



## ORIGINAL ARTICLE

# A genome-wide association and replication study of blood pressure in Ugandan early adolescents

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**Abstract**

**Background:** Genetic association studies of blood pressure (BP) have mostly been conducted in non-African populations. Using the Entebbe Mother and Baby Study (EMaBS), we aimed to identify genetic variants associated with BP among Ugandan adolescents.

**Methods:** Systolic and diastolic BP were measured among 10- and 11-year olds. Whole-genome genotype data were generated using Illumina omni 2.5M arrays and untyped variants were imputed. Genome-wide association study (GWAS) was conducted using linear mixed model regression to account for population structure. Linear regression analysis was used to assess whether variants previously associated with BP ( $p < 5.0 \times 10^{-8}$ ) in published BP GWASs were replicated in our study.

**Results:** Of the 14 million variants analyzed among 815 adolescents, none reached genome-wide significance ( $p < 5.0 \times 10^{-8}$ ) for association with systolic or diastolic BP. The most strongly associated variants were rs181430167 ( $p = 6.8 \times 10^{-7}$ ) for systolic BP and rs12991132 ( $p = 4.0 \times 10^{-7}$ ) for diastolic BP. Thirty-three (17 single nucleotide polymorphisms (SNPs) for systolic BP, 15 SNPs for diastolic BP and one SNP for both) of 330 variants previously identified as associated with BP were replicated in this study, but none remained significant after accounting for multiple testing.

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**Conclusion:** Variants showing suggestive associations are worthy of future investigation. Replication results suggest that variants influencing adolescent BP may overlap somewhat with those already established in previous studies, largely based on adults in Western settings.

**KEYWORDS**

adolescents, Africa, blood pressure, genetics, replication analysis, single nucleotide polymorphisms, Uganda

## 1 | INTRODUCTION

Genome-wide association studies (GWAS) predominantly from Caucasian and Asian populations have identified several single nucleotide polymorphisms (SNPs) associated with blood pressure (BP; Cho et al., 2009; Evangelou et al., 2018; Levy et al., 2009; Qian, Lu, Tan, Liu, & Lu, 2007; Warren et al., 2017; Xi et al., 2014). Despite having a high burden of hypertension, and opportunities for improved fine-mapping of causative variants, including higher genetic diversity and lower linkage disequilibrium (LD; Addo, Smeeth, & Leon, 2007; Luoni et al., 2005; Noubiap et al., 2017; Tishkoff et al., 2009), African populations are underrepresented in published genetic studies of BP (Peprah, Xu, Tekola-Ayele, & Royal, 2015). Among 38 studies that investigated genetic polymorphisms associated with hypertension in Africa-based populations (participant numbers ranging from 65 to 1939) reviewed in (Yako et al., 2018), all adopted a candidate gene approach rather than conducting a GWAS. It remains unclear whether variants associated with BP in non-African populations also influence BP among Africans or whether the patterns of genetic susceptibility differ markedly.

Blood pressure GWASs conducted among populations of African origin in the diaspora are rare, and often report different variants associated with BP compared to those reported in non-African populations (Adeyemo et al., 2009; Fox et al., 2011; Franceschini et al., 2013; Kidambi et al., 2012; Liang et al., 2017). Attempts to replicate genetic findings in independent populations have returned mixed results (Kayima et al., 2017; Kidambi et al., 2012; Li et al., 2017; Xi et al., 2014). The largest African American GWAS of BP included a meta-analysis of 29,378 individuals, and identified only one (the *SOX6* locus) of the five loci that were associated with BP in a multiethnic (African American, European and East Asian) sample of 99,382 individuals (Franceschini et al., 2013). Of the 17 SNPs most strongly associated with BP ( $p < 1 \times 10^{-4}$ ) in African Americans, three SNPs were replicated ( $p < .05$ ) in a West African sample (Adeyemo et al., 2009). Among Ugandan adults, 11 out of 27 BP related candidate SNPs (selected because of previous association with BP from BP GWASs or admixture mapping analysis) were replicated ( $p < .05$ ) with eight of the 11 SNPs having the same effect direction as in the discovery sample (Kayima et al., 2017).

Twin studies report that over 30% of BP variability is heritable (Biron, Mongeau, & Bertrand, 1976; Williams et al., 1991) but established variants associated with BP account for only 2%–5% of BP variation (Ehret & Caulfield, 2013; Salfati, Morrison, Boerwinkle, & Chakravarti, 2015). This strongly suggests the existence of important undiscovered variants. This “missing heritability” could be due to rare or to common SNPs, all conferring small increases or decreases in expected BP (Maher, 2008; Manolio et al., 2009). There is a need for both GWAS and replication studies to further elucidate and improve the generalizability of BP genetic findings.

The role of environmental and of lifestyle factors in hypertension among Africans is well documented as reviewed previously (Addo et al., 2007; Noubiap et al., 2017). Previously, we described the role of environmental and of lifestyle factors in adolescents' BP and the findings were reported in (Lule, Namara, Akurut, Lubyayi, et al., 2019; Lule, Namara, Akurut, Muhangi, et al., 2019). However, the contribution of genetic variants remains unknown and understudied (Yako et al., 2018). It is not clear whether genetic loci associated with hypertension among populations of non-African origin influence susceptibility to or protection from hypertension in populations on the African continent. Independent confirmation is necessary to validate BP SNPs in different populations. We used data from the Entebbe Mother and Baby Study (EMaBS) birth cohort (Elliott et al., 2007) to conduct 1) a GWAS of systolic and diastolic BP and 2) a replication study of candidate SNPs identified in previously published BP GWASs. The GWAS aimed to identify novel BP loci unique to this population while candidate gene analysis aimed to identify variants influencing BP across different ethnic groups.

We hypothesized that genetic variants (either unique or not unique to populations in Africa) would be associated with BP among Ugandan adolescents. Individuals of African origin have different genetic makeup from individuals of non-African ancestries (Addo et al., 2007; Luoni et al., 2005; Noubiap et al., 2017; Tishkoff et al., 2009). Identifying genetic variants associated with BP enhances our understanding of BP regulation and might highlight potential drug targets for hypertension treatment and prevention. Furthermore, the identification of variants associated with hypertension in both adolescence and adulthood could offer opportunities for early risk prediction.

## 2 | METHODS

### 2.1 | Ethical compliance

This study was approved by the Uganda Virus Research Institute Science and Ethics Committee; the Uganda National Council for Science & Technology; the London School of Hygiene & Tropical Medicine; and the Oxford Tropical Research Ethics Committee. Written informed assent and consent were obtained.

### 2.2 | Study design, population and setting

The EMaBS [trial registration ISRCTN32849447] in Uganda, was originally designed to investigate the influence of worms and their treatment in pregnancy and early childhood on vaccine response and on infections in childhood (Elliott et al., 2007). Briefly, between April 2003 and November 2005, 2,507 pregnant women in their second or third trimester were randomized in a  $2 \times 2$  factorial design to receive single dose albendazole (400 mg) or matching placebo and single dose praziquantel (40 mg/kg) or matching placebo. At 15 months of age, the resulting 2,345 live-born infants were randomized to receive quarterly albendazole or matching placebo up to 5 years of age.

### 2.3 | Phenotyping

The offspring continued under follow-up after the trial ended in 2011. From 20 May 2014 to 16 June 2016, cohort participants who were now aged 10–11 years were enrolled in a BP sub-study, as part of which additional anthropometric and BP data were collected (Lule, Namara, Akurut, Muhangi, et al., 2019). Adolescents were included in this study if they were aged 10 or 11 years and attending their routine annual follow-up visit during the BP sub-study period (11-year-olds who had previously enrolled as 10-year-olds were not included twice). Where necessary, enrollment was postponed until the participant was free of malaria (fever or axillary temperature  $\geq 37.5^\circ\text{C}$  and parasitemia) and other illnesses (Lule, Namara, Akurut, Muhangi, et al., 2019).

BP was measured as previously described (Lule, Namara, Akurut, Muhangi, et al., 2019). Briefly, on the BP study visit day, after 5 min rest period, trained nurses measured BP thrice 5 min apart, on the right arm supported at the heart level, with the participant seated upright all the way to the back of the chair, with legs uncrossed and feet flat on the floor. Automated Omron (M6, HEM-700) machines validated every 6 months by the Uganda National Bureau of Standards were used. Blood pressure phenotypes for this analysis were the mean of the second and third readings for systolic and diastolic BP, that is, systolic and diastolic BP were analyzed as two separate phenotypes. The second and third BP readings were, on average, lower than the first BP reading but

similar to each other for both systolic and diastolic BP (Lule, Namara, Akurut, Muhangi, et al., 2019).

