964 | 0.980 | 0.977 | 0.958 | 0.959 | 0.972 | 0.979 |
| rs743757 | 3 | 50476378 | CAC2D2 | Warren, ture Genetics 2017 | 0.984 | 0.954 | 0.922 | 0.947 | 0.958 | 0.959 | 0.946 | 0.979 |
| rs745821 | 18 | 48142854 | MAPK4 | Warren, ture Genetics 2017 | 0.984 | 0.992 | 0.980 | 0.977 | 0.958 | 0.959 | 0.975 | 0.979 |
| rs7515635 | 1 | 42408070 | HIVEP3 | Ehret, ture Genetics 2016 | 0.996 | 0.964 | 0.980 | 0.977 | 0.958 | 0.931 | 0.946 | 0.979 |
| rs751984 | 11 | 61278246 | LRRC10B | Kato, ture Genetics 2015 | 0.984 | 0.499 | 0.559 | 0.977 | 0.958 | 0.952 | 0.946 | 0.979 |
| rs7562 | 2 | 28635740 | FOSL2 | Warren, ture Genetics 2017 | 0.984 | 0.918 | 0.943 | 0.977 | 0.958 | 0.959 | 0.972 | 0.979 |
| rs757081 | 11 | 17351683 | NUCB2 | Tragante, AJHG 2014 | 0.984 | 0.767 | 0.914 | 0.977 | 0.949 | 0.700 | 0.759 | 0.979 |
| rs7592578 | 2 | 191439591 | TMEM194B | Warren, ture Genetics 2017 | 0.966 | 0.964 | 0.922 | 0.845 | 0.958 | 0.939 | 0.972 | 0.979 |

| rs76206723 | 7 | 40447971 | SUGCT | Warren, ture Genetics 2017 | 0.984 | 0.918 | 0.980 | 0.948 | 0.949 | 0.959 | 0.866 | 0.146 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs76326501 | 2 | 43167878 | AC016735.1 | Warren, ture Genetics 2017 | 0.984 | 0.871 | 0.980 | 0.977 | - | - | - | - |
| rs76452347 | 9 | 35906471 | HRCT1 | Liu, ture Genetics 2016 | 0.984 | 0.964 | 0.980 | 0.977 | 0.958 | 0.959 | 0.972 | 0.983 |
| rs76987554 | 6 | 134080855 | TARID/TCF21 | Liang, PLoS Genetics 2017 | 0.984 | 0.772 | 0.922 | 0.977 | 0.958 | 0.833 | 0.901 | 0.979 |
| rs78648104 | 6 | 50683009 | TFAP2D | Warren, ture Genetics 2017 | - | - | - | - | - | - | - | - |
| rs79089478 | 17 | 40317241 | KCNH4-HSD17B1 | Warren, ture Genetics 2017 | - | - | - | - | - | - | - | - |
| rs79146658 | 2 | 179786068 | CCDC141 | Warren, ture Genetics 2017 | 0.984 | 0.998 | 0.980 | 0.977 | - | - | - | - |
| rs8016306 | 14 | 63928546 | PPP2R5E | Warren, ture Genetics 2017 | 0.984 | 0.987 | 0.993 | 0.977 | 0.958 | 0.871 | 0.901 | 0.979 |
| rs8059962 | 16 | 81574197 | CMIP | Warren, ture Genetics 2017 | 0.984 | 0.964 | 0.993 | 0.977 | 0.958 | 0.988 | 0.975 | 0.979 |
| rs8068318 | 17 | 59483766 | TBX2 | Surendran, ture Genetics 2016 | 0.984 | 0.964 | 0.980 | 0.951 | 0.958 | 0.959 | 0.946 | 0.979 |
| rs8258 | 11 | 117283676 | CEP164 | Warren, ture Genetics 2017 | 0.984 | 0.868 | 0.914 | 0.947 | 0.958 | 0.867 | 0.866 | 0.979 |
| rs867186 | 20 | 33764554 | PROCR | Surendran, ture Genetics 2016 | 0.984 | 0.964 | 0.988 | 0.977 | 0.958 | 0.717 | 0.843 | 0.979 |
| rs871606 | 4 | 54799245 | CHIC2 | Wain, ture Genetics 2011 | 0.984 | 0.767 | 0.978 | 0.977 | 0.958 | 0.700 | 0.866 | 0.979 |
| rs880315 | 1 | 10796866 | CASZ1 | Takeuchi, Circulation 2010 | 0.984 | 0.871 | 0.922 | 0.977 | 0.958 | 0.833 | 0.901 | 1.000 |
| rs891511 | 7 | 150704843 | NOS3 | Liu, ture Genetics 2016 | 0.984 | 0.964 | 0.922 | 0.947 | 0.958 | 0.959 | 0.946 | 0.979 |
| rs894344 | 8 | 135612745 | ZFAT | Warren, ture Genetics 2017 | 0.984 | 0.964 | 0.993 | 0.977 | 0.958 | 0.887 | 0.901 | 0.979 |
| rs900145 | 11 | 13293905 | ARNTL | Liu, ture Genetics 2016 | 0.984 | 0.964 | 0.988 | 0.947 | 0.958 | 0.931 | 0.962 | 0.983 |
| rs918466 | 3 | 64710253 | ADAMTS9 | Ehret, ture Genetics 2016 | 0.984 | 0.964 | 0.993 | 0.948 | 0.958 | 0.959 | 0.960 | 0.979 |
| rs9306160 | 21 | 45107562 | RRP1B | Surendran, ture Genetics 2016 | 0.984 | 0.964 | 0.980 | 0.977 | 0.958 | 0.959 | 0.996 | 0.979 |
| rs9323988 | 14 | 98587630 | RP11-61O1.1 | Warren, ture Genetics 2017 | 0.984 | 0.770 | 0.914 | 0.977 | 0.958 | 0.931 | 0.946 | 0.979 |
| rs932764 | 10 | 95895940 | PLCE1 | Ehret, ture 2011 | 0.984 | 0.964 | 0.980 | 0.977 | 0.965 | 0.959 | 0.975 | 0.979 |
| rs9349379 | 6 | 12903957 | PHACTR1 | Surendran, ture Genetics 2016 | 0.984 | 0.964 | 0.980 | 0.977 | 0.958 | 0.975 | 0.972 | 0.979 |
| rs9372498 | 6 | 118572486 | SLC35F1 | Warren, ture Genetics 2017 | 0.984 | 0.964 | 0.988 | 0.977 | 0.958 | 0.931 | 0.903 | 0.979 |
| rs953492 | 1 | 243471192 | SDCCAG8 | Warren, ture Genetics 2017 | 0.984 | 0.772 | 0.914 | 0.977 | 0.958 | 0.700 | 0.843 | 1.000 |
| rs9549328 | 13 | 113636156 | MCF2L | Warren, ture Genetics 2017 | 0.984 | 0.767 | 0.914 | 0.977 | 0.958 | 0.795 | 0.866 | 0.979 |
| rs9687065 | 5 | 148391140 | ABLIM3,SH3TC2 | Kato, ture Genetics 2015 | 0.984 | 0.943 | 0.980 | 0.977 | 0.958 | 0.931 | 0.946 | 0.992 |
| rs9827472 | 3 | 56726646 | FAM208A | Warren, ture Genetics 2017 | 0.984 | 0.964 | 0.980 | 0.977 | 0.958 | 0.819 | 0.866 | 0.979 |
| rs9859176 | 3 | 134000025 | RYK | Warren, ture Genetics 2017 | 0.984 | 0.964 | 0.980 | 0.845 | 0.958 | 0.959 | 0.901 | 0.979 |
| rs9888615 | 14 | 53377540 | FERMT2 | Warren, ture Genetics 2017 | 0.984 | 0.604 | 0.559 | 0.977 | 0.958 | 0.700 | 0.843 | 0.979 |

## Asians

| rs ID | CHR | POS | Gene / Locus | Reference | FDR adjusted P-value | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | ALL | | | | WOD | | | |
| | | | | | SBP | DBP | MAP | PP | SBP | DBP | MAP | PP |
| rs10059921 | 5 | 87514515 | TMEM161B | Warren, ture Genetics 2017 | - | - | - | - | - | - | - | - |
| rs10077885 | 5 | 114390121 | TRIM36 | Ehret, ture Genetics 2016 | 0.924 | 0.976 | 0.972 | 0.915 | 0.898 | 0.974 | 0.968 | 0.904 |
| rs10078021 | 5 | 75038431 | POC5 | Warren, ture Genetics 2017 | 0.924 | 0.931 | 0.875 | 0.867 | 0.898 | 0.805 | 0.887 | 0.849 |
| rs1008058 | 5 | 122435627 | PRDM6 | Surendran, ture Genetics 2016 | 0.924 | 0.987 | 0.997 | 0.818 | 0.912 | 0.993 | 0.982 | 0.826 |
| rs1011018 | 7 | 139463264 | HIPK2 | Warren, ture Genetics 2017 | 0.924 | 0.981 | 0.994 | 0.818 | 0.912 | 0.993 | 0.982 | 0.821 |
| rs10224002 | 7 | 151415041 | PRKAG2 | Tragante, AJHG 2014 | 0.709 | 0.833 | 0.873 | 0.867 | 0.552 | 0.805 | 0.682 | 0.849 |
| rs10260816 | 7 | 46010100 | IGFBP3 | Kato, ture Genetics 2015 | 0.924 | 0.976 | 0.985 | 0.818 | 0.898 | 0.974 | 0.968 | 0.847 |
| rs1036477 | 15 | 48914926 | FBN1 | Tragante, AJHG 2014 | 0.998 | 0.981 | 0.994 | 0.891 | 0.997 | 0.988 | 0.982 | 0.896 |
| rs10407022 | 19 | 2249477 | AMH | Surendran, ture Genetics 2016 | 0.924 | 0.965 | 0.875 | 0.840 | 0.898 | 0.922 | 0.909 | 0.849 |
| rs1060105 | 12 | 123806219 | SBNO1 | Surendran, ture Genetics 2016 | - | - | - | - | - | - | - | - |
| rs10760117 | 9 | 123586737 | PSMD5 | Ehret, ture Genetics 2016 | 0.924 | 0.981 | 0.985 | 0.960 | 0.912 | 0.993 | 0.980 | 0.975 |
| rs10826995 | 10 | 32082658 | ARHGAP12 | Warren, ture Genetics 2017 | - | - | - | - | - | - | - | - |
| rs10850411 | 12 | 115387796 | TBX5-TBX3 | Ehret, ture 2011 | 0.924 | 0.981 | 0.985 | 0.818 | 0.898 | 0.974 | 0.968 | 0.822 |
| rs10916082 | 1 | 227252626 | CDC42BPA | Warren, ture Genetics 2017 | 0.924 | 0.981 | 0.994 | 0.867 | 0.912 | 0.993 | 0.982 | 0.849 |
| rs10922502 | 1 | 89360158 | GTF2B | Warren, ture Genetics 2017 | 0.927 | 0.981 | 0.994 | 0.891 | 0.900 | 0.993 | 0.980 | 0.896 |
| rs10943605 | 6 | 79655477 | PHIP | Liu, ture Genetics 2016 | 0.948 | 0.976 | 0.985 | 0.818 | 0.952 | 0.974 | 0.982 | 0.821 |
| rs10948071 | 6 | 43280713 | CRIP3 | Ganesh, AJHG 2014 | 0.924 | 0.981 | 0.985 | 0.818 | 0.898 | 0.993 | 0.968 | 0.821 |
| rs10995311 | 10 | 64564934 | ADO | Surendran, ture Genetics 2016 | 0.948 | 0.984 | 0.994 | 0.980 | 0.952 | 0.993 | 0.982 | 0.976 |
| rs110419 | 11 | 8252853 | LMO1 | Surendran, ture Genetics 2016 | 0.948 | 0.984 | 0.997 | 0.891 | 0.952 | 0.993 | 0.982 | 0.896 |
| rs11066280 | 12 | 112817783 | RPL6-ALDH1 | Kato, ture Genetics 2011 | 0.907 | 0.833 | 0.873 | 0.867 | 0.898 | 0.805 | 0.887 | 0.849 |
| rs111245230 | 9 | 113169775 | SVEP1 | Liu, ture Genetics 2016 | - | - | - | - | - | - | - | - |
| rs11128722 | 3 | 14958126 | FGD5 | Ehret, ture Genetics 2016 | 0.927 | 0.981 | 0.997 | 0.818 | 0.912 | 0.993 | 0.982 | 0.821 |
| rs11154027 | 6 | 121781390 | GJA1 | Warren, ture Genetics 2017 | 0.924 | 0.872 | 0.972 | 0.891 | 0.912 | 0.843 | 0.968 | 0.896 |
| rs11191548 | 10 | 104846178 | CYP17A1-NT5C2 | Newton-Cheh, ture Genetics 2009 | 0.924 | 0.981 | 0.985 | 0.818 | 0.912 | 0.974 | 0.968 | 0.847 |
| rs112184198 | 10 | 102604514 | PAX2 | Warren, ture Genetics 2017 | - | - | - | - | - | - | - | - |
| rs11222084 | 11 | 130273230 | ADAMTS8 | Wain, ture Genetics 2011 | 0.834 | 0.965 | 0.875 | 0.818 | 0.552 | 0.805 | 0.887 | 0.821 |
| rs11229457 | 11 | 58207203 | OR5B12 | Surendran, ture Genetics 2016 | 0.924 | 0.965 | 0.972 | 0.891 | 0.898 | 0.843 | 0.968 | 0.896 |
| rs112557609 | 1 | 56576924 | RP4-710M16.1-PPAP2B | Warren, ture Genetics 2017 | 0.924 | 0.981 | 0.989 | 0.818 | 0.912 | 0.993 | 0.982 | 0.840 |
| rs1126464 | 16 | 89704365 | DPEP1 | Surendran, ture Genetics 2016 | - | - | - | - | - | - | - | - |
| rs11442819 | 11 | 45208141 | PRDM11 | Warren, ture Genetics 2017 | - | - | - | - | - | - | - | - |
| rs11537751 | 11 | 47587452 | PTPMT1 | Liu, ture Genetics 2016 | - | - | - | - | - | - | - | - |

| rs11556924 | 7 | 129663496 | ZC3HC1 | Ehret, ture Genetics 2016 | 0.924 | 0.976 | 0.972 | 0.891 | 0.898 | 0.974 | 0.968 | 0.896 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs115795127 | 9 | 85993901 | FRMD3 | Liang, PLoS Genetics 2017 | - | - | - | - | - | - | - | - |
| rs11639856 | 16 | 24788645 | TNRC6A | Liu, ture Genetics 2016 | 0.948 | 0.981 | 0.994 | 0.980 | 0.952 | 0.993 | 0.982 | 0.976 |
| rs11643209 | 16 | 75331044 | CFDP1 | Warren, ture Genetics 2017 | 0.924 | 0.981 | 0.996 | 0.650 | 0.898 | 0.993 | 0.982 | 0.771 |
| rs11689667 | 2 | 85491365 | TCF7L1 | Warren, ture Genetics 2017 | 0.924 | 0.981 | 0.985 | 0.891 | 0.912 | 0.993 | 0.980 | 0.896 |
| rs1173771 | 5 | 32815028 | NPR3-C5orf23 | Ehret, ture 2011 | 0.924 | 0.833 | 0.875 | 0.915 | 0.898 | 0.805 | 0.887 | 0.896 |
| rs11953630 | 5 | 157845402 | EBF1 | Ehret, ture 2011 | 0.924 | 0.981 | 0.985 | 0.818 | 0.898 | 0.993 | 0.968 | 0.826 |
| rs11977526 | 7 | 46008110 | IGFBP1-IGFBP3 | Zhu, AJHG 2015 | 0.985 | 0.965 | 0.985 | 0.818 | 0.952 | 0.922 | 0.968 | 0.826 |
| rs12374077 | 3 | 185317674 | SENP2 | Warren, ture Genetics 2017 | 0.924 | 0.833 | 0.873 | 0.912 | 0.898 | 0.805 | 0.887 | 0.896 |
| rs12408022 | 1 | 217718789 | GPATCH2 | Warren, ture Genetics 2017 | 0.985 | 0.965 | 0.985 | 0.818 | 0.980 | 0.922 | 0.968 | 0.847 |
| rs1250259 | 2 | 216300482 | FN1 | Warren, ture Genetics 2017 | 0.924 | 0.981 | 0.972 | 0.818 | 0.898 | 0.974 | 0.968 | 0.821 |
| rs12521868 | 5 | 131784393 | C5orf56 | Surendran, ture Genetics 2016 | - | - | - | - | - | - | - | - |
| rs12579720 | 12 | 20173764 | PDE3A | Kato, ture Genetics 2015 | 0.948 | 0.872 | 0.972 | 0.891 | 0.952 | 0.805 | 0.968 | 0.865 |
| rs12627651 | 21 | 44760603 | CRYAA-SIK1 | Ehret, ture Genetics 2016 | 0.924 | 0.981 | 0.985 | 0.818 | 0.898 | 0.993 | 0.982 | 0.826 |
| rs12628032 | 22 | 19967980 | ARVCF | Warren, ture Genetics 2017 | 0.985 | 0.981 | 0.996 | 0.980 | 0.952 | 0.993 | 0.982 | 0.976 |
| rs12731740 | 1 | 208024820 | CD34 | Warren, ture Genetics 2017 | 0.924 | 0.981 | 0.994 | 0.650 | 0.898 | 0.993 | 0.982 | 0.780 |
| rs1275988 | 2 | 26914364 | KCNK3 | Ganesh, AJHG 2014 | 0.924 | 0.981 | 0.985 | 0.867 | 0.898 | 0.974 | 0.968 | 0.849 |
| rs12921187 | 16 | 4943019 | PPL | Warren, ture Genetics 2017 | 0.924 | 0.965 | 0.972 | 0.980 | 0.898 | 0.805 | 0.925 | 0.979 |
| rs12940887 | 17 | 47402807 | ZNF652 | Ehret, ture 2011 | 0.924 | 0.976 | 0.972 | 0.818 | 0.898 | 0.974 | 0.968 | 0.847 |
| rs12941318 | 17 | 1333598 | CRK | Warren, ture Genetics 2017 | 0.924 | 0.981 | 0.985 | 0.891 | 0.898 | 0.974 | 0.968 | 0.865 |
| rs12946454 | 17 | 43208121 | PLCD3 | Newton-Cheh, ture Genetics 2009 | 0.924 | 0.981 | 0.985 | 0.818 | 0.898 | 0.974 | 0.968 | 0.823 |
| rs12958173 | 18 | 42141977 | SETBP1 | Ehret, ture Genetics 2016 | 0.949 | 0.981 | 0.996 | 0.891 | 0.952 | 0.993 | 0.982 | 0.896 |
| rs13002573 | 2 | 164915208 | FIGN-GRB14 | Wain, ture Genetics 2011 | 0.924 | 0.976 | 0.985 | 0.918 | 0.898 | 0.974 | 0.968 | 0.904 |
| rs13082711 | 3 | 27537909 | SLC4A7 | Ehret, ture 2011 | 0.924 | 0.833 | 0.873 | 0.818 | 0.898 | 0.805 | 0.887 | 0.821 |
| rs13107325 | 4 | 103188709 | SLC39A8 | Ehret, ture 2011 | - | - | - | - | - | - | - | - |
| rs13139571 | 4 | 156645513 | GUCY1A3-GUCY1B3 | Ehret, ture 2011 | 0.924 | 0.981 | 0.985 | 0.818 | 0.898 | 0.993 | 0.968 | 0.847 |
| rs13209747 | 6 | 127115454 | RSPO3 | Francescini, AJHG 2013 | 0.948 | 0.981 | 0.985 | 0.891 | 0.952 | 0.988 | 0.982 | 0.896 |
| rs13238550 | 7 | 131059056 | MKLN1 | Warren, ture Genetics 2017 | 0.924 | 0.981 | 0.985 | 0.891 | 0.898 | 0.993 | 0.968 | 0.865 |
| rs1327235 | 20 | 10969030 | JAG1 | Ehret, ture 2011 | 0.948 | 0.981 | 0.994 | 0.918 | 0.912 | 0.993 | 0.982 | 0.896 |
| rs13333226 | 16 | 20365654 | UMOD | Padmabhan, PloS Genetics 2010 | 0.948 | 0.976 | 0.985 | 0.980 | 0.932 | 0.974 | 0.968 | 0.979 |
| rs13359291 | 5 | 122476457 | PRDM6 | Kato, ture Genetics 2015 | 0.924 | 0.981 | 0.972 | 0.818 | 0.898 | 0.974 | 0.968 | 0.840 |
| rs1344653 | 2 | 19730845 | OSR1 | Kato, ture Genetics 2015 | 0.924 | 0.873 | 0.972 | 0.891 | 0.912 | 0.805 | 0.968 | 0.896 |
| rs1378942 | 15 | 75077367 | CYP1A1-ULK3 | Newton-Cheh, ture Genetics 2009 | 0.924 | 0.981 | 0.972 | 0.818 | 0.898 | 0.983 | 0.968 | 0.826 |
| rs139236208 | 12 | 94880742 | CCDC41 | Warren, ture Genetics 2017 | - | - | - | - | - | - | - | - |
| rs139385870 | 1 | 1685921 | DK-CPSF3L | Warren, ture Genetics 2017 | 0.924 | 0.981 | 0.985 | 0.818 | 0.898 | 0.993 | 0.968 | 0.822 |
| rs1401454 | 11 | 16250183 | SOX6 | Francescini, AJHG 2013 | 0.948 | 0.981 | 0.985 | 0.980 | 0.952 | 0.974 | 0.968 | 0.979 |

| rs1421811 | 5 | 32714270 | NPR3-C5orf23 | Johnson, AJHG 2011 | 0.998 | 0.981 | 0.994 | 0.980 | 0.997 | 0.993 | 0.982 | 0.976 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs143112823 | 3 | 154707967 | RP11-439C8.2 | Warren, ture Genetics 2017 | - | - | - | - | - | - | - | - |
| rs1438896 | 2 | 145646072 | TEX41 | Warren, ture Genetics 2017 | 0.951 | 0.976 | 0.994 | 0.818 | 0.952 | 0.974 | 0.982 | 0.821 |
| rs1446468 | 2 | 164963486 | FIGN-GRB14 | Wain, ture Genetics 2011 | 0.927 | 0.981 | 0.985 | 0.980 | 0.912 | 0.993 | 0.968 | 0.975 |
| rs1458038 | 4 | 81164723 | FGF5 | Ehret, ture 2011 | 0.751 | 0.981 | 0.972 | 0.650 | 0.552 | 0.993 | 0.968 | 0.771 |
| rs147212971 | 6 | 166178451 | PDE10A | Warren, ture Genetics 2017 | 0.924 | 0.981 | 0.994 | 0.818 | 0.900 | 0.993 | 0.982 | 0.821 |
| rs1530440 | 10 | 63524591 | C10orf107 | Newton-Cheh, ture Genetics 2009 | 0.927 | 0.872 | 0.972 | 0.891 | 0.912 | 0.805 | 0.937 | 0.896 |
| rs1563788 | 6 | 43308363 | TTBK1,SLC22A7,ZNF318 | Kato, ture Genetics 2015 | 0.924 | 0.981 | 0.985 | 0.818 | 0.898 | 0.993 | 0.968 | 0.821 |
| rs1566497 | 4 | 169717148 | PALLD | Warren, ture Genetics 2017 | 0.924 | 0.981 | 0.985 | 0.867 | 0.898 | 0.993 | 0.980 | 0.849 |
| rs167479 | 19 | 11526765 | RGL3 | Surendran, ture Genetics 2016 | - | - | - | - | - | - | - | - |
| rs16823124 | 2 | 183224127 | PDE1A | Tragante, AJHG 2014 | 0.924 | 0.833 | 0.875 | 0.980 | 0.898 | 0.805 | 0.887 | 0.979 |
| rs16833934 | 3 | 163737250 | MIR1263 | Simino, AJHG 2014 | 0.924 | 0.931 | 0.972 | 0.891 | 0.898 | 0.805 | 0.887 | 0.865 |
| rs16849225 | 2 | 164906820 | FIGN-GRB14 | Kato, ture Genetics 2011 | 0.924 | 0.976 | 0.972 | 0.891 | 0.898 | 0.974 | 0.968 | 0.896 |
| rs16851397 | 3 | 141134818 | ZBTB38 | Surendran, ture Genetics 2016 | - | - | - | - | - | - | - | - |
| rs17030613 | 1 | 113190807 | ST7L-CAPZA1-MOV10 | Kato, ture Genetics 2011 | 0.924 | 0.965 | 0.960 | 0.980 | 0.898 | 0.843 | 0.909 | 0.975 |
| rs17059668 | 4 | 174584663 | chr4mb174 | Warren, ture Genetics 2017 | 0.985 | 0.981 | 0.994 | 0.980 | 0.979 | 0.993 | 0.982 | 0.976 |
| rs17080102 | 6 | 151004770 | PLEKHG1 | Francescini, AJHG 2013 | 0.709 | 0.833 | 0.549 | 0.891 | 0.552 | 0.805 | 0.682 | 0.896 |
| rs17249754 | 12 | 90060586 | ATP2B1 | Levy, ture Genetics 2009 | - | - | - | - | - | - | - | - |
| rs17367504 | 1 | 11862778 | MTHFR-NPPB | Newton-Cheh, ture Genetics 2009 | 0.948 | 0.981 | 0.985 | 0.980 | 0.952 | 0.993 | 0.980 | 0.976 |
| rs17428471 | 7 | 27337867 | EVX1-HOXA | Francescini, AJHG 2013 | 0.948 | 0.981 | 0.985 | 0.867 | 0.952 | 0.974 | 0.980 | 0.849 |
| rs17477177 | 7 | 106411858 | PIK3CG | Wain, ture Genetics 2011 | 0.948 | 0.981 | 0.997 | 0.818 | 0.952 | 0.993 | 0.982 | 0.826 |
| rs17608766 | 17 | 45013271 | GOSR2 | Ehret, ture 2011 | - | - | - | - | - | - | - | - |
| rs17638167 | 19 | 11584818 | ELAVL3 | Ehret, ture Genetics 2016 | 0.924 | 0.976 | 0.972 | 0.891 | 0.898 | 0.974 | 0.968 | 0.865 |
| rs1799945 | 6 | 26091179 | HFE | Ehret, ture 2011 | 0.924 | 0.984 | 0.996 | 0.818 | 0.900 | 0.993 | 0.982 | 0.821 |
| rs1801253 | 10 | 115805056 | ADRB1 | Johnson, Hypertension 2011 | 0.709 | 0.833 | 0.873 | 0.818 | 0.552 | 0.805 | 0.887 | 0.847 |
| rs1813353 | 10 | 18707448 | CACNB2 | Ehret, ture 2011 | 0.924 | 0.976 | 0.985 | 0.918 | 0.912 | 0.974 | 0.968 | 0.943 |
| rs1925153 | 6 | 56102780 | COL21A1 | Liu, ture Genetics 2016 | - | - | - | - | - | - | - | - |
| rs1953126 | 9 | 123640500 | PHF19 | Liu, ture Genetics 2016 | 0.924 | 0.833 | 0.875 | 0.891 | 0.898 | 0.805 | 0.925 | 0.849 |
| rs1975487 | 2 | 55809054 | PNPT1 | Ehret, ture Genetics 2016 | 0.998 | 0.981 | 0.985 | 0.891 | 0.997 | 0.974 | 0.980 | 0.885 |
| rs2004776 | 1 | 230848702 | AGT | Johnson, AJHG 2011 | 0.924 | 0.872 | 0.972 | 0.818 | 0.912 | 0.805 | 0.968 | 0.821 |
| rs2014408 | 11 | 16365282 | SOX6 | Johnson, AJHG 2011 | 0.924 | 0.965 | 0.875 | 0.832 | 0.898 | 0.974 | 0.937 | 0.847 |
| rs2014912 | 4 | 86715670 | ARHGAP24 | Kato, ture Genetics 2015 | 0.907 | 0.965 | 0.875 | 0.818 | 0.898 | 0.922 | 0.909 | 0.821 |
| rs2071518 | 8 | 120435812 | NOV | Wain, ture Genetics 2011 | 0.948 | 0.981 | 0.994 | 0.980 | 0.952 | 0.993 | 0.982 | 0.976 |
| rs2107595 | 7 | 19049388 | HDAC9 | Kato, ture Genetics 2015 | 0.924 | 0.976 | 0.985 | 0.818 | 0.898 | 0.974 | 0.968 | 0.826 |
| rs217727 | 11 | 2016908 | H19 | Tragante, AJHG 2014 | 0.998 | 0.965 | 0.985 | 0.818 | 0.997 | 0.922 | 0.968 | 0.821 |
| rs2188962 | 5 | 131770805 | C5orf56 | Liu, ture Genetics 2016 | - | - | - | - | - | - | - | - |

| rs2240736 | 17 | 59485393 | C17orf82,TBX2 | Kato, ture Genetics 2015 | 0.948 | 0.965 | 0.985 | 0.818 | 0.952 | 0.805 | 0.968 | 0.821 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs2270860 | 6 | 43270151 | SLC22A7 | Liu, ture Genetics 2016 | 0.924 | 0.981 | 0.985 | 0.818 | 0.898 | 0.993 | 0.968 | 0.821 |
| rs2282978 | 7 | 92264410 | CDK6 | Tragante, AJHG 2014 | 0.924 | 0.981 | 0.985 | 0.818 | 0.898 | 0.993 | 0.980 | 0.821 |
| rs2289081 | 2 | 20881840 | C2orf43 | Warren, ture Genetics 2017 | 0.998 | 0.981 | 0.997 | 0.914 | 0.997 | 0.993 | 0.982 | 0.896 |
| rs2291435 | 4 | 38387395 | TBC1D1-FLJ13197 | Ehret, ture Genetics 2016 | 0.924 | 0.976 | 0.985 | 0.891 | 0.898 | 0.981 | 0.968 | 0.896 |
| rs2302061 | 19 | 2226772 | DOT1L | Liu, ture Genetics 2016 | 0.985 | 0.981 | 0.994 | 0.840 | 0.994 | 0.988 | 0.982 | 0.849 |
| rs2304130 | 19 | 19789528 | ZNF101 | Surendran, ture Genetics 2016 | - | - | - | - | - | - | - | - |
| rs2306374 | 3 | 138119952 | MRAS | Warren, ture Genetics 2017 | - | - | - | - | - | - | - | - |
| rs2384550 | 12 | 115352731 | TBX5-TBX3 | Levy, ture Genetics 2009 | 0.948 | 0.987 | 0.997 | 0.912 | 0.952 | 1.000 | 0.982 | 0.896 |
| rs2467099 | 17 | 73949045 | ACOX1 | Warren, ture Genetics 2017 | 0.998 | 0.987 | 0.997 | 0.980 | 0.997 | 0.993 | 0.982 | 0.979 |
| rs2493292 | 1 | 3328659 | PRDM16 | Liu, ture Genetics 2016 | 0.924 | 0.965 | 0.875 | 0.818 | 0.898 | 0.843 | 0.889 | 0.826 |
| rs2521501 | 15 | 91437388 | FURIN-FES | Ehret, ture 2011 | 0.948 | 0.981 | 0.985 | 0.980 | 0.952 | 0.974 | 0.968 | 0.976 |
| rs2579519 | 2 | 96675166 | GPAT2-FAHD2CP | Warren, ture Genetics 2017 | 0.924 | 0.981 | 0.985 | 0.927 | 0.898 | 0.988 | 0.968 | 0.906 |
| rs2760061 | 1 | 228191075 | WNT3A | Warren, ture Genetics 2017 | 0.998 | 0.973 | 0.985 | 0.818 | 0.997 | 0.974 | 0.968 | 0.847 |
| rs2782980 | 10 | 115781527 | ADRB1 | Wain, ture Genetics 2011 | 0.924 | 0.981 | 0.985 | 0.650 | 0.898 | 0.974 | 0.968 | 0.771 |
| rs2854275 | 6 | 32628428 | HLA-DQB1 | Tragante, AJHG 2014 | - | - | - | - | - | - | - | - |
| rs2898290 | 8 | 11433909 | BLK-GATA4 | Ho, Jourl of Hypertension 2011 | 0.924 | 0.981 | 0.985 | 0.980 | 0.912 | 0.988 | 0.968 | 0.975 |
| rs2932538 | 1 | 113216543 | ST7L-CAPZA1-MOV10 | Ehret, ture 2011 | 0.948 | 0.987 | 0.997 | 0.891 | 0.952 | 0.994 | 0.982 | 0.896 |
| rs2969070 | 7 | 2512545 | CHST12-LFNG | Ehret, ture Genetics 2016 | 0.998 | 0.981 | 0.996 | 0.980 | 0.997 | 0.993 | 0.982 | 0.979 |
| rs2972146 | 2 | 227100698 | 2q36.3 | Surendran, ture Genetics 2016 | 0.924 | 0.981 | 0.997 | 0.818 | 0.912 | 0.993 | 0.982 | 0.821 |
| rs2978098 | 8 | 101676675 | SNX31 | Warren, ture Genetics 2017 | 0.778 | 0.833 | 0.873 | 0.891 | 0.898 | 0.805 | 0.887 | 0.896 |
| rs2978456 | 8 | 42324765 | SLC20A2 | Warren, ture Genetics 2017 | 0.924 | 0.981 | 0.985 | 0.840 | 0.898 | 0.993 | 0.968 | 0.849 |
| rs3184504 | 12 | 111884608 | SH2B3 | Levy, ture Genetics 2009 | - | - | - | - | - | - | - | - |
| rs319690 | 3 | 47927484 | MAP4 | Wain, ture Genetics 2011 | 0.948 | 0.981 | 0.994 | 0.818 | 0.952 | 0.974 | 0.982 | 0.847 |
| rs33063 | 16 | 69640217 | NFAT5 | Tragante, AJHG 2014 | 0.924 | 0.981 | 0.985 | 0.846 | 0.898 | 0.993 | 0.968 | 0.849 |
| rs34591516 | 8 | 142367087 | GPR20 | Surendran, ture Genetics 2016 | - | - | - | - | - | - | - | - |
| rs347591 | 3 | 11290122 | HRH1-ATG7 | Ganesh, Human Molecular Genetics 2013 | 0.998 | 0.976 | 0.985 | 0.912 | 0.952 | 0.974 | 0.968 | 0.896 |
| rs35199222 | 15 | 81013037 | ABHD17C | Warren, ture Genetics 2017 | 0.949 | 0.984 | 0.997 | 0.891 | 0.952 | 0.994 | 0.982 | 0.890 |
| rs35444 | 12 | 115552437 | TBX5-TBX3 | Kato, ture Genetics 2011 | 0.924 | 0.976 | 0.972 | 0.650 | 0.898 | 0.974 | 0.968 | 0.780 |
| rs36022378 | 3 | 49913705 | CAMKV-ACTBP13 | Warren, ture Genetics 2017 | 0.959 | 0.976 | 0.985 | 0.891 | 0.952 | 0.974 | 0.968 | 0.896 |
| rs36083386 | 6 | 152397912 | ESR1 | Warren, ture Genetics 2017 | 0.924 | 0.872 | 0.875 | 0.892 | 0.898 | 0.843 | 0.968 | 0.896 |
| rs3741378 | 11 | 65408937 | SIPA1 | Tragante, AJHG 2014 | 0.924 | 0.981 | 0.985 | 0.980 | 0.929 | 0.993 | 0.980 | 0.979 |
| rs3771371 | 2 | 71627539 | ZNF638 | Warren, ture Genetics 2017 | 0.948 | 0.981 | 0.985 | 0.891 | 0.952 | 0.974 | 0.968 | 0.896 |
| rs3774372 | 3 | 41877414 | ULK4 | Ehret, ture 2011 | 0.948 | 0.976 | 0.985 | 0.934 | 0.952 | 0.974 | 0.968 | 0.943 |
| rs381815 | 11 | 16902268 | PLEKHA7 | Levy, ture Genetics 2009 | 0.998 | 0.981 | 0.994 | 0.818 | 0.952 | 0.974 | 0.982 | 0.847 |
| rs3889199 | 1 | 59653742 | FGGY | Warren, ture Genetics 2017 | 0.924 | 0.981 | 0.997 | 0.650 | 0.898 | 0.993 | 0.982 | 0.771 |