### 2.4 | Genotyping and quality control

Earlier in 2013, whole-genome genotyping of 1,391 EMaBS participants was undertaken. Genotypic data were generated from red cell pellets that had been separated and stored at  $-80^\circ\text{C}$  until processing. Approximately 2.2 million genetic variants were generated at Wellcome Sanger Institute using the Illumina HumanOmni2.5M-8 (“octo”) Beadchip arrays, version 1.1 (Illumina Inc.). Quality control (using standard pipelines) was performed at the University of Oxford using commands in PLINK (version 1.7; Purcell et al., 2007) to remove individuals and variants with high levels of missingness or deviations from expected levels of heterozygosity or Hardy–Weinberg equilibrium ( $p < 1 \times 10^{-8}$ ). Untyped genetic variants and the variants identified for replication analysis were imputed in the EMaBS sample using a merged panel (1,000 Genomes Project Consortium et al., 2015, African genome variation project [AGVP] Gurdasani et al., 2015 and Uganda 2000 Genomes [UG2G]: genomes of Ugandan individuals of diverse ethnicity from rural Uganda) at the Wellcome Centre for Human Genetics. SHAPEIT2 (version 2.790; O’Connell et al., 2014), and IMPUTE2 (version 2.3.2; Marchini, Howie, Myers, McVean, & Donnelly, 2007) were used for imputation using settings as recommended for African populations. Only SNPs with an INFO score  $>0.3$  and a minor allele frequency  $>0.01$  were taken forward for analysis.

### 2.5 | Association analysis

The analysis included EMaBS adolescents with phenotypic and genotypic data. The two outcomes (mean systolic BP and mean diastolic BP) were analyzed separately. GWAS of BP (systolic and diastolic) as quantitative traits was done using mixed linear regression methods (accounting for population substructure) assuming an additive model and controlling for age and body mass index (BMI) as covariates in genome-wide complex trait analysis (GCTA) version 1.22 (Yang, Lee, Goddard, & Visscher, 2011). A  $p < 5 \times 10^{-8}$  was considered as the threshold to denote genome-wide significance for SNPs. Results for SNPs with  $p < 1 \times 10^{-6}$  are reported. Manhattan plots and Quantile–Quantile (Q–Q) plots were constructed to show the distributions of association  $p$ -values and the departure of the observed  $p$ -values from the null, respectively.

For the replication component of this study, previously published BP GWASs were searched to identify SNPs reported to be associated with systolic or diastolic BP ( $p < 5 \times 10^{-8}$  in the original GWAS) and these variants were considered for the replication. Replication analysis was conducted using

linear regression adjusting for age and BMI in Stata version 14 (College Station, Texas, USA). Variants were tested for association with the phenotype they were associated with in the published GWAS, that is variants associated with systolic BP in a published GWAS were tested for association with systolic BP but not with diastolic BP and vice versa.  $P < .05$  was considered the threshold for statistical significance for the replication study although results were also interpreted in light of a Bonferroni correction allowing for all tests done in the replication analysis.

The base pair position is based on the Genome Reference Consortium Human Build 37, February 2009 (GRCh37/hg19).

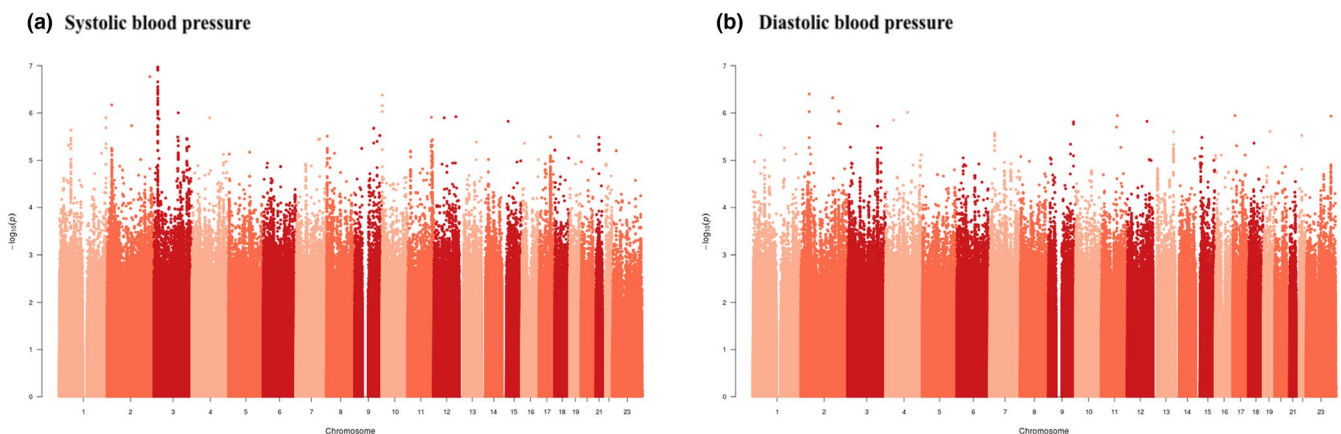
### 3 | RESULTS

The discovery GWAS analysis used data on 20,074,711 SNPs from 815 adolescents. These adolescents had a mean age of 10.4 years, a mean BMI of 16.0 kg/m<sup>2</sup>, mean systolic BP of 106.0 mmHg, and mean diastolic BP of 65.3 mmHg. Four hundred and seventeen (51%) of the adolescents were male. Detailed characteristics of EMaBS participants included and not included in the analysis are described in Table S1. Offspring included in the genetic analysis were similar for most characteristics to those not included, except that those included were more likely to have been delivered in Entebbe hospital than elsewhere and to have been exclusively breast-feeding at 6 weeks of age.

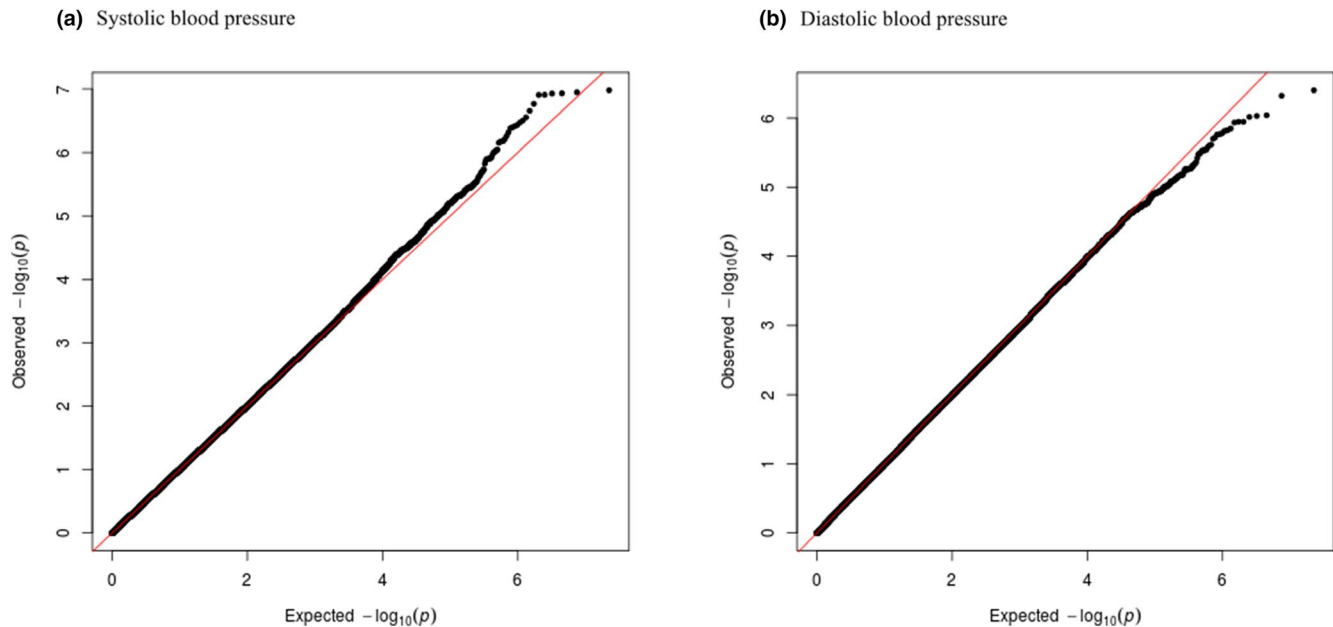
The distributions of association  $p$ -values (Manhattan plot) for systolic and diastolic BP phenotypes are shown in Figure 1 and the Q–Q plots in Figure 2. The observed  $P$ -values show no departure from the null (Figure 2), either for systolic or diastolic BP, with lambda values of 1.006 and 0.995, respectively. The results show adequate control for population sub-structure in the analysis.

The SNPs most strongly associated with BP are shown in Table 1. None of the SNPs reached genome-wide level of significance ( $p < 5 \times 10^{-8}$ ) for association with adolescent systolic or diastolic BP. Borderline significance ( $5 \times 10^{-8} < p < 1 \times 10^{-6}$ ) for association with systolic BP was achieved for four index SNPs at four separate loci; there were four SNPs showing borderline significant associations with diastolic BP at four separate loci. There was no overlap between the SNPs most strongly associated with systolic BP and those most strongly associated with diastolic BP. None of these index SNPs have been identified as associated with BP in previously published BP GWAS. The most strongly associated SNP for systolic BP with  $p$ -value  $6.8 \times 10^{-7}$  was rs181430167, located in the intron region of *KLHL29* on chromosome 2. The lowest  $p$ -value ( $4.0 \times 10^{-7}$ ) for association with diastolic BP was for rs12991132 located between *ZFP36L2*, *THADA*, *LOC1001297261* on chromosome 2.