| rs3918226 | 7 | 150690176 | NOS3 | Johnson, AJHG 2011 | - | - | - | - | - | - | - | - |
| rs409558 | 6 | 31708147 | MSH5-SAPCD1 | Liu, ture Genetics 2016 | 0.924 | 0.981 | 0.985 | 0.818 | 0.898 | 0.993 | 0.968 | 0.821 |
| rs419076 | 3 | 169100886 | MECOM | Ehret, ture 2011 | 0.924 | 0.833 | 0.875 | 0.818 | 0.898 | 0.805 | 0.889 | 0.823 |
| rs4245739 | 1 | 204518842 | MDM4 | Ganesh, Human Molecular Genetics 2013 | 0.924 | 0.976 | 0.972 | 0.891 | 0.898 | 0.922 | 0.968 | 0.865 |
| rs4247374 | 19 | 7252756 | INSR | Ehret, ture Genetics 2016 | - | - | - | - | - | - | - | - |
| rs4308 | 17 | 61559625 | ACE | Warren, ture Genetics 2017 | 0.948 | 0.981 | 0.985 | 0.980 | 0.952 | 0.993 | 0.980 | 0.979 |
| rs4360494 | 1 | 38455891 | SF3A3 | Warren, ture Genetics 2017 | - | - | - | - | - | - | - | - |
| rs4364717 | 9 | 21801530 | MTAP | Warren, ture Genetics 2017 | 0.924 | 0.981 | 0.997 | 0.818 | 0.898 | 0.993 | 0.982 | 0.821 |
| rs4373814 | 10 | 18419972 | CACNB2 | Ehret, ture 2011 | 0.924 | 0.872 | 0.960 | 0.980 | 0.912 | 0.843 | 0.968 | 0.976 |
| rs4387287 | 10 | 105677897 | OBFC1 | Surendran, ture Genetics 2016 | 0.924 | 0.981 | 0.985 | 0.867 | 0.898 | 0.988 | 0.968 | 0.849 |
| rs4454254 | 8 | 141060027 | TRAPPC9 | Warren, ture Genetics 2017 | 0.948 | 0.976 | 0.985 | 0.962 | 0.952 | 0.974 | 0.968 | 0.920 |
| rs4494250 | 10 | 96563757 | CYP2C19 | Liu, ture Genetics 2016 | 0.924 | 0.833 | 0.873 | 0.918 | 0.898 | 0.805 | 0.887 | 0.896 |
| rs449789 | 6 | 159699125 | FNDC1 | Warren, ture Genetics 2017 | 0.709 | 0.833 | 0.873 | 0.818 | 0.552 | 0.805 | 0.682 | 0.821 |
| rs452036 | 14 | 23865885 | MYH6 | Surendran, ture Genetics 2016 | 0.924 | 0.976 | 0.972 | 0.915 | 0.912 | 0.974 | 0.968 | 0.920 |
| rs4530754 | 5 | 122855416 | CSNK1G3 | Liu, ture Genetics 2016 | 0.924 | 0.981 | 0.985 | 0.818 | 0.912 | 0.993 | 0.982 | 0.826 |
| rs4590817 | 10 | 63467553 | C10orf107 | Ehret, ture 2011 | - | - | - | - | - | - | - | - |
| rs4601790 | 11 | 65353906 | EHBP1L1 | Simino, AJHG 2014 | 0.924 | 0.976 | 0.985 | 0.818 | 0.912 | 0.974 | 0.968 | 0.821 |
| rs4660293 | 1 | 40028180 | PABPC4 | Liu, ture Genetics 2016 | 0.927 | 0.981 | 0.985 | 0.891 | 0.912 | 0.981 | 0.968 | 0.896 |
| rs470113 | 22 | 40729614 | TNRC6B | Surendran, ture Genetics 2016 | 0.948 | 0.976 | 0.985 | 0.818 | 0.952 | 0.974 | 0.980 | 0.847 |
| rs4728142 | 7 | 128573967 | 7q32.1 | Surendran, ture Genetics 2016 | 0.924 | 0.981 | 0.994 | 0.818 | 0.898 | 0.993 | 0.982 | 0.821 |
| rs4746172 | 10 | 75855842 | VCL | Tragante, AJHG 2014 | 0.924 | 0.976 | 0.972 | 0.980 | 0.900 | 0.974 | 0.968 | 0.976 |
| rs4823006 | 22 | 29451671 | ZNRF3 | Liu, ture Genetics 2016 | 0.927 | 0.976 | 0.985 | 0.980 | 0.912 | 0.974 | 0.968 | 0.979 |
| rs4841569 | 8 | 11452177 | BLK-GATA4 | Simino, AJHG 2014 | - | - | - | - | - | - | - | - |
| rs4846049 | 1 | 11850365 | MTHFR-NPPB | Johnson, AJHG 2011 | 0.948 | 0.981 | 0.997 | 0.818 | 0.952 | 0.993 | 0.982 | 0.821 |
| rs4952611 | 2 | 40567743 | SLC8A1 | Warren, ture Genetics 2017 | 0.998 | 0.981 | 0.994 | 0.927 | 0.997 | 0.993 | 0.982 | 0.975 |
| rs5068 | 1 | 11905974 | MTHFR-NPPB | Newton-Cheh, ture Genetics 2009 | - | - | - | - | - | - | - | - |
| rs5219 | 11 | 17409572 | KCNJ11 | Liu, ture Genetics 2016 | 0.924 | 0.872 | 0.875 | 0.937 | 0.898 | 0.805 | 0.887 | 0.922 |
| rs55701159 | 2 | 25139596 | ADCY3 | Warren, ture Genetics 2017 | - | - | - | - | - | - | - | - |
| rs55780018 | 2 | 208526140 | METTL21A-AC079767.3 | Warren, ture Genetics 2017 | - | - | - | - | - | - | - | - |
| rs6015450 | 20 | 57751117 | GS-EDN3 | Ehret, ture 2011 | - | - | - | - | - | - | - | - |
| rs6081613 | 20 | 19465907 | SLC24A3 | Warren, ture Genetics 2017 | 0.948 | 0.981 | 0.994 | 0.950 | 0.932 | 0.993 | 0.982 | 0.957 |
| rs6095241 | 20 | 47308798 | PREX1 | Surendran, ture Genetics 2016 | 0.924 | 0.833 | 0.875 | 0.891 | 0.912 | 0.805 | 0.909 | 0.896 |
| rs6108168 | 20 | 8626271 | PLCB1 | Warren, ture Genetics 2017 | 0.924 | 0.931 | 0.972 | 0.986 | 0.912 | 0.874 | 0.968 | 0.979 |
| rs62012628 | 15 | 79070000 | ADAMTS7 | Warren, ture Genetics 2017 | - | - | - | - | - | - | - | - |
| rs62080325 | 17 | 42060631 | PYY | Warren, ture Genetics 2017 | - | - | - | - | - | - | - | - |
| rs62104477 | 19 | 30294991 | CCNE1 | Warren, ture Genetics 2017 | 0.948 | 0.981 | 0.985 | 0.867 | 0.952 | 0.974 | 0.980 | 0.849 |

| rs6271 | 9 | 136522274 | DBH | Ehret, ture Genetics 2016 | - | - | - | - | - | - | - | - |
|--------|---|-----------|-----|---------------------------|---|---|---|---|---|---|---|---|
| rs633185 | 11 | 100593538 | FLJ32810-TMEM133 | Ehret, ture 2011 | 0.948 | 0.981 | 0.985 | 0.822 | 0.952 | 0.974 | 0.980 | 0.847 |
| rs6487543 | 12 | 26438189 | SSPN | Warren, ture Genetics 2017 | 0.998 | 0.984 | 0.997 | 0.980 | 0.997 | 0.993 | 0.982 | 0.979 |
| rs661348 | 11 | 1905292 | LSP1-TNNT3 | Johnson, AJHG 2011 | 0.924 | 0.981 | 0.985 | 0.891 | 0.898 | 0.993 | 0.968 | 0.849 |
| rs6686889 | 1 | 25030470 | chr1mb25 | Warren, ture Genetics 2017 | 0.924 | 0.833 | 0.875 | 0.980 | 0.898 | 0.805 | 0.887 | 0.979 |
| rs6712094 | 2 | 165043460 | FIGN-GRB14 | Ganesh, AJHG 2014 | 0.948 | 0.981 | 0.991 | 0.915 | 0.952 | 0.993 | 0.982 | 0.904 |
| rs6722745 | 2 | 108875244 | SULT1C3 | Liu, ture Genetics 2016 | 0.948 | 0.976 | 0.985 | 0.980 | 0.952 | 0.974 | 0.968 | 0.976 |
| rs67330701 | 11 | 69079707 | MYEOV | Warren, ture Genetics 2017 | 0.924 | 0.981 | 0.985 | 0.818 | 0.898 | 0.993 | 0.968 | 0.826 |
| rs6797587 | 3 | 48197614 | CDC25A | Simino, AJHG 2014 | 0.924 | 0.981 | 0.985 | 0.818 | 0.898 | 0.993 | 0.980 | 0.847 |
| rs6825911 | 4 | 111381638 | ENPEP | Kato, ture Genetics 2011 | 0.751 | 0.965 | 0.875 | 0.818 | 0.647 | 0.883 | 0.887 | 0.821 |
| rs687621 | 9 | 136137065 | ABO | Surendran, ture Genetics 2016 | 0.924 | 0.931 | 0.875 | 0.891 | 0.898 | 0.805 | 0.887 | 0.896 |
| rs6891344 | 5 | 123136656 | CSNK1G3 | Ehret, ture Genetics 2016 | 0.924 | 0.833 | 0.875 | 0.912 | 0.898 | 0.805 | 0.909 | 0.896 |
| rs6911827 | 6 | 22130601 | CASC15 | Warren, ture Genetics 2017 | 0.924 | 0.981 | 0.985 | 0.891 | 0.898 | 0.993 | 0.968 | 0.896 |
| rs6969780 | 7 | 27159136 | HOXA3 | Liu, ture Genetics 2016 | 0.948 | 0.981 | 0.994 | 0.980 | 0.952 | 0.993 | 0.982 | 0.975 |
| rs709209 | 1 | 6278414 | RNF207 | Surendran, ture Genetics 2016 | 0.948 | 0.987 | 0.997 | 0.891 | 0.952 | 1.000 | 0.982 | 0.896 |
| rs7103648 | 11 | 47461783 | RAPSN, PSMC3, SLC39A13 | Ehret, ture Genetics 2016 | 0.924 | 0.976 | 0.972 | 0.818 | 0.898 | 0.974 | 0.968 | 0.847 |
| rs7126805 | 11 | 828916 | CRACR2B | Warren, ture Genetics 2017 | - | - | - | - | - | - | - | - |
| rs7129220 | 11 | 10350538 | ADM | Ehret, ture 2011 | - | - | - | - | - | - | - | - |
| rs7178615 | 15 | 66869072 | RP11-321F6.1 | Warren, ture Genetics 2017 | 0.924 | 0.981 | 0.994 | 0.650 | 0.900 | 0.974 | 0.982 | 0.771 |
| rs7236548 | 18 | 43097750 | SLC14A2 | Warren, ture Genetics 2017 | 0.924 | 0.981 | 0.994 | 0.818 | 0.898 | 0.993 | 0.982 | 0.847 |
| rs7248104 | 19 | 7224431 | INSR | Liu, ture Genetics 2016 | 0.907 | 0.965 | 0.875 | 0.818 | 0.898 | 0.922 | 0.889 | 0.826 |
| rs72765298 | 9 | 127900996 | SCAI | Warren, ture Genetics 2017 | - | - | - | - | - | - | - | - |
| rs7297416 | 12 | 54443090 | HOXC4 | Tragante, AJHG 2014 | - | - | - | - | - | - | - | - |
| rs7302981 | 12 | 50537815 | CERS5 | Surendran, ture Genetics 2016 | - | - | - | - | - | - | - | - |
| rs740406 | 19 | 2232221 | AMH | Kato, ture Genetics 2015 | 0.998 | 0.981 | 0.997 | 0.818 | 0.997 | 0.993 | 0.982 | 0.847 |
| rs7406910 | 17 | 46688256 | HOXB7 | Surendran, ture Genetics 2016 | 0.732 | 0.872 | 0.873 | 0.818 | 0.552 | 0.805 | 0.887 | 0.821 |
| rs740698 | 17 | 60767151 | MRC2 | Warren, ture Genetics 2017 | 0.948 | 0.981 | 0.997 | 0.818 | 0.932 | 0.993 | 0.982 | 0.847 |
| rs74181299 | 2 | 65283972 | CEP68 | Warren, ture Genetics 2017 | 0.948 | 0.984 | 0.994 | 0.912 | 0.952 | 0.993 | 0.982 | 0.896 |
| rs743757 | 3 | 50476378 | CAC2D2 | Warren, ture Genetics 2017 | 0.924 | 0.981 | 0.994 | 0.818 | 0.912 | 0.993 | 0.982 | 0.847 |
| rs745821 | 18 | 48142854 | MAPK4 | Warren, ture Genetics 2017 | 0.927 | 0.976 | 0.985 | 0.891 | 0.912 | 0.974 | 0.968 | 0.849 |
| rs7515635 | 1 | 42408070 | HIVEP3 | Ehret, ture Genetics 2016 | 0.924 | 0.833 | 0.873 | 0.980 | 0.898 | 0.805 | 0.887 | 0.979 |
| rs751984 | 11 | 61278246 | LRRC10B | Kato, ture Genetics 2015 | 0.751 | 0.872 | 0.873 | 0.818 | 0.898 | 0.805 | 0.887 | 0.847 |
| rs7562 | 2 | 28635740 | FOSL2 | Warren, ture Genetics 2017 | 0.948 | 0.976 | 0.985 | 0.912 | 0.932 | 0.974 | 0.968 | 0.896 |
| rs757081 | 11 | 17351683 | NUCB2 | Tragante, AJHG 2014 | 0.924 | 0.981 | 0.985 | 0.903 | 0.898 | 0.974 | 0.968 | 0.896 |
| rs7592578 | 2 | 191439591 | TMEM194B | Warren, ture Genetics 2017 | 0.998 | 0.981 | 0.997 | 0.980 | 0.997 | 0.993 | 0.982 | 0.979 |
| rs76206723 | 7 | 40447971 | SUGCT | Warren, ture Genetics 2017 | 0.948 | 0.984 | 0.994 | 0.891 | 0.952 | 0.993 | 0.982 | 0.896 |

| rs76326501 | 2 | 43167878 | AC016735.1 | Warren, ture Genetics 2017 | - | - | - | - | - | - | - | - |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs76452347 | 9 | 35906471 | HRCT1 | Liu, ture Genetics 2016 | - | - | - | - | - | - | - | - |
| rs76987554 | 6 | 134080855 | TARID/TCF21 | Liang, PLoS Genetics 2017 | - | - | - | - | - | - | - | - |
| rs78648104 | 6 | 50683009 | TFAP2D | Warren, PLoS Genetics 2017 | 0.924 | 0.976 | 0.985 | 0.891 | 0.898 | 0.974 | 0.968 | 0.896 |
| rs79089478 | 17 | 40317241 | KCNH4-HSD17B1 | Warren, ture Genetics 2017 | - | - | - | - | - | - | - | - |
| rs79146658 | 2 | 179786068 | CCDC141 | Warren, ture Genetics 2017 | - | - | - | - | - | - | - | - |
| rs8016306 | 14 | 63928546 | PPP2R5E | Warren, ture Genetics 2017 | 0.907 | 0.973 | 0.875 | 0.818 | 0.898 | 0.922 | 0.887 | 0.826 |
| rs8059962 | 16 | 81574197 | CMIP | Warren, ture Genetics 2017 | 0.948 | 0.981 | 0.994 | 0.945 | 0.952 | 0.993 | 0.982 | 0.943 |
| rs8068318 | 17 | 59483766 | TBX2 | Surendran, ture Genetics 2016 | 0.948 | 0.872 | 0.972 | 0.818 | 0.912 | 0.805 | 0.968 | 0.821 |
| rs8258 | 11 | 117283676 | CEP164 | Warren, ture Genetics 2017 | 0.927 | 0.981 | 0.994 | 0.818 | 0.932 | 0.993 | 0.982 | 0.847 |
| rs867186 | 20 | 33764554 | PROCR | Surendran, ture Genetics 2016 | 0.998 | 0.976 | 0.985 | 0.867 | 0.997 | 0.974 | 0.982 | 0.849 |
| rs871606 | 4 | 54799245 | CHIC2 | Wain, ture Genetics 2011 | 0.924 | 0.976 | 0.972 | 0.891 | 0.898 | 0.974 | 0.968 | 0.896 |
| rs880315 | 1 | 10796866 | CASZ1 | Takeuchi, Circulation 2010 | - | - | - | - | - | - | - | - |
| rs891511 | 7 | 150704843 | NOS3 | Liu, ture Genetics 2016 | - | - | - | - | - | - | - | - |
| rs894344 | 8 | 135612745 | ZFAT | Warren, ture Genetics 2017 | 0.964 | 0.981 | 0.994 | 0.980 | 0.997 | 0.994 | 0.982 | 0.979 |
| rs900145 | 11 | 13293905 | ARNTL | Liu, ture Genetics 2016 | 0.907 | 0.833 | 0.873 | 0.927 | 0.898 | 0.805 | 0.887 | 0.906 |
| rs918466 | 3 | 64710253 | ADAMTS9 | Ehret, ture Genetics 2016 | 0.924 | 0.981 | 0.994 | 0.818 | 0.912 | 0.993 | 0.982 | 0.847 |
| rs9306160 | 21 | 45107562 | RRP1B | Surendran, ture Genetics 2016 | 0.924 | 0.981 | 0.985 | 0.912 | 0.912 | 0.993 | 0.968 | 0.904 |
| rs9323988 | 14 | 98587630 | RP11-61O1.1 | Warren, ture Genetics 2017 | 0.948 | 0.981 | 0.994 | 0.980 | 0.952 | 0.993 | 0.982 | 0.976 |
| rs932764 | 10 | 95895940 | PLCE1 | Ehret, ture 2011 | 0.924 | 0.918 | 0.875 | 0.897 | 0.898 | 0.805 | 0.889 | 0.901 |
| rs9349379 | 6 | 12903957 | PHACTR1 | Surendran, ture Genetics 2016 | - | - | - | - | - | - | - | - |
| rs9372498 | 6 | 118572486 | SLC35F1 | Warren, ture Genetics 2017 | 0.924 | 0.976 | 0.985 | 0.650 | 0.898 | 0.974 | 0.980 | 0.771 |
| rs953492 | 1 | 243471192 | SDCCAG8 | Warren, ture Genetics 2017 | 0.998 | 0.981 | 0.994 | 0.867 | 0.997 | 0.993 | 0.982 | 0.849 |
| rs9549328 | 13 | 113636156 | MCF2L | Warren, ture Genetics 2017 | 0.924 | 0.981 | 0.985 | 0.818 | 0.898 | 0.993 | 0.968 | 0.821 |
| rs9687065 | 5 | 148391140 | ABLIM3,SH3TC2 | Kato, ture Genetics 2015 | 0.924 | 0.976 | 0.972 | 0.891 | 0.898 | 0.974 | 0.968 | 0.896 |
| rs9827472 | 3 | 56726646 | FAM208A | Warren, ture Genetics 2017 | 0.985 | 0.833 | 0.972 | 0.818 | 0.997 | 0.805 | 0.968 | 0.821 |
| rs9859176 | 3 | 134000025 | RYK | Warren, ture Genetics 2017 | 0.998 | 0.981 | 0.997 | 0.891 | 0.997 | 0.993 | 0.982 | 0.896 |
| rs9888615 | 14 | 53377540 | FERMT2 | Warren, ture Genetics 2017 | 0.924 | 0.965 | 0.960 | 0.867 | 0.898 | 0.805 | 0.887 | 0.849 |

**Figure 9** QQ plots of meta-analyses using the 2DF joint test in European ancestry in Aim 3

Blue line represents the results using all participants and red line represents the results from participants without diuretics

**European Americans**
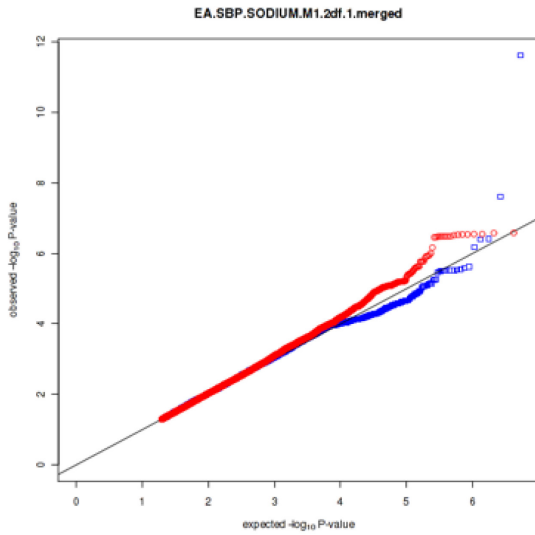


SBP
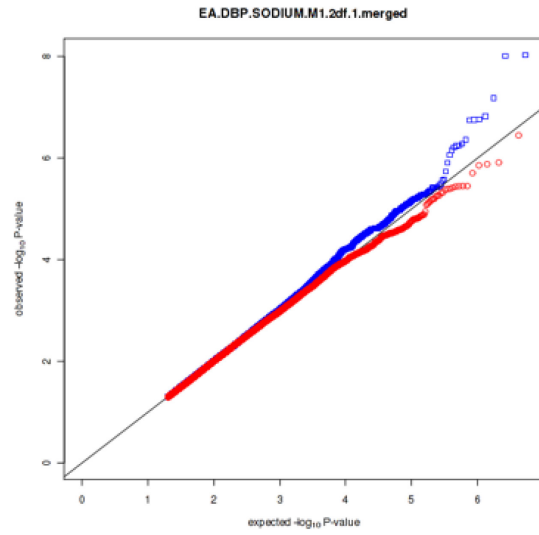
DBP
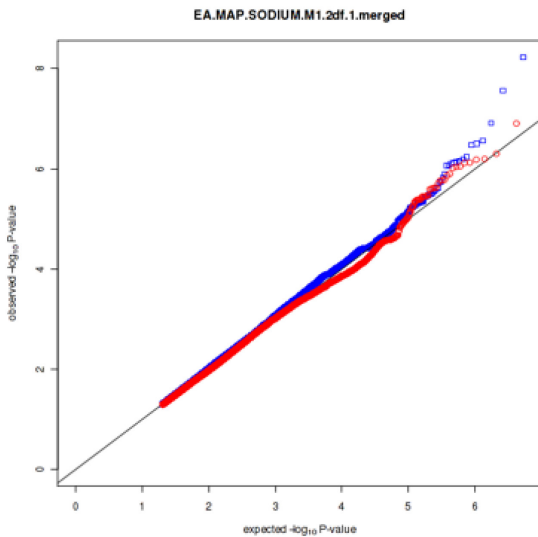
MAP
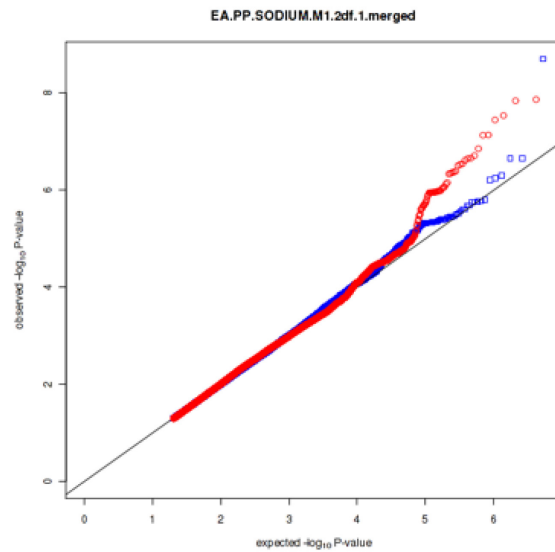
PP

**African Americans**
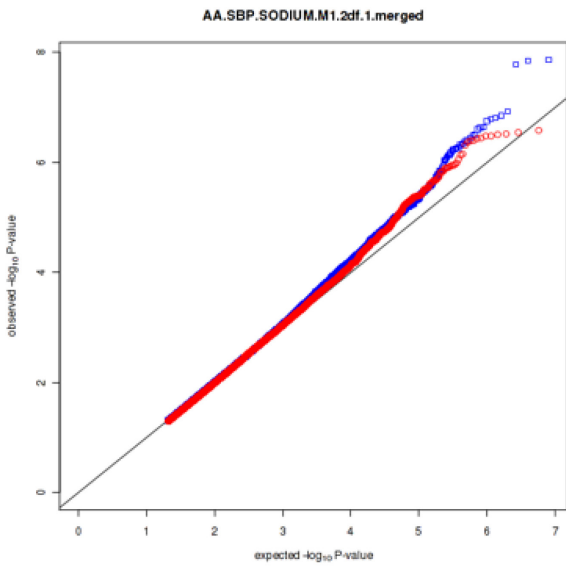


SBP
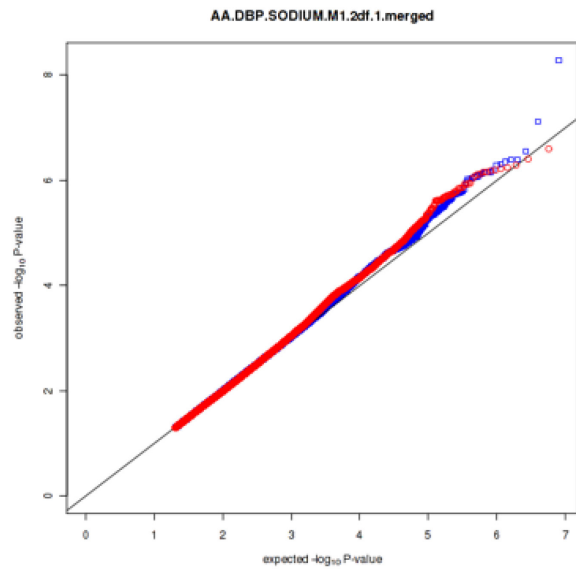
DBP
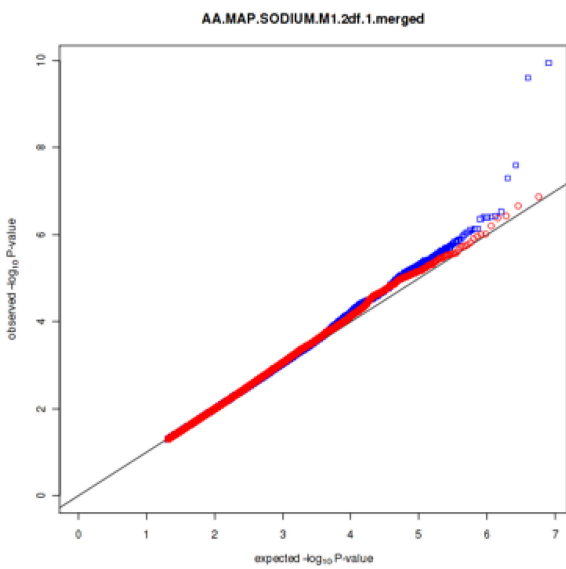


MAP
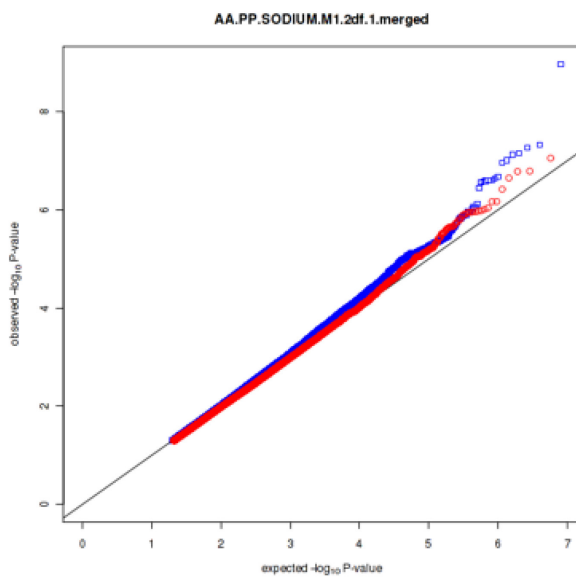
PP

**Asians (Chinese)**



SBP
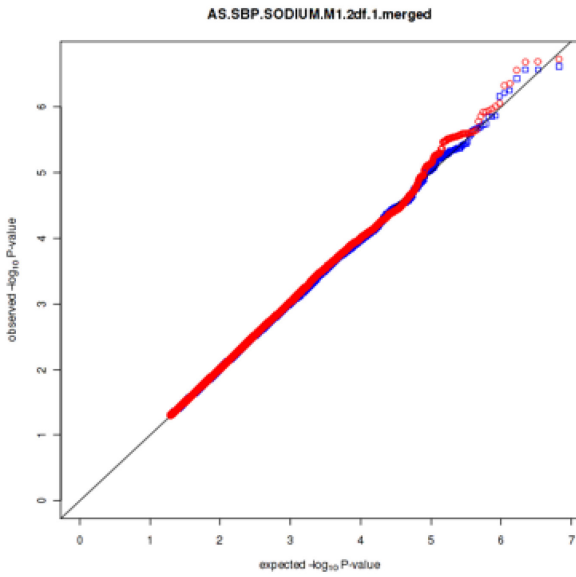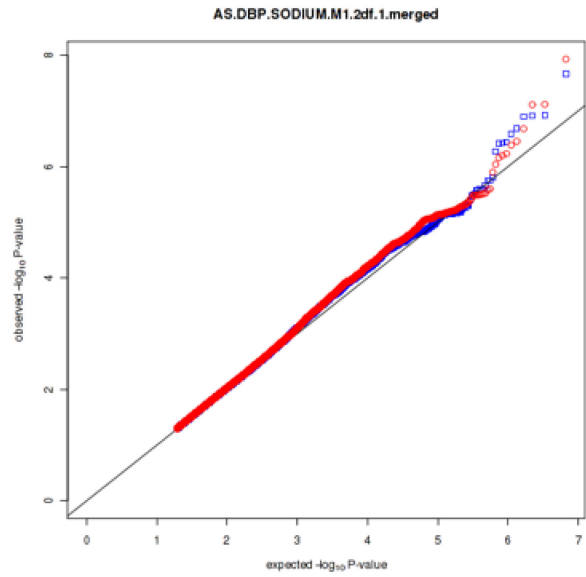


DBP
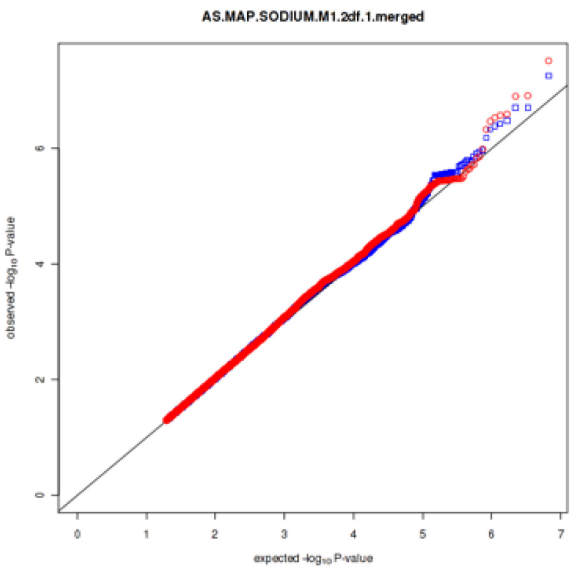


MAP
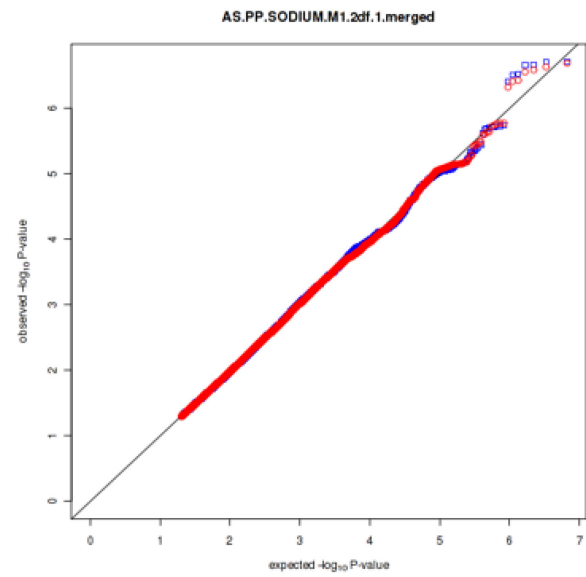


PP

**Figure 10** Miami plots for SBP, DBP, MAP, and PP using the 2 DF joint test in European ancestry in Aim 3

Above Manhattan plots represent the results using all participants and below Manhattan plots represent the results from participants without diuretics