Of the 389 SNPs (Adeyemo et al., 2009; Cho et al., 2009; Ehret et al., 2016; International Consortium for Blood Pressure Genome-Wide Association Studies et al., 2011; Evangelou et al., 2018; Fox et al., 2011; Franceschini et al., 2013; Ganesh et al., 2014, 2013; Ho et al., 2011; Hoffmann et al., 2017; Johnson, Newton-Cheh, et al., 2011; Johnson, Gaunt, et al., 2011; Kato et al., 2015, 2011; Kidambi et al., 2012; Levy et al., 2009; Li et al., 2017; Liang et al., 2017; Liu et al., 2016; Newton-Cheh, Johnson, et al., 2009; Newton-Cheh, Larson, et al., 2009; Parmar et al., 2016; Simino et al., 2014; Surendran et al., 2016; Takeuchi et al., 2010; Tragante et al., 2014; Wain et al., 2017, 2011; Warren et al., 2017) identified for replication, 330 (85%) SNPs were included in the replication analysis. Fifty-nine SNPs that were either rare ( $<0.01$ ) or poorly imputed (INFO score  $<0.3$ ) in the EMaBS sample were not included in the replication analysis. Thirty SNPs of the 330 SNPs included in the replication had been previously associated with BP in populations of African origins. Forty SNPs had been previously associated with both systolic and



**FIGURE 1** Manhattan plots for the association of SNPs with (a) systolic blood pressure and (b) diastolic blood pressure adjusting for age and body mass index as fixed covariates



**FIGURE 2** Quantile–Quantile (Q–Q) plots for the two phenotypes and the genomic control coefficient ( $\lambda$ ). (a) systolic blood pressure and (b) diastolic blood pressure

**TABLE 1** Genome-wide association study results: SNPs associated with blood pressure (systolic or diastolic) at  $p < 1.0 \times 10^{-7}$

Chr	Nearest gene <sup>a</sup>	Position <sup>b</sup>	SNP	Distance to gene (kb)	Type	EA	RA	EAF	$\beta$	SE	$p$ -value
Systolic blood pressure											
2	KLHL29	23904233	rs181430167	0	Intron	C	T	0.05	4.62	9.24	$6.8 \times 10^{-7}$
10	LINC00701	2565732	rs71502208	500	Unknown	A	G	0.22	2.51	5.05	$9.3 \times 10^{-7}$
3	SGOL1/SGOL-ASI	20295100	rs139992073	200	Unknown	C	T	0.14	2.83	5.74	$9.7 \times 10^{-7}$
3	PLXNA1	126737466	rs73861745	0	Intron	A	G	0.26	2.25	4.57	$9.9 \times 10^{-7}$
Diastolic blood pressure											
2	ZFP36L2/THADA/ LOC1001297261	43291689	rs12991132	500	Unknown	A	G	0.59	-1.87	3.61	$4.0 \times 10^{-7}$
2	COBLL	165534347	rs111770209	20	Unknown	T	C	0.94	-3.82	7.53	$4.8 \times 10^{-7}$
2	DNAH7	196853830	rs13403027	0	Intron	A	G	0.71	-1.91	3.87	$9.1 \times 10^{-7}$
4	ANK2	114209732	rs29356	0	Intron	T	C	0.69	1.91	3.87	$9.6 \times 10^{-7}$

Abbreviations: Chr, chromosomes; EA, effect allele; EAF, effect allele frequency; RA, reference allele; SE, standard error; SNP, single nucleotide polymorphism;  $\beta$ , effect size estimates correspond to mean difference in mmHg per effect allele for systolic or diastolic blood pressure, adjusted for age and body mass index.

<sup>a</sup>Named according to the nearest annotated gene(s).

<sup>b</sup>Given with respect to Build 37 (GRCh37/hg19).

diastolic BP and were tested for association with both. Tables 2 and 3 show results from the replication analysis. Briefly, 33 SNPs (17 for systolic, 15 for diastolic and one for both systolic and diastolic BP) were associated with BP in this population, with the same effect direction as the discovery population for 14 of the SNPs (five for systolic BP and eight for diastolic BP and one for both systolic and diastolic BP).

Of the 30 SNPs previously known to be associated with BP specifically in individuals of African origin, three (*ATP2B* rs2681492, *MDM4* rs2169137 and *EVX1/HOXA* rs17428471) were associated with BP in the present study.

Only the *EVX1/HOXA* rs17428471 had the same effect direction as in the discovery population. The *BAT2/BAT5* rs805303 variant was associated with systolic BP and diastolic BP of the 40 SNPs tested for association with both traits. The G allele of the *BAT2/BAT5* rs805303 variant was associated with higher systolic and higher diastolic BP among adolescents in this study: the same effect direction observed in the discovery population for both traits.

There were 370 independent tests (197 for systolic BP, 173 for diastolic BP) conducted, thus approximately 19 SNPs ( $370 \times 0.05 = 18.5$ ) would be expected to be associated

**TABLE 2** Loci associated with systolic blood pressure identified from previous GWAS and results of replication in Entebbe Mother and Baby Study (EMaBS) sample