**SBP**
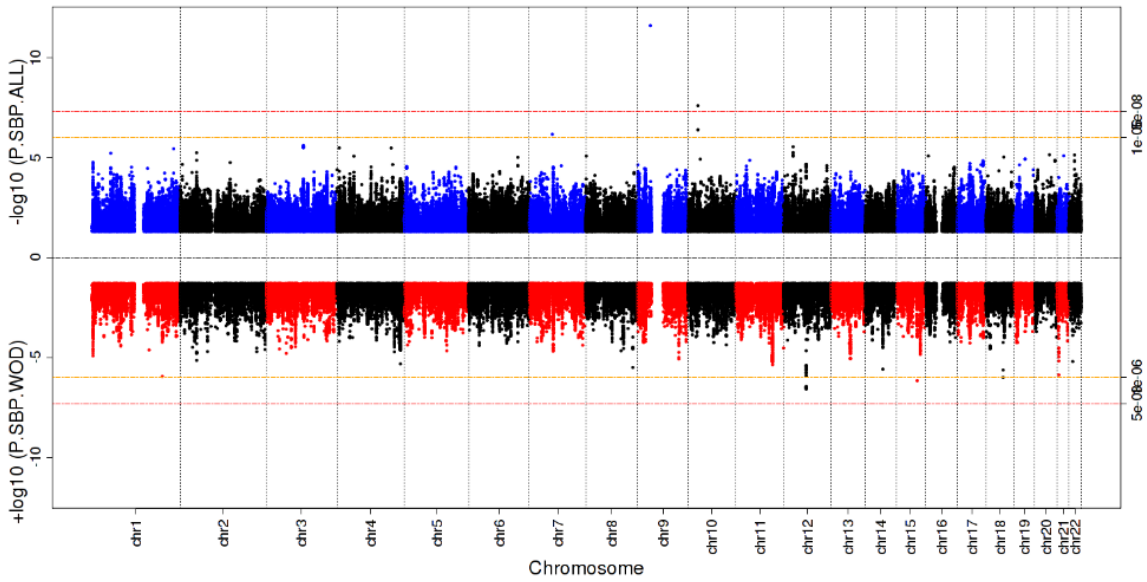


**DBP**
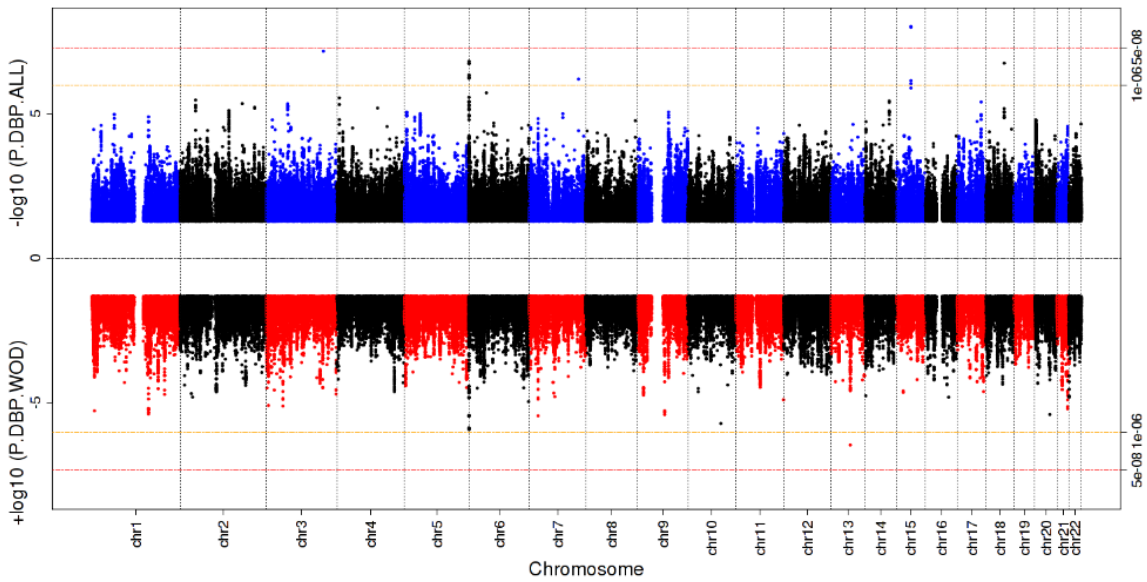
**MAP**
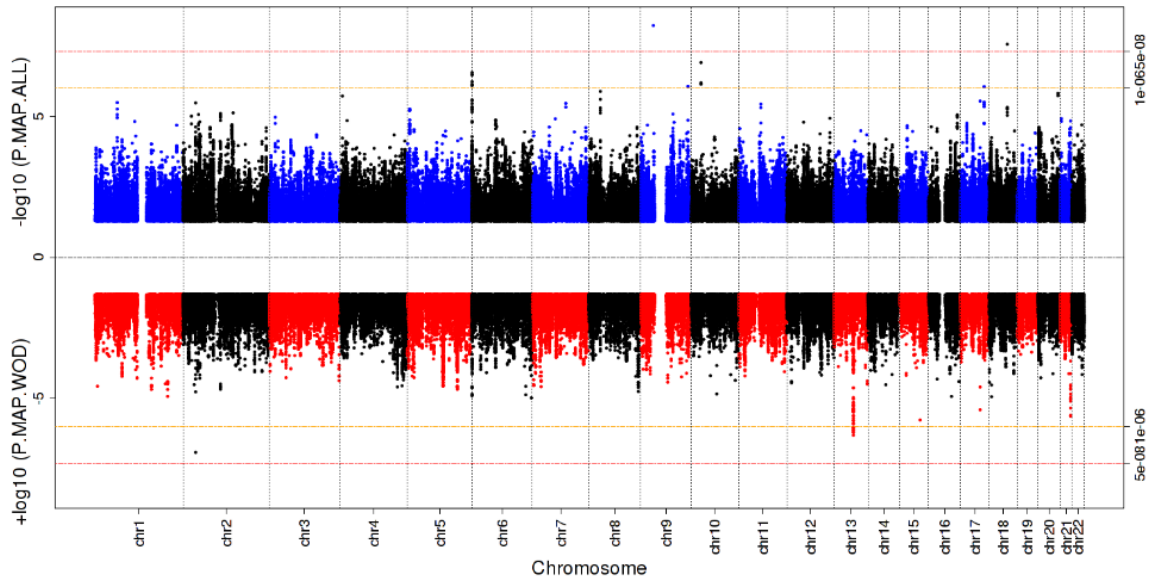


**PP**
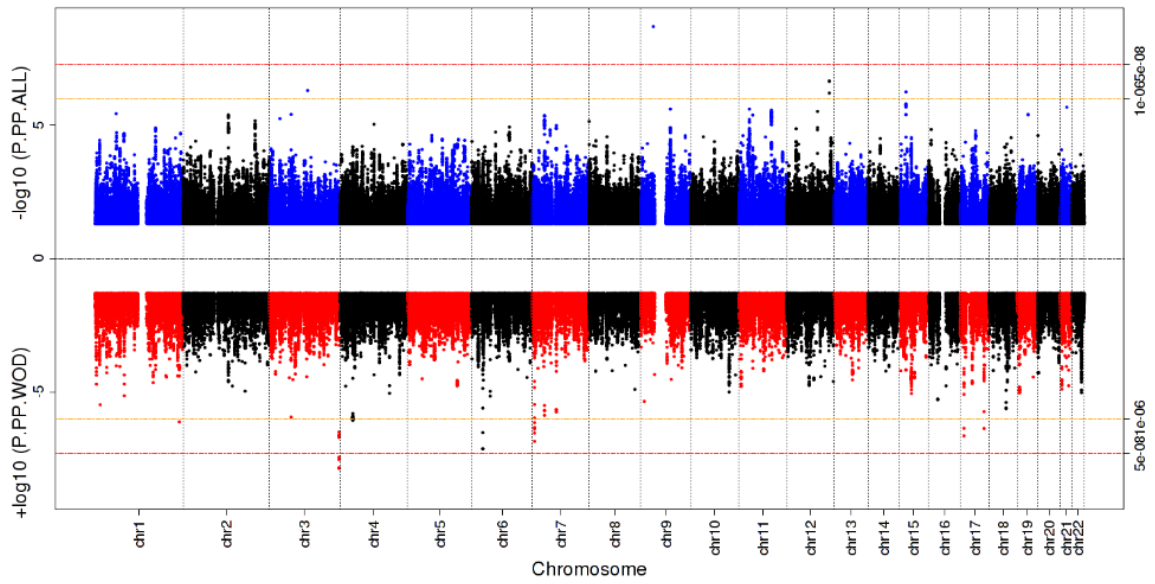
**Figure 11** Miami plots for SBP, DBP, MAP, and PP using the 2 DF joint test in African ancestry in Aim 3

Above Manhattan plots represent the results using all participants and below Manhattan plots represent the results from participants without diuretics

**SBP**



**DBP**

**MAP**



**PP**



119
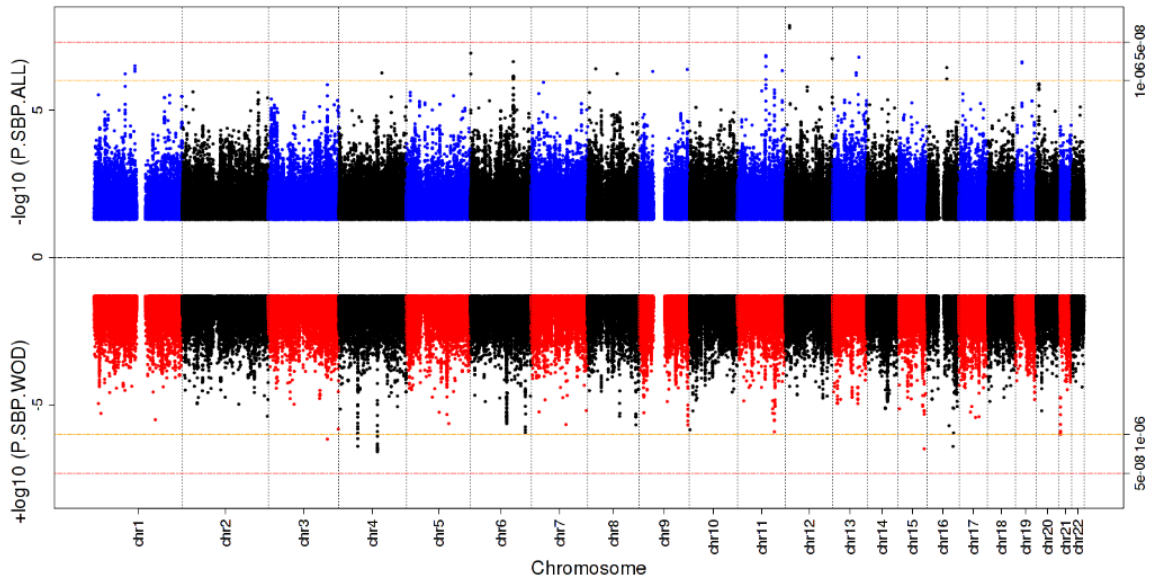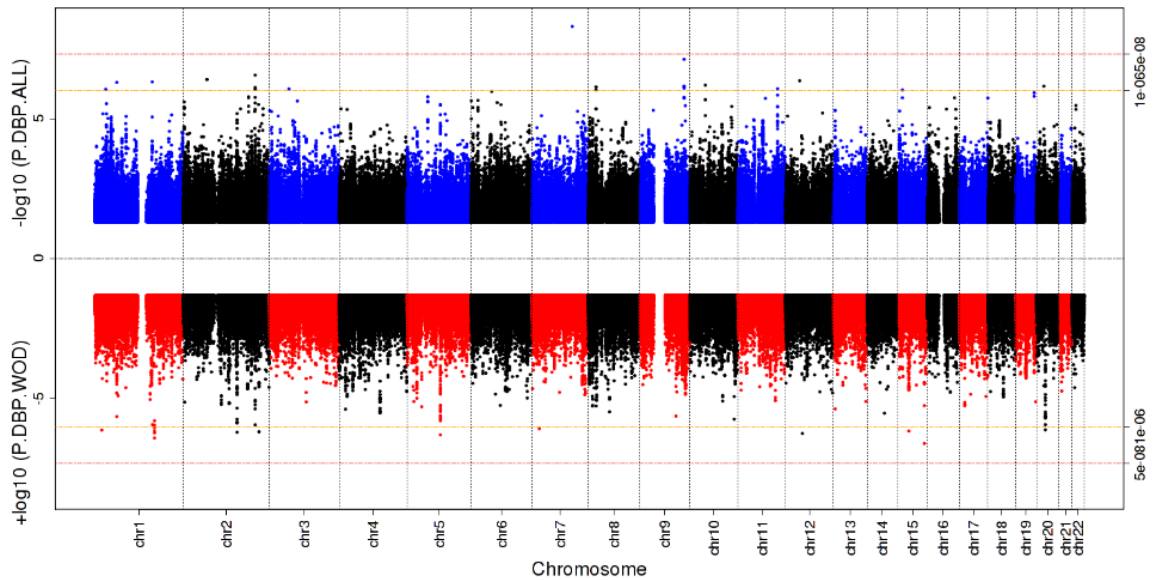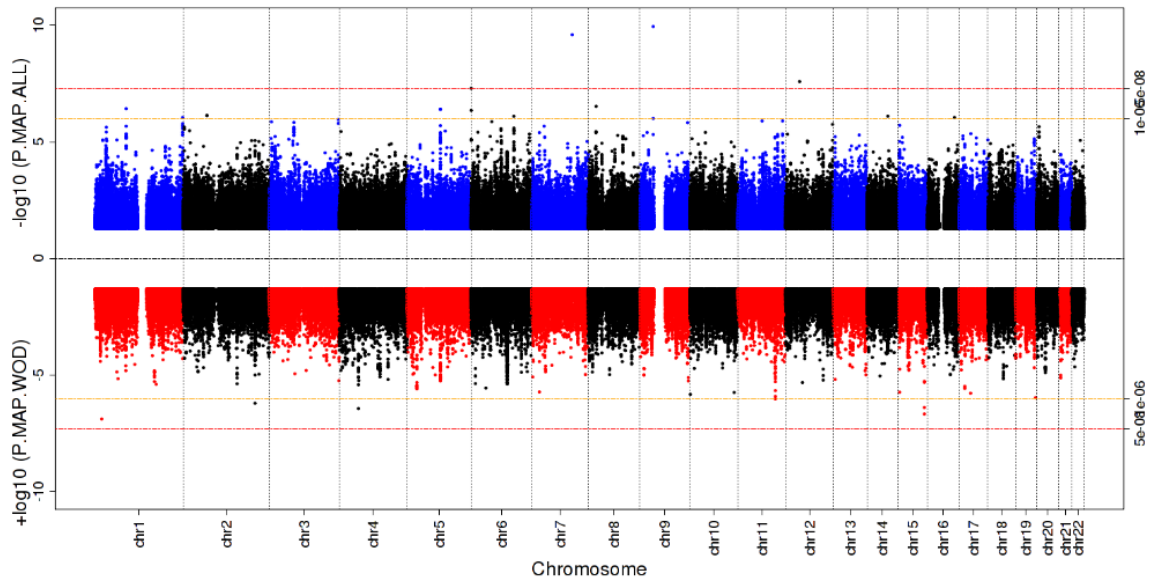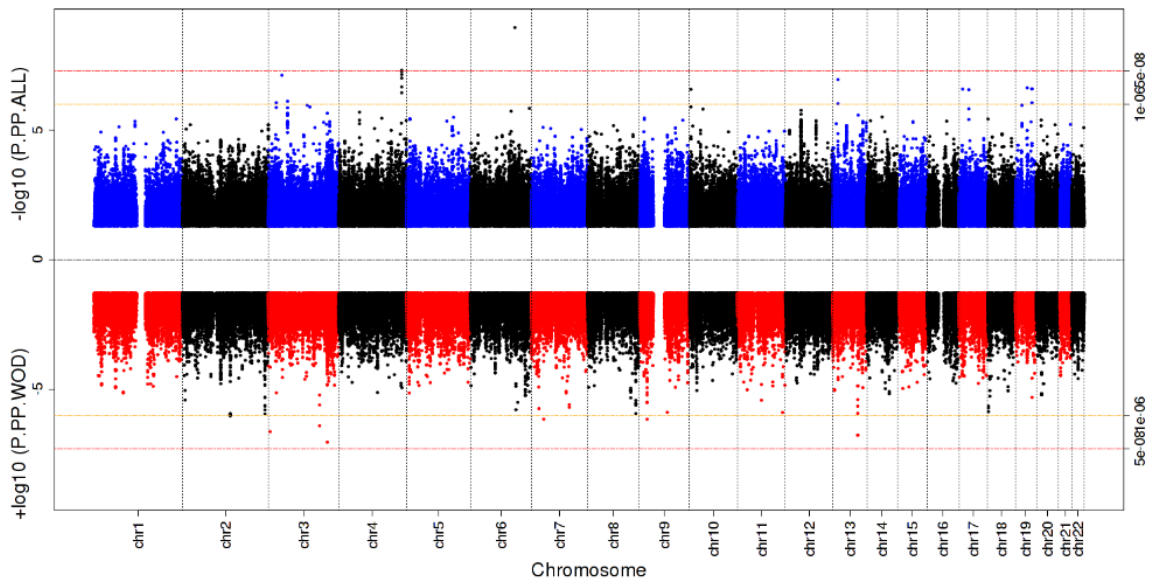
**Figure 12** Miami plots for SBP, DBP, MAP, and PP using the 2 DF joint test in Asians in Aim 3

Above Manhattan plots represent the results using all participants and below Manhattan plots represent the results from participants without diuretics