Chr	SNP	Position <sup>a</sup>	Nearest gene	Population	EA/ RA	Discovery sample				EMaBS sample			
						EAF	$\beta$	SE	<i>p</i> -value	EAF	$\beta^b$	SE	<i>p</i> -value
1	rs839755	43856410	SZT2	E	A/C	0.62	-0.27	0.03	$5.4 \times 10^{-18}$	0.81	0.29	0.70	$6.8 \times 10^{-1}$
<b>1</b>	<b>rs4926499</b>	<b>249155909</b>	<b>AL672294.1</b>	<b>E</b>	<b>C/G</b>	<b>0.82</b>	<b>0.30</b>	<b>0.04</b>	<b><math>1.3 \times 10^{-11}</math></b>	<b>0.98</b>	<b>-5.12</b>	<b>2.00</b>	<b><math>1.1 \times 10^{-2}</math></b>
1	rs1043069	180859368	XPR1	E	T/G	0.62	0.23	0.03	$5.2 \times 10^{-14}$	0.63	0.02	0.62	$9.7 \times 10^{-1}$
1	rs4651224	184585182	C1orf21	E	T/C	0.45	0.20	0.03	$9.0 \times 10^{-11}$	0.94	0.75	1.24	$5.5 \times 10^{-1}$
1	rs2807337	22577371	WNT4	E	T/C	0.37	0.19	0.03	$2.8 \times 10^{-9}$	0.43	-0.70	0.58	$2.3 \times 10^{-1}$
<b>1</b>	<b>rs7514579</b>	<b>94051350</b>	<b>BCAR3</b>	<b>E</b>	<b>A/C</b>	<b>0.77</b>	<b>0.22</b>	<b>0.03</b>	<b><math>5.5 \times 10^{-10}</math></b>	<b>0.50</b>	<b>1.25<sup>c</sup></b>	<b>0.67</b>	<b><math>4.0 \times 10^{-2}</math></b>
1	rs17396055	94730954	ARHGAP29	E	A/G	0.33	-0.17	0.03	$4.0 \times 10^{-8}$	0.08	0.80	1.02	$4.3 \times 10^{-1}$
1	rs12042924	197297417	CRB1	E	T/C	0.53	-0.18	0.03	$2.6 \times 10^{-9}$	0.86	-1.29	0.86	$1.3 \times 10^{-1}$
1	rs7555285	209970355	IRF6	E	C/G	0.80	0.23	0.04	$1.1 \times 10^{-9}$	0.83	-0.52	0.77	$5.0 \times 10^{-1}$
1	rs33996239	203109801	ADORA1	E	T/C	0.06	-0.37	0.07	$3.4 \times 10^{-8}$	0.09	-0.13	1.08	$9.0 \times 10^{-1}$
1	rs2932538	113216543	MOV10	E	G/A	0.75	0.39	—	$1.2 \times 10^{-9}$	0.85	0.15	0.80	$8.6 \times 10^{-1}$
1	rs7515635	42408070	HIVEP3	E	T/C	0.47	0.31	0.04	$4.8 \times 10^{-12}$	0.68	0.08	0.65	$9.0 \times 10^{-1}$
1	rs17367504	11862778	MTHFR-NPPB	E	G/A	0.14	-0.85	0.11	$2.0 \times 10^{-13}$	0.09	0.66	1.10	$5.5 \times 10^{-1}$
1	rs2493292	3328659	PRDM16	E/AA	T/C	0.15	0.37	0.07	$1.4 \times 10^{-8}$	0.17	-0.36	0.82	$6.6 \times 10^{-1}$
1	rs880315	10796866	CASZ1	AS	C/T	0.34	1.08	0.03	$2.2 \times 10^{-8}$	0.11	-0.91	0.96	$3.5 \times 10^{-1}$
1	rs3820068	15798197	CELA2A	E	A/G	0.81	0.43	0.06	$1.1 \times 10^{-8}$	0.63	0.81	0.63	$2.0 \times 10^{-1}$
1	rs10922502	89360158	GTF2B	E	A/G	0.62	-0.38	0.05	$2.2 \times 10^{-15}$	0.67	-0.32	0.64	$6.1 \times 10^{-1}$
<b>2</b>	<b>rs2972146</b>	<b>227100698</b>	<b>2q36.3</b>	<b>E</b>	<b>T/G</b>	<b>0.65</b>	<b>0.17</b>	<b>—</b>	<b><math>8.4 \times 10^{-9}</math></b>	<b>0.86</b>	<b>-0.19</b>	<b>0.86</b>	<b><math>4.0 \times 10^{-2}</math></b>
2	rs1446468	164963486	FIGN-GRB14	E	T/C	0.53	-0.50	0.07	$1.8 \times 10^{-12}$	0.95	0.46	1.34	$7.3 \times 10^{-1}$
2	rs16849225	164906820	FIGN-GRB14	AS	C/T	0.61	0.75	0.11	$3.5 \times 10^{-11}$	0.89	-1.04	0.93	$2.7 \times 10^{-1}$
2	rs7562	28635740	FOSL2	E	T/C	0.52	0.26	0.05	$1.9 \times 10^{-8}$	0.26	0.20	0.67	$7.6 \times 10^{-1}$
2	rs13420463	37517566	PRKD3	E	A/G	0.77	0.36	0.05	$7.0 \times 10^{-11}$	0.45	0.03	0.63	$9.6 \times 10^{-1}$
2	rs55780018	208526140	METTL21A- AC079767.3	E	T/C	0.54	-0.39	0.05	$5.9 \times 10^{-16}$	0.75	0.59	0.74	$4.2 \times 10^{-1}$
<b>2</b>	<b>rs1275988</b>	<b>26914364</b>	<b>KCNK3</b>	<b>E</b>	<b>T/C</b>	<b>0.23</b>	<b>-0.60</b>	<b>0.09</b>	<b><math>2.6 \times 10^{-10}</math></b>	<b>0.14</b>	<b>2.01</b>	<b>0.85</b>	<b><math>1.8 \times 10^{-2}</math></b>
<b>2</b>	<b>rs6712094</b>	<b>165043460</b>	<b>FIGN-GRB14</b>	<b>E</b>	<b>A/G</b>	<b>0.70</b>	<b>0.60</b>	<b>0.10</b>	<b><math>9.9 \times 10^{-9}</math></b>	<b>0.89</b>	<b>-3.72</b>	<b>1.01</b>	<b><math>2.6 \times 10^{-4}</math></b>
2	rs1344653	19730845	OSR1	E/AS	A/G	0.54	-0.27	0.04	$7.8 \times 10^{-12}$	0.67	0.07	0.66	$9.1 \times 10^{-1}$
2	rs2300481	66782467	MEIS1	E	T/C	0.39	0.20	0.03	$1.6 \times 10^{-10}$	0.37	0.73	0.61	$2.3 \times 10^{-1}$
2	rs35590893	43716933	HADA	E	A/G	0.27	-0.24	0.03	$1.7 \times 10^{-12}$	0.13	0.52	0.86	$5.5 \times 10^{-1}$
2	rs67720684	18975439	NT5C1B	E	A/C	0.24	0.19	0.04	$3.8 \times 10^{-8}$	0.36	-0.41	0.60	$5.0 \times 10^{-1}$
2	rs28377357	112769721	MERTK	E	A/G	0.29	-0.21	0.03	$9.6 \times 10^{-11}$	0.31	0.87	0.64	$1.8 \times 10^{-1}$
2	rs72816333	60096560	RP11-444A22.1	E	A/T	0.83	0.23	0.04	$5.5 \times 10^{-9}$	0.96	-0.15	1.48	$9.2 \times 10^{-1}$
2	rs28558491	187816321	ZSWIM2	E	T/C	0.74	-0.21	0.03	$7.5 \times 10^{-10}$	0.29	0.55	0.67	$4.1 \times 10^{-1}$
2	rs6723509	122000745	TFCP2L1	E	T/C	0.86	0.25	0.04	$7.6 \times 10^{-9}$	0.91	0.78	1.00	$4.4 \times 10^{-1}$
2	rs1044822	230629138	TRIP12	E	T/C	0.15	-0.25	0.04	$5.2 \times 10^{-9}$	0.09	-0.41	1.07	$7.0 \times 10^{-1}$
2	rs12694277	213188795	ERBB4	E	T/C	0.30	-0.20	0.03	$1.8 \times 10^{-9}$	0.62	-0.05	0.61	$9.4 \times 10^{-1}$
2	rs6739913	185033065	ZNF804A	E	A/G	0.28	0.18	0.03	$6.5 \times 10^{-8}$	0.21	0.21	0.71	$7.6 \times 10^{-1}$
<b>2</b>	<b>rs2920899</b>	<b>55279681</b>	<b>RTN4</b>	<b>E</b>	<b>T/G</b>	<b>0.79</b>	<b>0.20</b>	<b>0.04</b>	<b><math>9.5 \times 10^{-8}</math></b>	<b>0.86</b>	<b>1.58<sup>c</sup></b>	<b>0.78</b>	<b><math>4.0 \times 10^{-2}</math></b>
3	rs9810888	53635595	CACNA1D	AS	G/T	0.39	0.53	0.10	$5.5 \times 10^{-8}$	0.60	-1.15	0.60	$5.4 \times 10^{-2}$
3	rs11128722	14958126	FGD5	E	A/G	0.56	-0.31	0.05	$3.6 \times 10^{-11}$	0.32	0.39	0.10	$5.2 \times 10^{-1}$
3	rs9859176	134000025	RYK	E	T/C	0.40	0.32	0.05	$1.3 \times 10^{-11}$	0.17	0.57	0.77	$4.6 \times 10^{-1}$
3	rs419076	169100886	MECOM	E	T/C	0.47	0.41	—	$1.8 \times 10^{-13}$	0.57	-0.60	0.61	$3.2 \times 10^{-1}$
3	rs347591	11290122	HRH1	E/AS/AA	G/T	0.35	-0.53	0.11	$1.5 \times 10^{-8}$	0.57	-0.41	0.60	$4.9 \times 10^{-1}$
3	rs13082711	27537909	SL4A7	E	T/C	0.78	-0.24	—	$3.8 \times 10^{-9}$	0.95	-0.33	1.41	$8.1 \times 10^{-1}$

(Continues)

TABLE 2 (Continued)

Chr	SNP	Position <sup>a</sup>	Nearest gene	Population	EA/ RA	Discovery sample				EMaBS sample			
						EAF	$\beta$	SE	<i>p</i> -value	EAF	$\beta^b$	SE	<i>p</i> -value
3	rs319690	47927484	MAP4	E	T/C	0.50	0.42	0.07	$4.7 \times 10^{-8}$	0.44	0.72	0.62	$2.5 \times 10^{-1}$
3	rs12638085	30405936	TGFBR2	E	A/T	0.35	0.22	0.03	$5.6 \times 10^{-12}$	0.12	-1.31	0.92	$1.6 \times 10^{-1}$
3	rs6788984	41107173	CTNNA1	E	A/G	0.86	0.30	0.04	$3.8 \times 10^{-12}$	0.71	-0.05	0.66	$9.4 \times 10^{-1}$
<b>3</b>	<b>rs9875380</b>	<b>132780356</b>	<b>TMEM108</b>	<b>E</b>	<b>T/C</b>	<b>0.46</b>	<b>-0.18</b>	<b>0.03</b>	<b><math>6.5 \times 10^{-9}</math></b>	<b>0.26</b>	<b>-1.55<sup>c</sup></b>	<b>0.68</b>	<b><math>2.3 \times 10^{-2}</math></b>
3	rs863930	135949737	PCCB	E	A/C	0.54	0.19	0.03	$5.1 \times 10^{-10}$	0.63	-0.77	0.62	$2.2 \times 10^{-1}$
3	rs78151625	158316726	MLF1	E	T/C	0.83	-0.25	0.04	$1.6 \times 10^{-9}$	-0.82	3.49	3.49	$8.1 \times 10^{-1}$
3	rs6774721	49381898	ARIH2	E	C/T	0.88	0.28	0.05	$6.4 \times 10^{-9}$	0.83	-0.94	0.85	$3.7 \times 10^{-1}$
3	rs9857362	74710462	CNTN3	E	A/C	0.53	0.17	0.03	$1.6 \times 10^{-8}$	0.83	0.65	0.77	$3.9 \times 10^{-1}$
4	rs1458038	81164723	FGF5	E	T/C	0.29	0.71	—	$1.5 \times 10^{-23}$	0.04	1.28	1.53	$4.1 \times 10^{-1}$
4	rs2291435	38387395	TBC1D1-FLJ13197	E/AA	T/C	0.52	-0.34	0.04	$1.9 \times 10^{-14}$	0.30	-0.54	0.64	$4.0 \times 10^{-1}$
4	rs13112725	106911742	NPNT	E	C/G	0.76	0.44	0.06	$1.5 \times 10^{-14}$	0.61	-0.62	0.60	$3.0 \times 10^{-1}$
4	rs231708	2694773	FAM193A	E	C/G	0.69	-0.12	0.03	$4.7 \times 10^{-18}$	0.24	1.14	0.68	$9.6 \times 10^{-2}$
4	rs7439567	138464842	P11-714L20.1	E	T/C	0.42	0.25	0.03	$2.3 \times 10^{-16}$	0.81	-0.58	0.76	$4.4 \times 10^{-1}$
4	rs2610990	18008232	LCORL	E	A/G	0.26	-0.29	0.03	$2.8 \times 10^{-17}$	0.19	-1.19	0.77	$1.2 \times 10^{-1}$
<b>4</b>	<b>rs17035181</b>	<b>157678511</b>	<b>PDGFC</b>	<b>E</b>	<b>T/G</b>	<b>0.85</b>	<b>0.31</b>	<b>0.04</b>	<b><math>7.6 \times 10^{-13}</math></b>	<b>0.75</b>	<b>-1.47</b>	<b>0.71</b>	<b><math>3.8 \times 10^{-2}</math></b>
4	rs1347345	95938386	MPR1B	E	A/G	0.62	-0.18	0.03	$6.9 \times 10^{-9}$	0.87	0.23	0.88	$8.0 \times 10^{-1}$
4	rs12511987	46595623	GABRA2	E	T/G	0.82	-0.23	0.04	$5.4 \times 10^{-9}$	0.94	-0.53	1.45	$7.2 \times 10^{-1}$
4	rs2014912	86715670	ARHGAP24	E/AS	T/C	0.16	0.62	0.08	$5.4 \times 10^{-17}$	0.16	1.16	0.82	$1.6 \times 10^{-1}$
5	rs13359291	122476457	PRDM6	E/AS	A/G	0.31	0.53	0.07	$8.9 \times 10^{-16}$	0.16	0.66	0.77	$3.9 \times 10^{-1}$
5	rs1173771	32815028	NPR3-C5orf23	E	G/A	0.60	0.50	—	$1.8 \times 10^{-16}$	0.82	1.09	0.82	$1.9 \times 10^{-1}$
5	rs11953630	157845402	EBF1	E	T/C	0.37	-0.41	—	$3.0 \times 10^{-11}$	0.13	-0.34	0.88	$7.0 \times 10^{-1}$
5	rs10077885	114390121	TRIM36	E	A/C	0.50	-0.28	0.04	$1.6 \times 10^{-10}$	0.65	0.20	0.63	$7.5 \times 10^{-1}$
5	rs6595838	127868199	FBN2	E	A/G	0.30	0.34	0.05	$7.6 \times 10^{-12}$	0.63	0.62	0.59	$2.9 \times 10^{-1}$
5	rs1173766	32804528	NPR3	AS	C/T	0.60	0.63	0.11	$1.9 \times 10^{-8}$	0.66	1.13	0.64	$7.8 \times 10^{-1}$
5	rs10069690	1279790	TERT	E	T/C	0.26	0.31	0.04	$4.8 \times 10^{-17}$	0.66	-0.54	0.65	$4.0 \times 10^{-1}$
5	rs709668	96174186	CTD-2260A17.2	E	A/G	0.20	-0.29	0.04	$6.0 \times 10^{-15}$	0.40	-0.43	0.59	$4.7 \times 10^{-1}$
5	rs246973	68007803	SLC30A5	E	T/C	0.29	0.25	0.03	$1.5 \times 10^{-13}$	0.40	2.51	1.53	$1.0 \times 10^{-1}$
5	rs702395	140086677	ZMAT2	E	T/C	0.44	0.23	0.03	$3.5 \times 10^{-14}$	0.29	-0.15	0.65	$8.2 \times 10^{-1}$
5	rs13179413	55868097	AC022431.2	E	T/C	0.28	0.22	0.03	$1.1 \times 10^{-10}$	0.21	-0.23	0.72	$7.5 \times 10^{-1}$
<b>5</b>	<b>rs62373688</b>	<b>127352807</b>	<b>CTC-228N24.3</b>	<b>E</b>	<b>A/T</b>	<b>0.13</b>	<b>0.27</b>	<b>0.04</b>	<b><math>1.5 \times 10^{-9}</math></b>	<b>0.24</b>	<b>1.40<sup>c</sup></b>	<b>0.70</b>	<b><math>4.6 \times 10^{-2}</math></b>
5	rs74774746	33411769	TARS	E	C/G	0.26	-0.19	0.04	$5.6 \times 10^{-8}$	0.14	1.49	0.88	$9.2 \times 10^{-2}$
5	rs1008058	122435627	PRDM6	E	A/G	0.14	0.55	—	$3.0 \times 10^{-10}$	0.13	0.31	0.89	$7.3 \times 10^{-1}$
6	rs79030490	134087689	TARID-TCF21	AA	A/C	0.09	-1.83	0.31	$3.0 \times 10^{-9}$	0.11	0.99	1.19	$4.0 \times 10^{-1}$
6	rs76987554	134080855	TARID-TCF21	AA	C/T	0.91	1.85	0.31	$2.2 \times 10^{-9}$	0.90	-0.88	1.20	$4.6 \times 10^{-1}$
6	rs1799945	26091179	HFE	E	G/C	0.14	0.63	—	$7.7 \times 10^{-12}$	0.02	-1.84	2.17	$4.0 \times 10^{-1}$
<b>6</b>	<b>rs805303</b>	<b>31616366</b>	<b>BAT2-BAT5</b>	<b>E</b>	<b>G/A</b>	<b>0.61</b>	<b>0.38</b>	—	<b><math>1.5 \times 10^{-11}</math></b>	<b>0.40</b>	<b>1.66<sup>c</sup></b>	<b>0.61</b>	<b><math>7.0 \times 10^{-3}</math></b>
6	rs6911827	22130601	CASC15	E	T/C	0.45	0.30	0.05	$2.0 \times 10^{-10}$	0.82	0.81	0.81	$3.2 \times 10^{-1}$
6	rs2270860	43270151	SLC22A7	E/AA	T/C	0.37	0.32	0.05	$2.9 \times 10^{-11}$	0.78	-1.20	0.71	$9.1 \times 10^{-2}$
<b>6</b>	<b>rs1563788</b>	<b>43308363</b>	<b>TTBK1- SLC22A7- ZNF318</b>	<b>E/AS</b>	<b>T/C</b>	<b>0.31</b>	<b>0.51</b>	<b>0.06</b>	<b><math>2.2 \times 10^{-16}</math></b>	<b>0.78</b>	<b>-1.46</b>	<b>0.71</b>	<b><math>4.0 \times 10^{-2}</math></b>
6	rs13209747	127115454	RSPO3	E/AA/AS	T/C	0.19	0.85	0.21	$2.6 \times 10^{-10}$	0.07	-0.13	1.09	$9.1 \times 10^{-1}$
6	rs17080102	151004770	PLEKHG1	E/AA/AS	C/G	0.10	-1.02	0.25	$4.8 \times 10^{-8}$	0.15	-0.61	0.81	$4.5 \times 10^{-1}$
6	rs9368222	20686996	CDKAL1	E	A/C	0.27	0.23	0.03	$1.8 \times 10^{-11}$	0.17	-0.07	0.81	$9.3 \times 10^{-1}$
6	rs10782230	126228512	NCOA7	E	A/G	0.48	0.21	0.03	$2.9 \times 10^{-12}$	0.41	0.71	0.62	$2.6 \times 10^{-1}$
6	rs2745599	1613686	FOXC1	E	A/G	0.55	0.22	0.03	$9.8 \times 10^{-12}$	0.10	-1.48	0.95	$1.2 \times 10^{-1}$

(Continues)

TABLE 2 (Continued)