**SBP**



**DBP**

**MAP**



**PP**



121
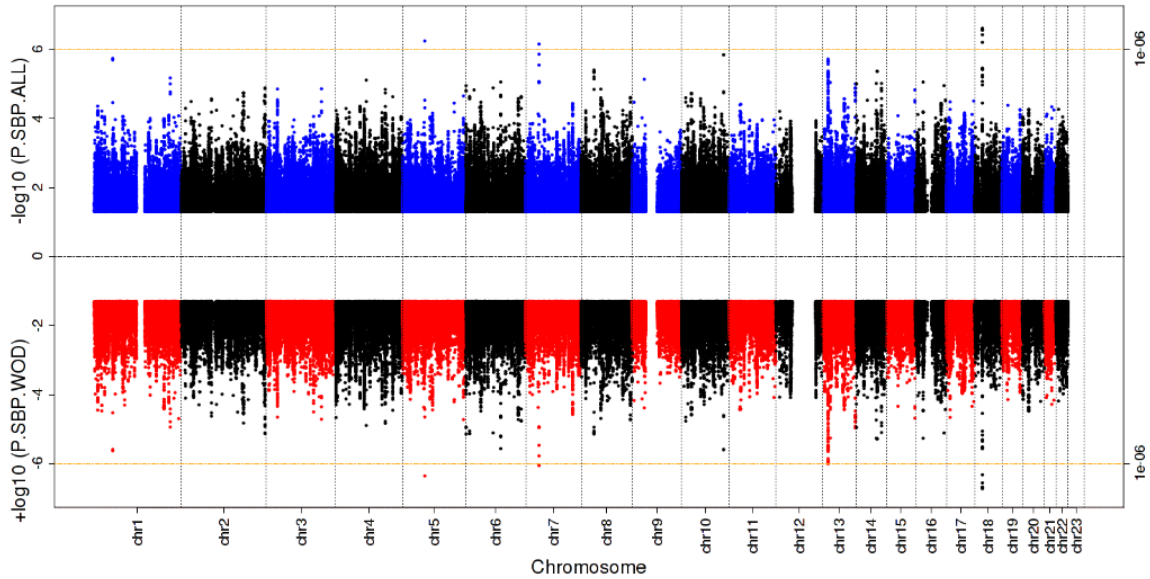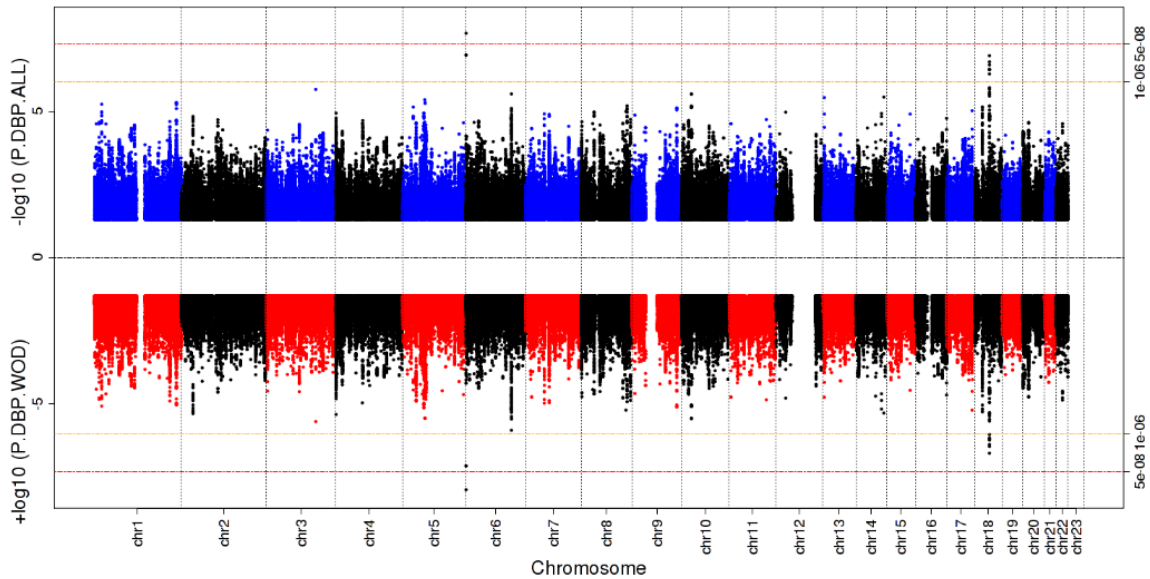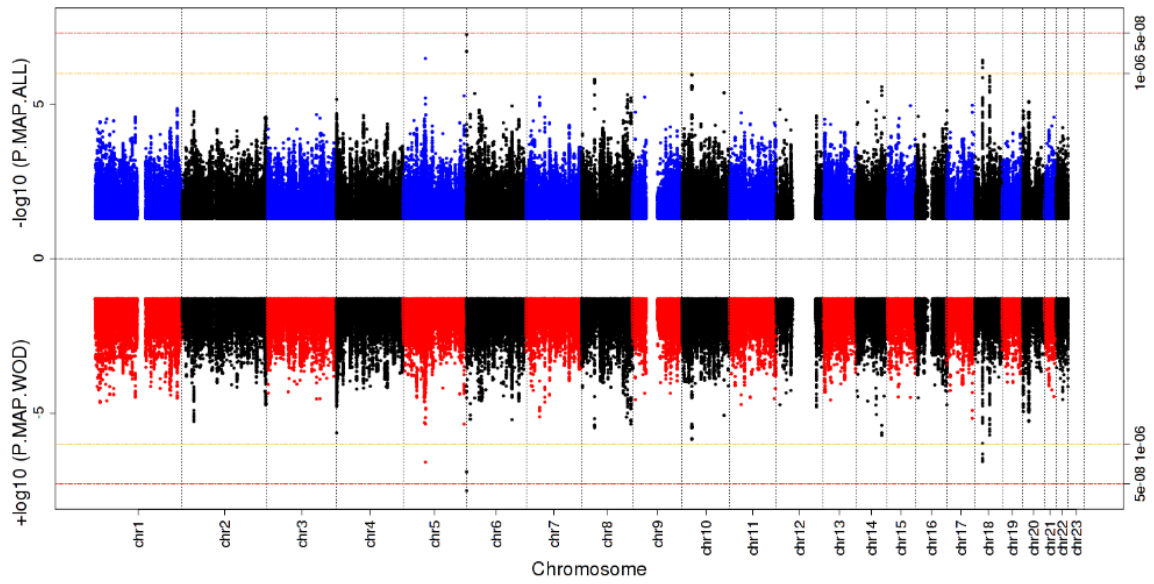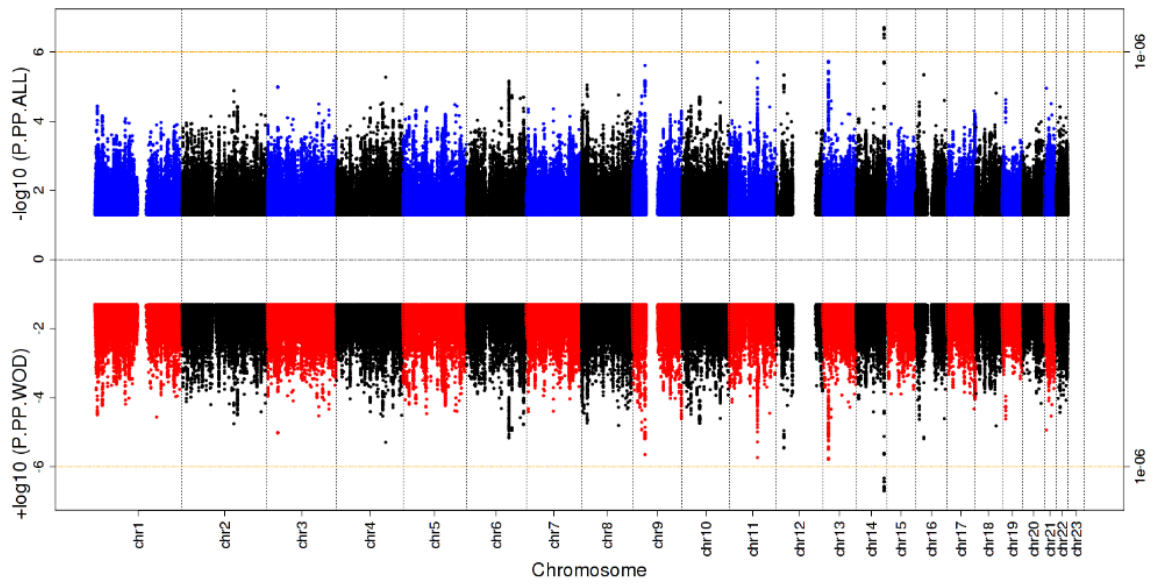
**Figure 13** Regional plots for significant loci using LocusZoom in Aim 3

EA: European American; AA: African Americans; AS: Asians (Chinese)
ALL: All Participants; WOD: Participants without diuretics
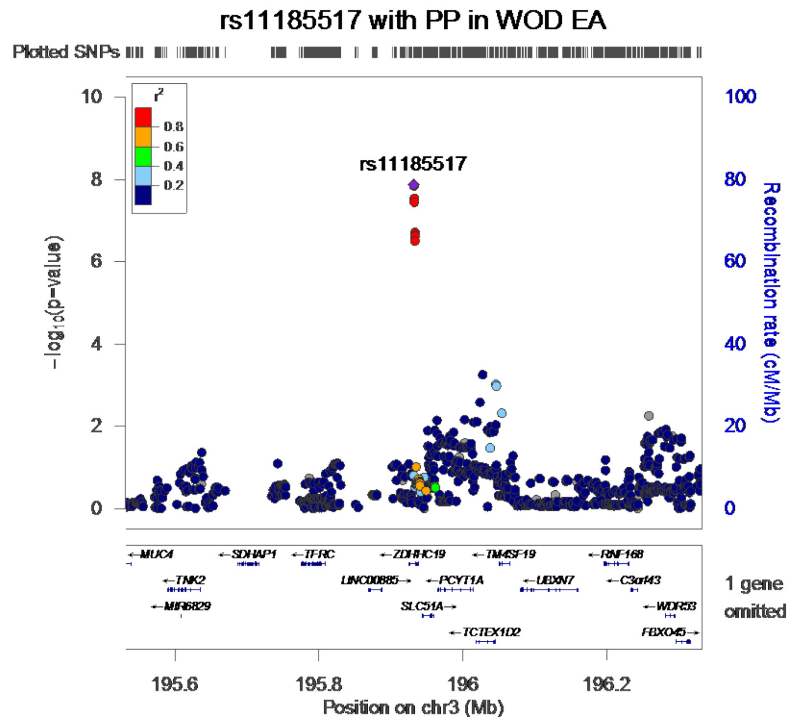


Locus 1 with PP in WOD EA
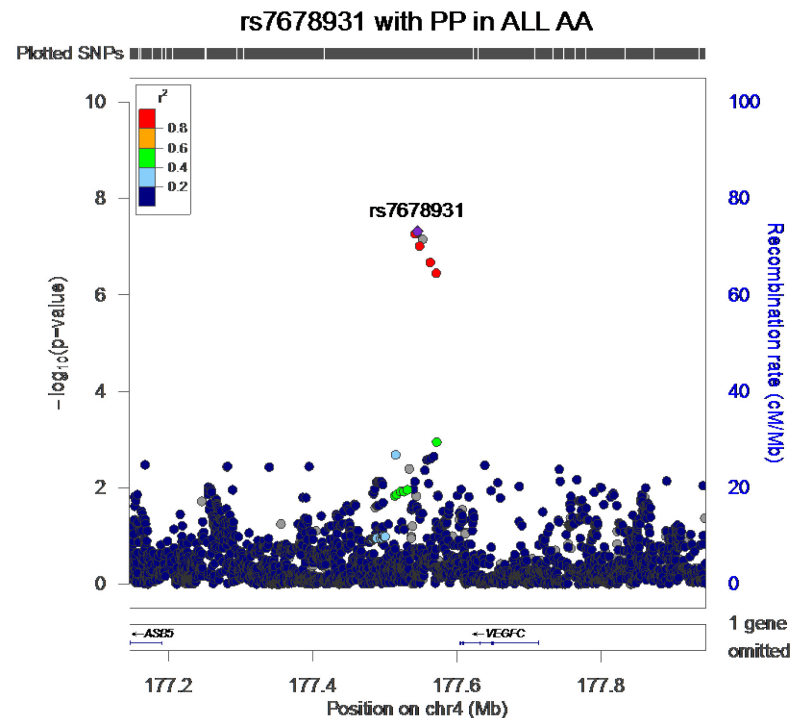


Locus 2 with PP in ALL AA
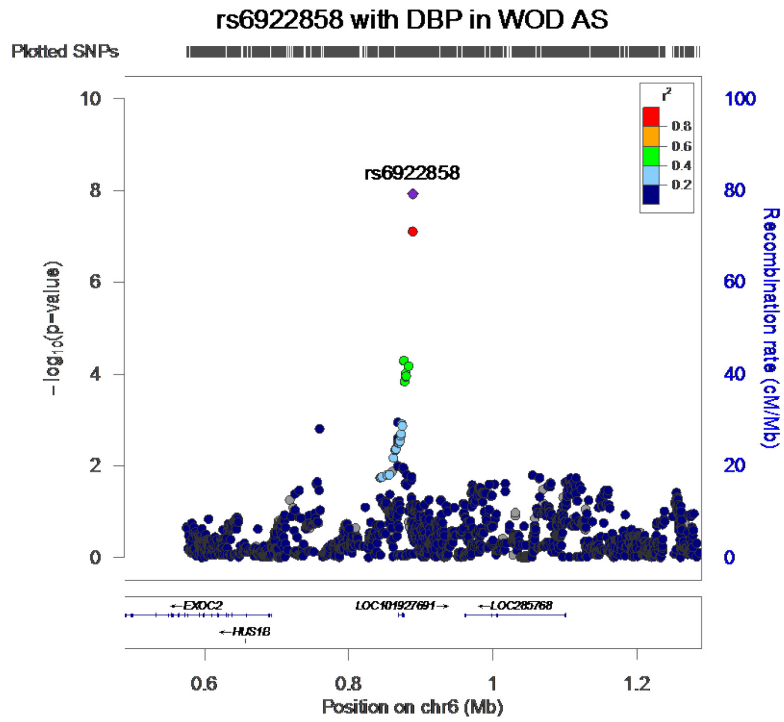
Locus 3 with DBP in WOD AS
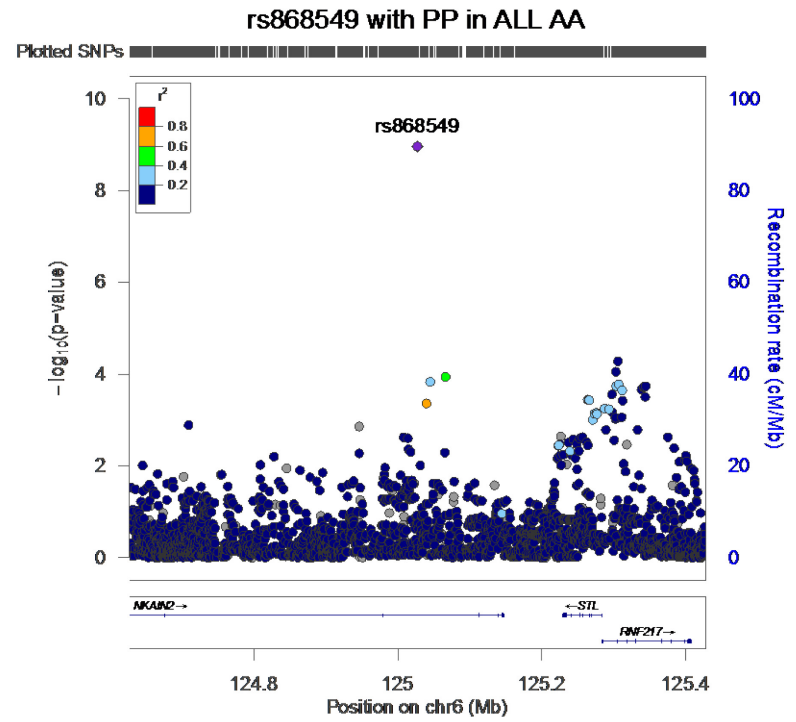
Locus 4 with PP in ALL AA
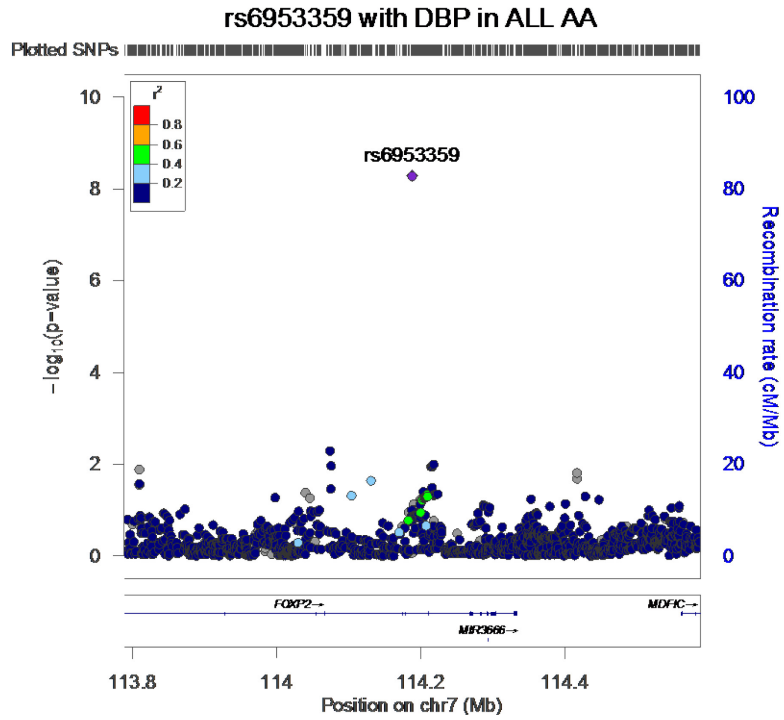
Locus 5 with DBP in ALL AA
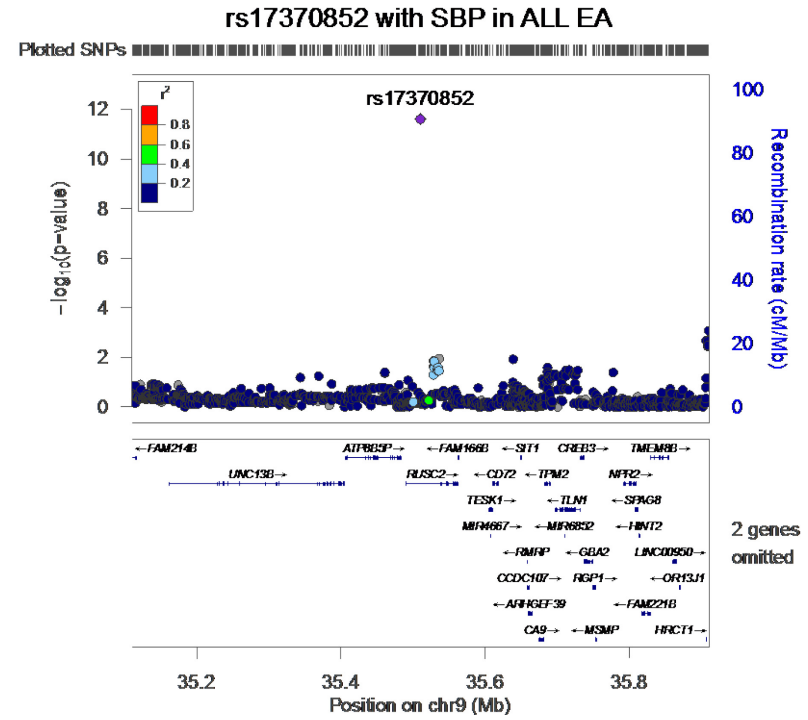
Locus 6 with SBP in ALL EA
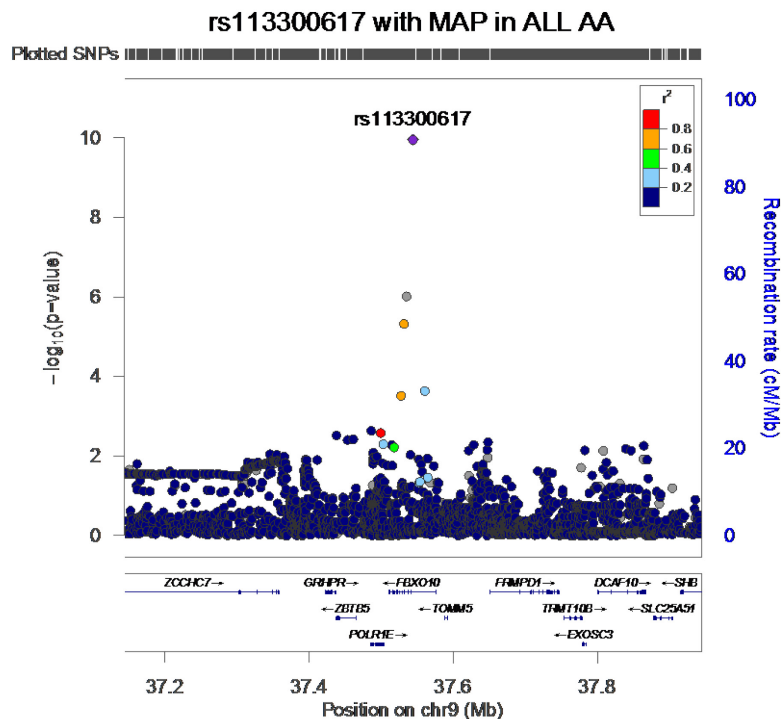
Locus 7 with MAP in ALL AA
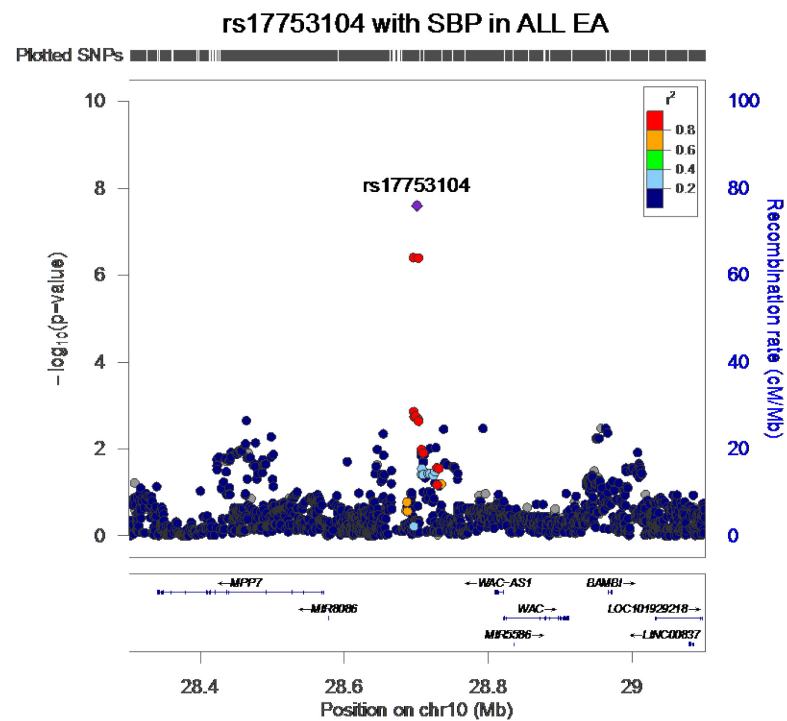
Locus 8 with SBP in ALL EA
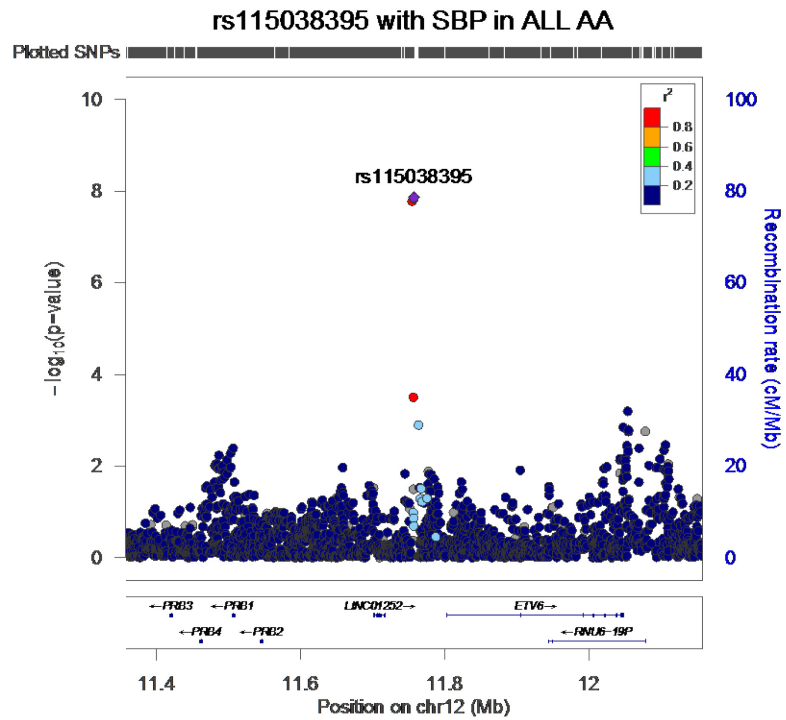
Locus 9 with SBP in ALL AA
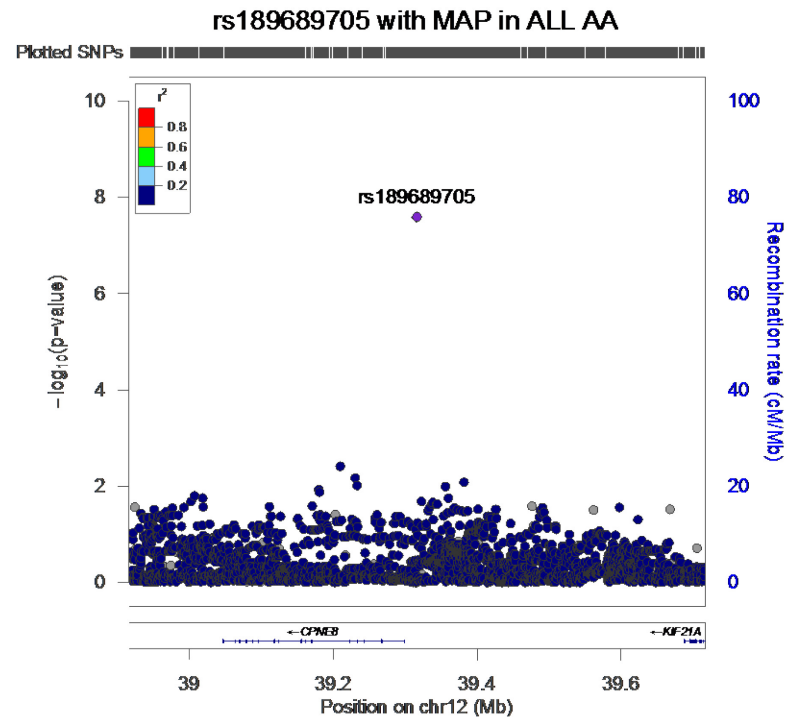
Locus 10 with MAP in ALL AA
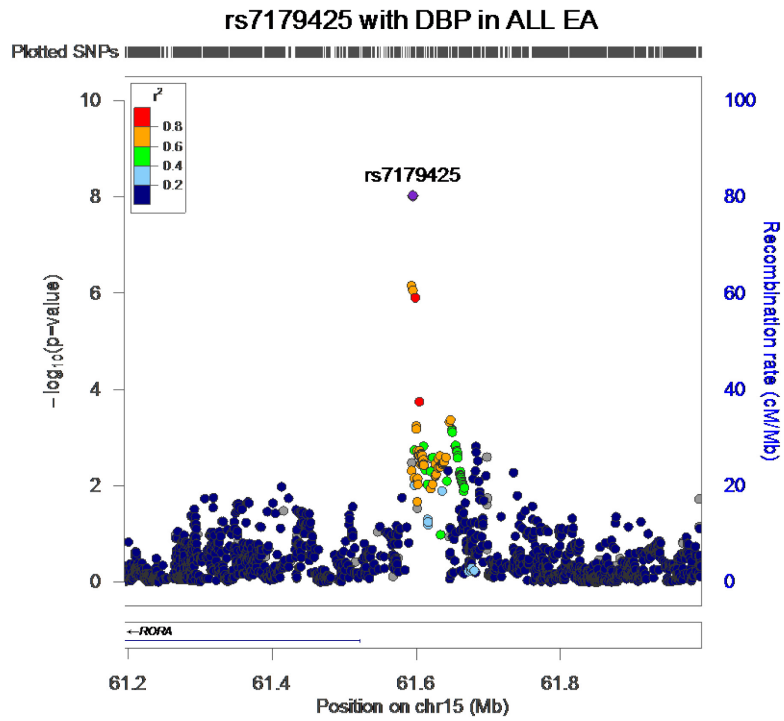
Locus 11 with DBP in ALL EA
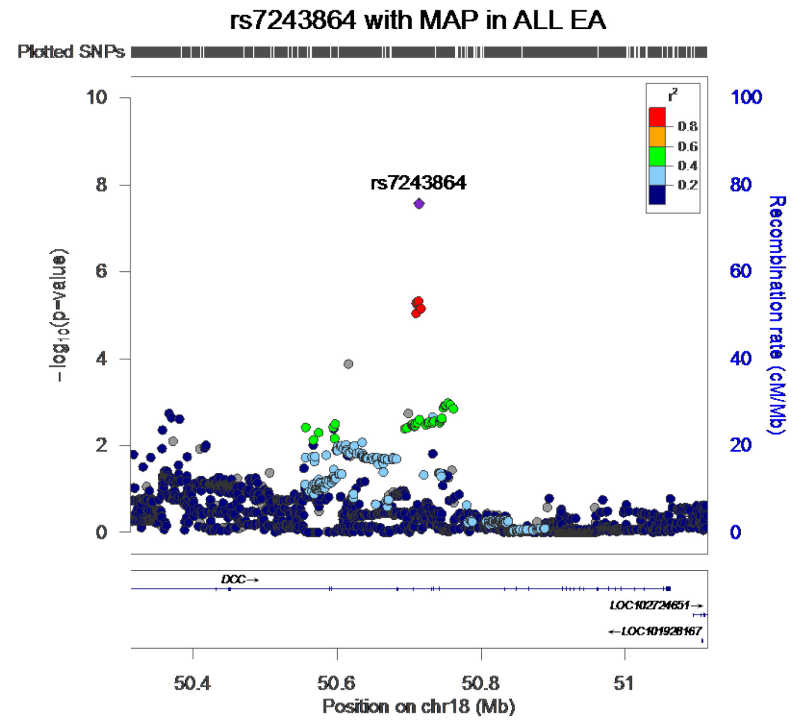


Locus 12 with MAP in ALL EA

## CHAPTER V: Conclusion

### 5.1 Review of main findings

Blood pressure has long been known to be associated with high sodium intake, low potassium intake, and a high sodium-potassium ratio. In this dissertation, the rich combination of high-quality measurements of sodium and potassium intake and genotype data from multiethnic cohort studies of participants from European, African, and Asian ancestries have enabled the identification of genomic regions and genetic variants associated with sodium and potassium intake. To examine the association and interaction among sodium intake, potassium intake, genetics, and blood pressure, this dissertation has used a range of approaches: single-variant and gene-based approaches; effect modification by demographic factors (age, sex, and education); and gene-by-sodium interactions on blood pressure traits.

In Aim 1, we conducted the largest genome-wide association investigation of 24-hour urinary sodium excretion, 24-hour urinary potassium excretion, and sodium-to-potassium ratio with and without adjustment for BMI and height using five European ancestry cohorts (N=7,363), followed by replication in an African (N=1,246) ancestry and an Asian cohort (N=2,475). A total of 52, 75, and 27 SNPs were significant ($P < 5 \times 10^{-8}$) or suggestive SNPs ($P < 5 \times 10^{-6}$) with 24-hour sodium excretion, 24-hour potassium excretion, and their ratio from the meta-analysis in European ancestry populations, respectively; three of those SNPs were replicated either in African ancestry or Asian populations (P<0.05). The genes near identified SNPs from the 24-hour sodium excretion GWAS include the Fc fragment of IgG receptor genes

(*FCGR2B-FCGR2C- FCGR3A*) that are associated with the human immune system [75] and genes associated with the activity of GTPases (*GTPBP1* on chromosome 22 and *CDC42SE1* on chromosome 1). GTPases have been suggestively associated with blood pressure regulation, hypertension, kidney function, and other traits that are related to the cardiovascular system and disease [78] [79]. From the 24-hour potassium excretion GWAS, several SNPs were found near genes *DLEU2, CUL3*, and *ABO,* which are suggestively associated with the regulation of blood pressure and CVD through the renin-angiotensin system or resistance to aldosterone [83] [85] [86]. From the sodium-to-potassium ratio GWAS, we found SNPs near *KIRREL3,* which has an important role involving renal filtration in the kidney [91].

In Aim 2, we employed state-of-the-art gene-based approaches to confirm the associations from Aim 1, using SKAT with both common and rare genetic variants in two European cohorts (GENOA and FHS). In GENOA, we found a total of 6 gene regions that had P-value < 0.05, and 3 gene regions (24-hour sodium excretion*: SETD7* and *ASH1L*; 24-hour potassium excretion: *RP11-431M7.2*) were significant after FDR correction (FDR adjusted P value < 0.1). In FHS, 3 out of 5 gene regions (24-hour potassium excretion: *BRO3BP* and *LINC00672*; sodium-to-potassium ratio: *RP11-433C9.2*) had FDR adjusted P-value less than 0.1. We also evaluated the interaction between genes and three demographic variables (age ≥ 65 years, sex, and college education completion) on 24-hour urinary sodium excretion, 24-hour urinary potassium excretion, and sodium-to-potassium ratio using iSKAT, and found five interactions in *TAPSAR1, CTC-228N24, RP11-433C9.2,* and *RP11-483H11.1* that had an FDR adjusted P value less than 0.1 in GENOA.

In Aim 3, the meta-analysis of a genome-wide gene-by-sodium interaction study on blood pressure measures (SBP, DBP, MAP, and PP) was conducted using 6 cohorts comprising

more than 6,000 participants of European, African, and Asian ancestry, and identified 12 independent genome-wide significant genetic loci ($P < 5 \times 10^{-8}$). The genes near the top signal include *NKAIN2* on chromosome 6, which is associated with the regulation of sodium and potassium ion transporting within or between cells [127]. We identified genes near significant SNPs that included *ZDHHC19,* which encodes a protein that may interact with other proteins including endothelial nitric oxide synthase (eNOS), which is important for cardiovascular homeostasis [128] as well as *RUSC2,* which is associated with the activity of GTPases and regulation of blood pressure [80, 131] [132].

## 5.2 Significance and implications

This dissertation has used high-quality measurement in multiethnic studies to improve the understanding of 1) the role of genomic regions and genetic variations in sodium intake, potassium intake, and sodium-to-potassium ratio , 2) the impact of interactions between genetic factors and demographic factors (age, sex, and education level) on sodium and potassium intake, and 3) the effect of gene-by-sodium intake interaction on blood pressure traits using both traditional and state-of-the-art methods in genetic epidemiology.