Chr	SNP	Position <sup>a</sup>	Nearest gene	Population	EA/ RA	Discovery sample				EMaBS sample			
						EAF	$\beta$	SE	<i>p</i> -value	EAF	$\beta^b$	SE	<i>p</i> -value
6	rs9885632	131311909	EPB41L2	E	T/C	0.73	0.24	0.03	$4.3 \times 10^{-12}$	0.94	0.64	1.39	$6.4 \times 10^{-1}$
6	rs7763294	140383733	CITED2	E	T/G	0.32	-0.20	0.03	$6.4 \times 10^{-10}$	0.10	0.32	0.97	$7.4 \times 10^{-1}$
7	rs2969070	2512545	CHST12-LFNG	E	A/G	0.63	-0.30	0.05	$1.4 \times 10^{-10}$	0.97	-0.01	1.80	$1.0 \times 10^{-0}$
7	rs11556924	129663496	ZC3HC1	E	T/C	0.38	-0.28	0.05	$7.6 \times 10^{-9}$	0.01	-0.24	1.58	$8.8 \times 10^{-1}$
7	rs13238550	131059056	MKLN1	E	A/G	0.40	0.33	0.05	$1.9 \times 10^{-12}$	0.09	-0.14	1.14	$9.0 \times 10^{-1}$
7	rs1011018	139463264	HIPK2	E	A/G	0.20	-0.33	0.06	$1.5 \times 10^{-8}$	0.61	-0.17	0.59	$7.8 \times 10^{-1}$
7	rs4728142	128573967	7q32.1	E	A/G	0.43	-0.24	-	$3.5 \times 10^{-8}$	0.23	-0.27	0.69	$7.0 \times 10^{-1}$
7	rs17477177	106411858	PIK3CG	E	T/C	0.72	-0.55	0.08	$5.7 \times 10^{-11}$	0.94	-0.86	1.15	$4.5 \times 10^{-1}$
7	rs17428471	27337867	EVX1-HOXA	E/AA/AS	T/G	0.14	1.20	0.24	$2.1 \times 10^{-12}$	0.13	1.39	0.90	$1.3 \times 10^{-1}$
7	rs11563582	27351650	EVX1-HOXA	AA	A/G	0.13	1.61	0.28	$7.1 \times 10^{-9}$	0.17	0.56	0.81	$4.9 \times 10^{-1}$
7	rs848445	77572461	PHTF2	E	T/C	0.23	-0.20	0.03	$2.3 \times 10^{-9}$	0.08	-0.09	1.03	$9.3 \times 10^{-1}$
7	rs6963105	75097488	POM121C	E	A/G	0.43	-0.19	0.03	$3.8 \times 10^{-9}$	0.06	0.17	1.15	$8.8 \times 10^{-1}$
7	rs10274928	28142088	JAZF1	E	A/G	0.49	0.16	0.03	$8.2 \times 10^{-8}$	0.66	-0.05	0.63	$9.3 \times 10^{-1}$
7	rs11771693	150050111	RARRES2	E	A/G	0.67	0.18	0.03	$1.9 \times 10^{-8}$	0.52	-0.25	0.62	$6.8 \times 10^{-1}$
8	rs4841569	11452177	BLK-GATA4	E/AS	G/A	0.51	0.47	0.02	$5.6 \times 10^{-10}$	0.91	0.33	1.13	$7.7 \times 10^{-1}$
8	rs2898290	11433909	BLK-GATA4	E	T/C	0.53	0.53	0.80	$3.2 \times 10^{-8}$	0.61	-0.71	0.60	$2.3 \times 10^{-1}$
<b>8</b>	<b>rs1986971</b>	<b>10268736</b>	<b>MSRA</b>	<b>E</b>	<b>A/G</b>	<b>0.70</b>	<b>0.26</b>	<b>0.03</b>	<b><math>1.6 \times 10^{-14}</math></b>	<b>0.80</b>	<b>1.45<sup>c</sup></b>	<b>0.73</b>	<b><math>4.8 \times 10^{-2}</math></b>
8	rs1906672	38130025	WHSC1L1	E	A/G	0.23	0.30	0.04	$1.2 \times 10^{-16}$	0.16	0.08	0.82	$9.2 \times 10^{-1}$
8	rs72688070	81393697	Y_RNA	E	T/C	0.17	-0.27	0.04	$2.8 \times 10^{-11}$	0.44	-0.62	0.60	$3.0 \times 10^{-1}$
<b>8</b>	<b>rs62491354</b>	<b>9730663</b>	<b>TNKS</b>	<b>E</b>	<b>A/G</b>	<b>0.13</b>	<b>0.31</b>	<b>0.04</b>	<b><math>3.3 \times 10^{-12}</math></b>	<b>0.13</b>	<b>-2.38</b>	<b>0.80</b>	<b><math>3.0 \times 10^{-3}</math></b>
8	rs4129585	143312933	TSNARE1	E	A/C	0.44	0.19	0.03	$1.0 \times 10^{-9}$	0.06	-1.10	1.18	$3.5 \times 10^{-1}$
8	rs6557876	25900675	EBF2	E	C/T	0.25	-0.37	0.05	$2.8 \times 10^{-14}$	0.50	-0.20	0.60	$7.4 \times 10^{-1}$
8	rs894344	135612745	ZFAT	E	A/G	0.60	-0.26	0.05	$3.2 \times 10^{-8}$	0.65	-0.17	0.64	$8.0 \times 10^{-1}$
9	rs10760117	123586737	PSMD5	E	T/G	0.42	0.28	0.05	$6.1 \times 10^{-10}$	0.78	-1.39	0.72	$5.3 \times 10^{-2}$
9	rs1332813	9350706	PTPRD	E	T/C	0.35	0.22	0.03	$2.3 \times 10^{-12}$	0.36	0.02	0.62	$9.7 \times 10^{-1}$
<b>9</b>	<b>rs7045409</b>	<b>95201540</b>	<b>CENPP</b>	<b>E</b>	<b>A/T</b>	<b>0.37</b>	<b>-0.19</b>	<b>0.03</b>	<b><math>2.6 \times 10^{-9}</math></b>	<b>0.90</b>	<b>2.16</b>	<b>0.94</b>	<b><math>2.2 \times 10^{-2}</math></b>
9	rs1891730	130309028	FAM129B	E	T/C	0.62	-0.18	0.03	$7.7 \times 10^{-9}$	0.39	-1.13	0.61	$6.2 \times 10^{-2}$
9	rs28558845	4334791	GLIS3	E	C/G	0.16	-0.26	0.04	$1.2 \times 10^{-9}$	0.24	0.29	0.72	$6.9 \times 10^{-1}$
10	rs1133400	134459388	INPP5A	E	A/G	0.79	-0.30	0.04	$2.5 \times 10^{-15}$	0.86	0.11	0.88	$9.0 \times 10^{-1}$
10	rs11191548	104846178	CYP17A1-NT5C2	E	T/C	0.91	1.16	0.12	$7.0 \times 10^{-24}$	0.98	-0.41	1.62	$8.0 \times 10^{-1}$
<b>10</b>	<b>rs112184198</b>	<b>102604514</b>	<b>PAX2</b>	<b>E</b>	<b>A/G</b>	<b>0.10</b>	<b>-0.66</b>	<b>0.08</b>	<b><math>3.6 \times 10^{-18}</math></b>	<b>0.06</b>	<b>3.67</b>	<b>1.37</b>	<b><math>8.0 \times 10^{-3}</math></b>
10	rs1813353	18707448	CACNB2	E	T/C	0.68	0.57	—	$2.6 \times 10^{-12}$	0.84	-0.74	0.84	$3.8 \times 10^{-1}$
10	rs932764	95895940	PLCE1	E	G/A	0.44	0.48	—	$7.1 \times 10^{-16}$	0.15	0.59	0.85	$4.9 \times 10^{-1}$
10	rs1801253	115805056	ADRB1	E	G/C	0.27	-0.57	0.09	$4.7 \times 10^{-10}$	0.34	0.21	0.64	$7.5 \times 10^{-1}$
10	rs4387287	105677897	OBFC1	E/AS	A/C	0.16	0.36	—	$9.1 \times 10^{-10}$	0.73	-0.00	0.67	$1.0 \times 10^{-0}$
10	rs4590817	63467553	C10orf107	E	G/C	0.84	0.65	—	$4.0 \times 10^{-12}$	0.84	-0.55	0.78	$4.8 \times 10^{-1}$
10	rs7912283	133773019	PPP2R2D	E	A/G	0.35	0.21	0.03	$6.4 \times 10^{-11}$	0.89	-0.31	0.89	$7.3 \times 10^{-1}$
10	rs12572586	74751579	PLA2G12B	E	T/C	0.94	-0.39	0.06	$1.2 \times 10^{-9}$	0.95	1.91	1.41	$1.8 \times 10^{-1}$
10	rs11197813	118523933	HSPA12A	E	A/G	0.70	-0.18	0.03	$3.5 \times 10^{-8}$	0.82	0.97	0.74	$1.9 \times 10^{-1}$
10	rs4373814	18419972	CACNB2	E	G/C	0.55	-0.37	—	$4.8 \times 10^{-11}$	0.39	-0.82	0.60	$1.7 \times 10^{-1}$
11	rs7103648	47461783	RAPSN-PSMC3- SLC39A13	E	A/G	0.61	-0.33	0.05	$4.4 \times 10^{-13}$	0.85	0.97	0.85	$2.6 \times 10^{-1}$
11	rs751984	61278246	LRRIC10B	E	T/C	0.88	0.41	0.07	$3.8 \times 10^{-9}$	0.79	0.04	0.72	$9.5 \times 10^{-1}$
11	rs661348	1905292	LSP1-TNNT3	E	T/C	0.57	-0.65	0.11	$7.0 \times 10^{-10}$	0.86	0.89	0.98	$3.3 \times 10^{-1}$
11	rs7129220	10350538	ADM	E	G/A	0.89	-0.62	—	$3.0 \times 10^{-12}$	0.92	-1.02	1.16	$3.8 \times 10^{-1}$

(Continues)



TABLE 2 (Continued)

Chr	SNP	Position <sup>a</sup>	Nearest gene	Population	EA/ RA	Discovery sample				EMaBS sample			
						EAF	$\beta$	SE	<i>p</i> -value	EAF	$\beta^b$	SE	<i>p</i> -value
11	rs633185	100593538	FLJ32810- TMEM133	E	G/C	0.28	-0.57	—	$1.2 \times 10^{-17}$	0.23	-0.92	0.71	$2.0 \times 10^{-1}$
11	rs4757391	16302939	SOX6	E/AS/AA	T/C	0.21	0.56	0.12	$5.7 \times 10^{-10}$	0.74	0.19	0.65	$7.7 \times 10^{-1}$
11	rs11229457	58207203	OR5B12	E/AS	T/C	0.24	-0.31	—	$2.7 \times 10^{-8}$	0.29	-0.36	0.62	$5.6 \times 10^{-1}$
11	rs381815	16902268	PLEKHA7	E	T/C	0.26	0.57	—	$5.3 \times 10^{-11}$	0.26	-0.27	0.71	$5.6 \times 10^{-1}$
11	rs3741378	65408937	RELA	E	T/C	0.14	-0.55	—	$3.4 \times 10^{-10}$	0.76	-1.04	0.69	$1.3 \times 10^{-1}$
11	rs4385883	51539339	TRIM48	E	T/A	0.29	-0.25	0.04	$1.4 \times 10^{-12}$	0.53	-0.10	0.60	$8.6 \times 10^{-1}$
11	rs11041530	7701503	CYB5R2	AA	C/G	0.11	-1.35	0.25	$4.0 \times 10^{-8}$	0.17	0.49	0.82	$5.5 \times 10^{-1}$
11	rs1401454	16250183	SOX6	AA	T/C	0.46	0.55	0.16	$5.6 \times 10^{-8}$	0.46	-0.60	0.59	$3.1 \times 10^{-1}$
11	rs7941684	5532222	UBQLN3	AA	T/G	0.80	-1.23	0.22	$2.4 \times 10^{-8}$	0.82	-0.69	0.80	$3.8 \times 10^{-1}$
11	rs11031051	30355707	ARL14EP	E	A/C	0.69	-0.22	0.03	$7.7 \times 10^{-12}$	0.58	0.26	0.61	$6.7 \times 10^{-1}$
<b>11</b>	<b>rs67976715</b>	<b>68023742</b>	<b>C11orf24</b>	<b>E</b>	<b>C/G</b>	<b>0.23</b>	<b>0.21</b>	<b>0.04</b>	<b><math>6.8 \times 10^{-9}</math></b>	<b>0.07</b>	<b>-2.44</b>	<b>1.23</b>	<b><math>4.8 \times 10^{-2}</math></b>
11	rs10743086	8774923	ST5	E	A/G	0.21	-0.21	0.04	$3.6 \times 10^{-8}$	0.33	0.96	0.61	$1.2 \times 10^{-1}$
12	rs11067763	116198341	MED13L	AS	A/G	0.62	0.81	0.10	$5.7 \times 10^{-16}$	0.78	0.42	0.68	$5.4 \times 10^{-1}$
12	rs10858966	90567026	ATP2B1	E	C/G	0.29	0.26	0.03	$9.2 \times 10^{-15}$	0.02	0.86	2.17	$6.9 \times 10^{-1}$
12	rs2024385	12888438	APOLD1	E	A/T	0.42	-0.26	0.03	$5.9 \times 10^{-18}$	0.46	-0.57	0.59	$3.4 \times 10^{-1}$
12	rs11571376	1059556	RAD52	E	C/G	0.70	-0.18	0.03	$5.7 \times 10^{-8}$	0.73	-0.49	0.71	$4.9 \times 10^{-1}$
12	rs6487543	26438189	SSPN	E	A/G	0.77	0.30	0.05	$6.3 \times 10^{-10}$	0.08	-0.41	1.05	$7.0 \times 10^{-1}$
<b>12</b>	<b>rs2681492</b>	<b>90013089</b>	<b>ATP2B1</b>	<b>E/AS/AA</b>	<b>G/A</b>	<b>0.17</b>	<b>-0.97</b>	<b>0.16</b>	<b><math>5.8 \times 10^{-8}</math></b>	<b>0.15</b>	<b>1.84</b>	<b>0.79</b>	<b><math>2.1 \times 10^{-2}</math></b>
12	rs10850411	115387796	TBX5-TBX3	E	T/C	0.70	0.35	—	$5.4 \times 10^{-8}$	0.61	-0.45	0.60	$4.5 \times 10^{-1}$
<b>12</b>	<b>rs17249754</b>	<b>90060586</b>	<b>ATP2B1</b>	<b>E</b>	<b>G/A</b>	<b>0.84</b>	<b>0.93</b>	<b>—</b>	<b><math>1.8 \times 10^{-18}</math></b>	<b>0.85</b>	<b>-1.58</b>	<b>0.80</b>	<b><math>4.8 \times 10^{-2}</math></b>
12	rs10437954	58003922	ARHGEF25	E	A/G	0.90	-0.41	0.05	$1.6 \times 10^{-14}$	0.67	0.61	0.66	$3.5 \times 10^{-1}$
12	rs5742643	102837863	IGF1	E	A/G	0.25	-0.22	0.03	$2.0 \times 10^{-10}$	0.26	-0.67	0.69	$3.3 \times 10^{-1}$
12	rs7963801	79685226	SYT1	E	T/C	0.41	-0.24	0.03	$2.8 \times 10^{-14}$	0.01	3.33	2.54	$1.9 \times 10^{-1}$
12	rs7976167	24210599	SOX5	E	T/C	0.69	0.18	0.03	$3.8 \times 10^{-8}$	0.84	1.61	0.82	$5.1 \times 10^{-2}$
13	rs9532243	32191408	RXFP2	E	A/C	0.48	0.22	0.03	$8.2 \times 10^{-14}$	0.55	-0.33	0.59	$5.8 \times 10^{-1}$
13	rs606950	22298923	FGF9	E	A/G	0.62	0.27	0.03	$3.2 \times 10^{-18}$	0.47	0.88	0.60	$1.4 \times 10^{-1}$
13	rs78474310	73826901	KLF5	E	A/G	0.96	-0.47	0.07	$1.5 \times 10^{-10}$	0.99	-0.72	3.38	$8.3 \times 10^{-1}$
13	rs9526707	51489186	RNASEH2B	E	A/G	0.32	-0.20	0.03	$2.7 \times 10^{-10}$	0.12	-1.59	0.91	$8.0 \times 10^{-2}$
13	rs9549328	113636156	MCF2L	E	T/C	0.23	0.32	0.06	$1.5 \times 10^{-8}$	0.15	0.59	0.89	$5.1 \times 10^{-1}$
14	rs8014182	103859962	MARK3	E	T/C	0.14	-0.33	0.04	$5.2 \times 10^{-14}$	0.02	0.19	1.93	$9.2 \times 10^{-1}$
14	rs11159091	75074316	LTBP2	E	A/G	0.46	0.20	0.03	$6.7 \times 10^{-11}$	0.01	2.00	2.77	$4.7 \times 10^{-1}$
14	rs11623535	72462381	RGS6	E	A/G	0.74	0.21	0.03	$1.0 \times 10^{-9}$	0.57	0.71	0.60	$2.4 \times 10^{-1}$
14	rs17115145	30122409	PRKD1	E	T/C	0.40	0.18	0.03	$7.4 \times 10^{-9}$	0.57	-0.33	0.58	$5.7 \times 10^{-1}$
14	rs9888615	53377540	FERMT2	E	T/C	0.29	-0.32	0.05	$3.5 \times 10^{-10}$	0.62	0.38	0.63	$5.4 \times 10^{-1}$
14	rs8016306	63928546	PPP2R5E	E	A/G	0.80	0.34	0.06	$3.7 \times 10^{-9}$	0.15	-0.10	0.84	$9.1 \times 10^{-1}$
15	rs1563894	68635775	TGA11	E	A/G	0.19	-0.09	—	$2.9 \times 10^{-8}$	0.69	0.17	0.63	$7.8 \times 10^{-1}$
15	rs2521501	91437388	FURIN-FES	E	T/A	0.31	0.65	—	$5.2 \times 10^{-9}$	0.21	-0.39	0.76	$6.1 \times 10^{-1}$
15	rs1378942	75077367	CYP1A1-ULK3	E	C/A	0.35	0.61	—	$5.7 \times 10^{-23}$	0.97	-0.03	1.70	$9.9 \times 10^{-1}$
15	rs35199222	81013037	ABHD17C	E	A/G	0.45	0.32	0.05	$5.2 \times 10^{-12}$	0.07	0.39	1.18	$7.5 \times 10^{-1}$
15	rs11632436	86295286	RP11-158M2.4	E	C/G	0.50	0.22	0.03	$2.0 \times 10^{-13}$	0.21	-0.31	0.73	$6.7 \times 10^{-1}$
15	rs3743157	85680532	PDE8A	E	A/C	0.17	0.29	0.04	$4.2 \times 10^{-13}$	0.71	0.10	0.66	$8.8 \times 10^{-1}$
15	rs4965529	100145224	MEF2A	E	T/G	0.17	-0.26	0.04	$5.4 \times 10^{-11}$	0.31	-0.16	0.64	$8.0 \times 10^{-1}$
16	rs11639856	24788645	TNRC6A	E/AA	A/T	0.19	-0.34	0.06	$1.3 \times 10^{-8}$	0.19	0.90	0.78	$2.5 \times 10^{-1}$
16	rs11643209	75331044	CFDP1	E	T/G	0.42	-0.34	0.05	$1.8 \times 10^{-12}$	0.74	0.08	0.70	$9.1 \times 10^{-1}$
16	rs7187540	85318302	LINC00311	E	A/C	0.34	-0.20	0.03	$1.0 \times 10^{-8}$	0.15	0.01	0.89	$9.9 \times 10^{-1}$