After the completion of the 1000 Genomes Project, advances in genomics and other 'omics' technologies have accelerated the focus on developing personalized and precision health approaches where individual genetics and other sources of variability in disease treatment and prevention are considered [138]. While personalized and precision medicine mostly focuses on prevention and treatment of an individual's disease, there has also been a significant growth in the interest of precision public health, which extends the personalized medicine approach into a public health context [139]. For example, Evangelatos et al. claim that "directing preventive

efforts to populations most at risk for certain diseases could be more effective if guided by stratification based on genetic information" [139]. While personalized and precision medicine could help to heal people who are already sick and have disease, precision public health may help to prevent disease by targeting subsets of the population based on their traditional risk factors as well as genetic or omic markers. Khoury et al. outlines the idea that precision public health is simply ensuring that the right intervention is made available to the right population at the right time [140]. However, genomic information does not add significantly more information to risk prediction above and beyond traditional epidemiologic risk factors because the identified genetic markers on disease are acting through those risk factors or only have small main effects on disease [141]. More studies are needed to provide a sufficiently extensive and robust evidence for prevention recommendations using individual genetic profiles for any of the chronic diseases.

In this context, the initial discoveries from Aim 1 may help shed an initial light on the importance of the genetic architecture of sodium and potassium intake. In addition, in Aim 2, we identified preliminary evidence of effect modification of those genetic effects on sodium and/or potassium intake by traditional epidemiological factors such as age, sex, and education. This finding raises the important long-range question about how to tailor messaging about dietary behaviors to be more precise in order to have the desired health benefits for different, already known, subsets of the population with different dietary intakes. This same issue is important for our findings in Aim 3, which suggest that genetic variations may modify the relationship between sodium intake and blood pressure. If replication supports this finding, it could have a major effect on stratifying treatment and prevention recommendations for millions of adults who have high blood pressure or hypertension, since it would indicate which subgroups of the population had an increased risk of elevated blood pressure through sodium consumption.

**5.3 Strengths**

This dissertation has many strengths that reflect the decades of work it takes to create high-quality genetic epidemiology cohort studies. The genome-wide association analyses in Aim 1 and 3 were conducted in multiethnic cohort studies, which is a valuable strength. Since sodium and potassium intake vary greatly across culture and race/ethnicity, the genetic effects on sodium and potassium intake and/or gene-by-sodium intake interactions could also differ across populations. This dissertation includes populations with both higher and lower mean sodium and potassium intake, which allowed us to generalize these results across a variety of populations. In addition, the variability of sodium and potassium intake within and across populations likely increased our power to detect effects.

In Aim 1, we used multiple dietary phenotypes as outcomes (sodium intake, potassium intake, and sodium-to-potassium ratio) that are mostly associated with blood pressure regulation to contribute to the comprehensive understanding of genetic architecture of three phenotypes. In addition, each of the participating cohorts in this dissertation has high-quality measurements of sodium and potassium intake from urinary samples, enabling us to initiate an international collaboration of multiethnic genome-wide meta-analysis in Aim 1 and 3. Throughout the dissertation, we assumed that 24-hour urinary sodium and potassium excretion levels were measures of recent intake because they are regarded as the gold standard for sodium and potassium intake assessment. For the genotyping data in Aim 1 and 3, we used 1000 Genomes Project imputed genotypes that passed a strict QC assessment in each cohort, and we further excluded SNPs based on their allele frequency, imputation quality, and their match with the 1000 Genomes reference panel data through the study-level and meta-level QC steps.

In Aim 2, we used rare genetic variants in addition to common variants in the analysis, which allowed us to investigate the effect of both common and rare variants on sodium and potassium intake.

Regarding the methods of statistical analysis, the dissertation covers both traditional and state-of-the-art approaches in genetic epidemiology, which allow a comprehensive understanding of the results. In Aim 1, we employed a traditional genetic analysis method (GWAS meta-analysis) to investigate the genetic determinants of sodium and potassium intake. Secondly, an advanced gene-based approach was utilized to confirm the associations from Aim 1 and evaluate effect modification by demographic factors. Lastly, genome-wide gene-by-sodium intake interactions were evaluated across the genome using a powerful statistical approach, joint meta-analysis of SNP and SNP by environment (SNP $\times$ E) regression coefficients (2DF joint test) [124].

## 5.4 Limitations

Although the analyses in this dissertation were conducted in the largest collection of multiethnic cohorts for each Aim, the total sample size was still insufficient to have the power to detect many significant results from the genome-wide SNP and gene-by-environment interaction analyses. In addition, since collecting 24-hour or half-day urine samples is time consuming and costly, not many cohorts have both 24-hour/half-day urine samples and genotyping data. In addition, as there was only one cohort of African and Asian ancestry in Aim 1, we could not conduct the meta-analysis in those race/ethnicity populations. In Aim 2, the gene-based association analysis and gene-by-environment interaction analysis were conducted in only two small European ancestry cohorts, and based on the sample size in each cohort we could not

evaluate the association and interactions if the number of genetic markers in a region was higher than the recommended value by SKAT. In Aim 3, since we only one Asian ancestry cohort, we could not conduct the meta-analysis in that ancestry group.

Generally, 24-hour urinary sodium and potassium excretion is regarded as the gold standard for assessment of sodium and potassium intake and is more accurate than those from self-reported dietary questionnaires [20-22]. Since collecting 24-hour urinary samples is very challenging, sodium and potassium excretions from half-day and spot urine samples are often measured instead. In Aims 1 and 3, sodium and potassium intake were measured from half-day and spot urine samples in some of the participating cohorts, which might decrease the accuracy of the measurement. However, the estimated 24-hour sodium and potassium excretion measured from half-day and spot-urine samples using a special formula (simple volume-time linear extrapolation and Kawasaki formula) have reasonably high correlation coefficients with those from 24-hour urine samples (0.837 and 0.53-0.82, respectively) [11, 25]. In a future study, we plan to conduct sensitivity analyses to assess the effect of suboptimal urine quality measurements by excluding samples in which sodium and potassium intake was measured from spot urine and compare the results to the larger meta-analysis [142].

The low rate of replication of significant or suggestive genetic loci from European discovery set in the African and Asian cohorts in Aim 1 may be due to different genetic linkage disequilibrium structures in each ancestry. In addition, the genetic effects may only manifest in certain environmental contexts (gene-by-environment interaction) [143]. As a result, a SNP found in a specific race/ethnicity group may not replicat in another group. Thus, we need other European ancestry cohorts as replication sets or to employ gene-based approaches to replicate our findings in populations of different race/ancestry groups.

In Aim 2, we evaluated the association between sodium and potassium intake and genes near significant or suggestive genetic loci that were identified in Aim 1. However, the regions evaluated in Aim 2 only included the gene regions near identified genetic loci, and excluded the regions near genetic loci in non-gene regions from Aim 1. To expand the regions that were tested in Aim 2, we plan to include non-gene regions in the analysis of association and interactions by defining regions as the location of the index SNP $\pm$ 20kb.

## 5.5 Future work

In Aims 1 and 3, we identified genome-wide significant or suggestive genetic loci associated with sodium and potassium intake as well as gene-by-sodium intake interactions. However, we need large and independent multiethnic cohorts to confirm the associations from Aim 1. In Aim 1, potential replication cohorts include 1) Genetic epidemiology network of salt sensitivity (GenSalt) study (N=1,823) [144], 2) UK Biobank (N=500,000) [136], 3) Jackson Heart Study (JHS, N=633), and 4) Nurses' Health Study and Health Professionals Follow-up Study (NHS & HPFS, N=1,650) [145-147]. To expand on the results in Aim 3, we are currently suggesting collaborations with additional cohorts to confirm suggestive or significant loci found from the discovery stage. Potential cohorts include 1) 24-hour urine sample: Prevention of REnal and Vascular ENd-stage Disease (PREVEND) (N=3,649) [61]; 2) Spot urine sample: Heredity and Phenotype Intervention (HAPI) Heart Study (N=844) [70], Multiethnic Study of Atherosclerosis (MESA) cohort (N=2,462) [135] and UK Biobank (N=500,000) [136]; and 3) FFQ: Health and Retirement Study (N=8,035) [137]. In addition, we plan to explore the gene-by-potassium intake interactions, which would expand our understanding of dietary effects on genetics of blood pressure.

The strength of the gene-based approach is that we can evaluate associations or interactions across race/ethnicity groups because the gene is a functional unit that does not vary by race/ethnicity group. Since we only used two European ancestry cohorts in Aim 2, we plan to include larger cohorts across multiple race/ethnicities to conduct a meta-analysis of the results as well as replicate the results in larger cohorts. In addition, gene-based approaches using only functional genetic variants could be employed in Aim 2. Functional polymorphisms include the genetic variants that have been proven or predicted to influence gene expression or protein functions. It is important to know if a polymorphism is functional to better understand the mechanistic basis by which a polymorphism is associated with a specific health outcome [148]. Using weighting based on bioinformatic evaluation of each variant's potential to have a functional effect would be an important next step in gene-based analysis [149].

Blood pressure traits, as well as its risk factors -- intakes of sodium and potassium -- are complex phenotypes. To have better insight into the genetics of complex traits and their mechanisms in disease risk, integrating the information from the genome, and epigenome, environmental exposures, as well as their interactions are needed. We plan to expand our initial findings using gene expression data, epigenetic data, and other related environmental factors to evaluate the underlying evidence for personalized and precision approaches to reduce the burden of disease in populations.

<center>**APPENDICES**</center>

**Appendix 1** Descriptions of participating cohorts

**Genetic Epidemiology Network of Arteriopathy (GENOA), USA**: GENOA is one of four networks in the NHLBI Family-Blood Pressure Program (FBPP). [The FBPP Investigators. Multi-center genetic study of hypertension: The Family Blood Pressure Program (FBPP). Hypertension 2002;39:3-9.; Daniels PR, Kardia SL, Hanis CL, Brown CA, Hutchinson R, Boerwinkle E, Turner ST; Genetic Epidemiology Network of Arteriopathy study. Familial aggregation of hypertension treatment and control in the Genetic Epidemiology Network of Arteriopathy (GENOA) study. Am J Med. 2004 May 15;116(10):676-81. PubMed PMID: 15121494.] GENOA's long-term objective is to elucidate the genetics of target organ complications of hypertension, including both atherosclerotic and arteriolosclerotic complications involving the heart, brain, kidneys, and peripheral arteries. The longitudinal GENOA Study recruited European-American and African-American sibships with at least 2 individuals with clinically diagnosed essential hypertension before age 60 years. All other members of the sibship were invited to participate regardless of their hypertension status. Participants were diagnosed with hypertension if they had either 1) a previous clinical diagnosis of hypertension by a physician with current anti-hypertensive treatment, or 2) an average systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg based on the second and third readings at the time of their clinic visit. Exclusion criteria were secondary hypertension,

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alcoholism or drug abuse, pregnancy, insulin-dependent diabetes mellitus, or active malignancy. During the first exam (1995-2000), 1,583 European Americans from Rochester, MN and 1,854 African Americans from Jackson, MS were examined. Between 2000 and 2005, 1,241 of the European Americans and 1,482 of the African Americans returned for a second examination. Because African-American probands for GENOA were recruited through the Atherosclerosis Risk in Communities (ARIC) Jackson field center participants, we excluded ARIC participants from analyses.

FBPP Investigators. Multi-center genetic study of hypertension: The Family Blood Pressure Program (FBPP). Hypertension. 2002 Jan; 39(1):3-9.

Daniels PR, Kardia SL, Hanis CL, Brown CA, Hutchinson R, Boerwinkle E, Turner ST, Genetic Epidemiology Network of Arteriopathy study.

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**Prevention of REnal and Vascular ENd-stage Disease (PREVEND), Netherland:**

PREVEND is an ongoing prospective study investigating the natural course of increased levels of urinary albumin excretion and its relation to renal and cardiovascular disease. Details of the protocol have been described elsewhere (www.prevend.org). PREVEND genetics is supported by the Dutch Kidney Foundation (Grant E033), the EU project grant GENECURE (FP-6 LSHM CT 2006 037697), the National Institutes of Health (grant 2R01LM010098), The Netherlands organisation for health research and development (NWO-Groot grant 175.010.2007.006, NWO VENI grant 916.761.70, ZonMw grant 90.700.441), and the Dutch Inter University Cardiology

Hillege HL, Fidler V, Diercks GF, van Gilst WH, de Zeeuw D, van Veldhuisen DJ, Gans RO, Janssen WM, Grobbee DE, de Jong PE. Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. Circulation. 2002 Oct 1;106(14):1777-82.

**Framingham Heart Study (FHS), USA**: FHS began in 1948 with the recruitment of an original cohort of 5,209 men and women (mean age 44 years; 55 percent women). In 1971 a second generation of study participants was enrolled; this cohort (mean age 37 years; 52% women) consisted of 5,124 children and spouses of children of the original cohort. A third-generation cohort of 4,095 children of offspring cohort participants (mean age 40 years; 53 percent women) was enrolled in 2002-2005 and are seen every 4 to 8 years. Details of study designs for the three cohorts are summarized elsewhere. At each clinic visit, a medical history was obtained with a focus on cardiovascular content, and participants underwent a physical examination including measurement of height and weight from which BMI was calculated. Systolic and diastolic blood pressures were measured twice by a physician on the left arm of the resting and seated participant using a mercury column sphygmomanometer. Blood pressures were recorded to the nearest even number. The means of two separate systolic and diastolic blood pressure readings at each clinic examination were used for statistical analyses.

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Splansky GL, Corey D, Yang Q et al. The Third Generation Cohort of the National Heart, Lung, and Blood Institute's Framingham Heart Study: design, recruitment, and initial examination. Am J Epidemiol. 2007;165:1328-1335. PMID 17372189

**Heredity and Phenotype Intervention (HAPI) Heart, USA**: The Heredity and Phenotype Intervention (HAPI) Heart Study was initiated in 2002 to measure the cardiovascular response to 4 short-term interventions affecting cardiovascular risk factors and to identify the genetic and environmental determinants of these responses.  The interventions were carried out in 868 relatively healthy Amish adults aged 20 years and older who were recruited between 2003 and 2006.  Fasting blood samples were collected for measurement of blood chemistries and isolation of DNA for genetic analysis.

Mitchell BD, McArdle PF, Shen H, Rampersaud E, Pollin TI, Bielak LF, Jaquish C, Douglas JA, Roy-Gagnon MH, Sack P, Naglieri R. The genetic response to short-term interventions affecting cardiovascular function: rationale and design of the Heredity and Phenotype Intervention (HAPI) Heart Study. American heart journal. 2008 May 1;155(5):823-8.

**Hypertension Genetic Epidemiology Network (HyperGEN), USA**: HyperGEN is 1 of 4 NHLBI "Networks," coordinated under the family blood pressure program aimed to characterize genes promoting hypertension and related conditions. Participants were recruited from hypertensive sibships ascertained through population-based cohorts or from the community-at-large and were later extended to include other siblings and offspring of the original sibpair. Information on race, demographics, height, weight, current medications (via self-report) and co-morbid conditions as well as clinical measures (fasting serum chemistries, fasting lipids, and urine chemistries) was collected. Participants with type 1 diabetes or advanced renal disease (defined as serum creatinine level > 2 mg/dL) were excluded from the original study since these two conditions can cause secondary hypertension and the goal of HyperGEN was to identify novel essential hypertension loci.

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**Jackson Heart Study (JHS), USA**: The Jackson Heart Study is a longitudinal, community-based observational cohort study investigating the role of environmental and genetic factors in the development of cardiovascular disease in African Americans.  Between 2000 and 2004, a total of 5301 participants were recruited from a tri-county area (Hinds, Madison, and Rankin Counties) that encompasses Jackson, MS. Details of the design and recruitment for the Jackson Heart Study cohort has been previously published.[1-3]   Briefly, approximately 30% of participants were former members of the Atherosclerosis Risk in Communities (ARIC) study.  The remainder were recruited by either 1) random selection from the Accudata list, 2) commercial listing, 3) a constrained volunteer sample, in which recruitment was distributed among defined demographic cells in proportions designed to mirror those in the overall population, or through the Jackson Heart Study Family Study.

Wyatt SB, Diekelmann N, Henderson F, Andrew ME, Billingsley G, Felder SH et al. A community-driven model of research participation: the Jackson Heart Study Participant Recruitment and Retention Study. Ethn Dis 2003; 13(4):438-455.

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Fuqua SR, Wyatt SB, Andrew ME, et al. Recruiting African-American research participation in the Jackson Heart Study: methods, response rates, and sample description. Ethn Dis 2005; 15:S6-29.

**Genetic Epidemiology Network of Salt Sensitivity (GenSalt)**: GenSalt is a multi-center, family based study designed to identify, through dietary sodium and potassium intervention, salt-sensitivitivity susceptibility genes which may underlie essential hypertension in rural Han Chinese families. Approximately 629 families with at least one 'proband' with high blood pressure were recruited and tested for a wide variety of physiological, metabolic and biochemical measures at baseline and at multiple times during the 3-week intervention. The intervention consisted of one week on a low sodium diet, followed by one week on a high sodium diet, and finally one week on a high sodium diet with a potassium supplement.

GenSalt Collaborative Research Group. GenSalt: rationale, design, methods and baseline characteristics of study participants. J Hum Hypertens. 2007 Aug; 21(8):639-46.

**Healthy Twin Study, Korea (HTS), South Korea**: The Healthy Twin Study is a cohort of adult like-sex twin pairs aged 30 years or over and their first-degree family members who have been recruited since 2005. The participants underwent comprehensive health examinations and completed an extensive questionnaire survey. The initial recruitment process was done through mail, based on the National Twin and Family Registry, independent of their health status. The zygosity of twins was screened by a zygosity questionnaire that had a predictive power of 97.5% and was further validated by 16 short tandem repeat markers (for more than two thirds of the subjects). One of the inclusion criteria of the Healthy Twin Study was like-sex twins; thus, the number of dizygotic twins was relatively small in this study. Siblings, adjusted for age and sex, were combined with dizygotic twins as necessary. Self-reported family relationships were further

examined by genome-wide single nucleotide polymorphism data by using Affymetrix GeneChip version 6.0. Any dubious family relation conflicting with the genetic information was deleted.

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