(Continues)

TABLE 2 (Continued)

Chr	SNP	Position <sup>a</sup>	Nearest gene	Population	EA/ RA	Discovery sample				EMaBS sample			
						EAF	$\beta$	SE	<i>p</i> -value	EAF	$\beta^b$	SE	<i>p</i> -value
17	rs4925159	18185510	TOP3A	E	A/G	0.43	0.22	0.03	$9.7 \times 10^{-13}$	0.73	0.29	0.63	$6.5 \times 10^{-1}$
17	rs34430710	56876627	PPM1E	E	A/T	0.68	-0.21	0.03	$5.0 \times 10^{-11}$	0.89	0.95	0.89	$2.9 \times 10^{-1}$
17	rs1036902	58950791	BCAS3	E	T/C	0.84	-0.25	0.04	$1.7 \times 10^{-9}$	0.19	-0.14	0.73	$8.5 \times 10^{-1}$
17	rs1551355	30032420	RP11-805L22.1	E	T/C	0.23	0.21	0.04	$3.9 \times 10^{-9}$	0.03	-0.05	1.94	$9.8 \times 10^{-1}$
17	rs12940887	47402807	ZNF652	E	T/C	0.38	0.36	—	$1.8 \times 10^{-10}$	0.07	-0.48	1.43	$7.4 \times 10^{-1}$
17	rs57927100	75317300	SEPT9	E	C/G	0.26	-0.31	0.05	$4.0 \times 10^{-14}$	0.78	-0.60	0.70	$3.9 \times 10^{-1}$
17	rs2467099	73949045	ACOX1	E	T/C	0.22	-0.30	0.06	$3.3 \times 10^{-8}$	0.12	-0.82	0.95	$3.9 \times 10^{-1}$
17	rs12941318	1333598	CRK	E	T/C	0.49	-0.27	0.05	$2.5 \times 10^{-8}$	0.75	0.67	0.66	$3.1 \times 10^{-1}$
17	rs12946454	43208121	PLCD3	E	T/A	0.28	0.50	0.17	$1.0 \times 10^{-8}$	0.06	-0.06	1.20	$9.6 \times 10^{-1}$
17	rs7406910	46688256	HOXB7	E/AS	T/C	0.12	-0.46	—	$3.8 \times 10^{-8}$	0.26	0.38	0.65	$5.6 \times 10^{-1}$
17	rs112280096	79367409	RP11-1055B8.6	E	A/C	0.36	-0.20	0.04	$1.3 \times 10^{-9}$	0.06	0.68	1.45	$6.4 \times 10^{-1}$
18	rs12958173	42141977	SETBP1	E	A/C	0.31	0.36	0.05	$1.4 \times 10^{-13}$	0.32	0.72	0.63	$2.6 \times 10^{-1}$
18	rs12454712	60845884	BCL2	E	T/C	0.62	0.19	0.03	$5.8 \times 10^{-9}$	0.76	0.86	0.70	$2.2 \times 10^{-1}$
18	rs10048404	54578482	WDR7	E	T/C	0.37	-0.26	0.03	$1.9 \times 10^{-16}$	0.05	-1.12	1.33	$4.9 \times 10^{-1}$
18	rs11876341	48799991	MEX3C	E	A/G	0.69	-0.21	0.03	$1.8 \times 10^{-10}$	0.94	2.01	1.48	$1.8 \times 10^{-1}$
19	rs4247374	7252756	INSR	E	T/C	0.14	-0.59	0.08	$1.2 \times 10^{-18}$	0.02	-0.93	2.23	$6.7 \times 10^{-1}$
20	rs1327235	10969030	JAG1	E	G/A	0.46	0.34	—	$1.9 \times 10^{-8}$	0.59	-0.03	0.59	$9.6 \times 10^{-1}$
20	rs6015450	57751117	GNAS-EDN3	E	G/A	0.12	0.90	—	$3.9 \times 10^{-23}$	0.18	0.51	0.74	$5.0 \times 10^{-1}$
21	rs12627651	44760603	CRYAA-SIK1	E	A/G	0.29	0.39	0.05	$2.6 \times 10^{-14}$	0.07	1.70	1.28	$5.9 \times 10^{-1}$
22	rs4823006	29451671	ZNRF3	E/AA	G/A	0.42	-0.26	0.05	$7.9 \times 10^{-9}$	0.40	0.86	0.58	$1.4 \times 10^{-1}$
22	rs28578714	50727921	PLXNB2	E	T/C	0.61	0.21	0.03	$2.5 \times 10^{-10}$	0.53	-0.59	0.58	$3.1 \times 10^{-1}$

Note: Bold indicate  $p < 5.0 \times 10^{-2}$  for replication analysis.

Abbreviations: AA, African ancestry; AS, Asian ancestry; Chr, chromosomes; E, European ancestry; EA, effect allele; EAF, effect allele frequency; RA, reference allele; SE, standard error; SNP, single nucleotide polymorphism;  $\beta$ , Effect size estimates correspond to mean difference in mmHg per effect allele for systolic or diastolic blood pressure, adjusted for age and body mass index.

<sup>a</sup>Given with respect to Build 37 (GRCh37/hg19).

<sup>b</sup>Adjusted for age and body mass index.

<sup>c</sup>Indicate same  $\beta$  direction in both the discovery and EMaBS populations.

with BP at  $p < .05$  by chance alone. None of the replicated SNPs met a Bonferroni corrected significance threshold ( $0.05/370 = 1.35 \times 10^{-4}$ ), although one (rs6712094 intergenic between *FIGN* and *GRB14*) was very close ( $p = 2.6 \times 10^{-4}$ ) for association with systolic BP. The most strongly associated SNPs for association with diastolic BP were rs805303 between *BAT2* and *BAT5* ( $p = 1.0 \times 10^{-3}$ ) and *PDLIM5* rs7694000 ( $p = 1.3 \times 10^{-3}$ ).

## 4 | DISCUSSION

To our knowledge, this is the first genetic analysis examining variants associated with BP among African adolescents. We hypothesized that common genetic variants (unique or not unique to populations in Africa) were associated with systolic and, or diastolic BP in Ugandan adolescents and that these associations may overlap with associated variants identified in previous studies of Africans. The GWAS revealed no novel or previously identified variant associated with systolic or diastolic BP in our

study population. Thirty-three SNPs were associated with BP in the replication analysis, with the direction of effect consistent with the discovery population for 14 SNPs. There were no SNPs reaching a Bonferroni-adjusted significance level. None of the replicated SNPs were located in genes with monogenic effect on hypertension (Ehret & Caulfield, 2013).

The SNPs most strongly associated with either systolic or diastolic BP were of borderline significance and none have been reported as associated with BP in previous BP GWASs. The most strongly associated SNPs were mostly common variants with modest effect sizes and might uniquely influence BP in African population. It is important for larger genetic studies of African population to investigate the role of these SNPs in BP regulation among Africans. These top SNPs are potential candidates for replication analysis in African populations.

The failure to identify variants strongly associated with BP presumably occurred because the study was underpowered to detect effects of rare variants or small effects of common variants. Blood pressure is most likely a polygenic

**TABLE 3** Loci associated with diastolic blood pressure identified from previous GWAS and results of replication in Entebbe Mother and Baby Study (EMaBS) sample

Chr	SNP	Position <sup>a</sup>	Nearest gene	Population	EA/ RA	Discovery sample				EMaBS sample			
						EAF	$\beta$	SE	p-value	EAF	$\beta^b$	SE	p-value
1	rs17367504	11862778	MTHFR/NPPB	E	G/A	0.15	-0.55	—	$3.5 \times 10^{-19}$	0.09	-0.53	0.97	$5.8 \times 10^{-1}$
<b>1</b>	<b>rs2169137</b>	<b>204497913</b>	<b>MDM4</b>	<b>E/AS/AA</b>	<b>G/C</b>	<b>0.27</b>	<b>-0.36</b>	<b>0.07</b>	<b><math>5.9 \times 10^{-8}</math></b>	<b>0.23</b>	<b>1.32</b>	<b>0.61</b>	<b><math>3.1 \times 10^{-2}</math></b>
1	rs13306561	11865804	MTHFR	E/AS/AA	G/A	0.15	-0.52	0.09	$3.0 \times 10^{-19}$	0.27	0.04	0.58	$9.4 \times 10^{-1}$
1	rs2932538	113216543	MOV10	E	G/A	0.75	0.24	—	$9.9 \times 10^{-10}$	0.85	-0.25	0.70	$3.6 \times 10^{-1}$
1	rs4846049	11850365	MTHFR-NPPB	E	T/G	0.33	-0.55	0.10	$6.7 \times 10^{-8}$	0.51	0.72	0.50	$1.6 \times 10^{-1}$
1	rs6686889	25030470	chr1mb25	E	T/C	0.25	0.19	0.03	$3.6 \times 10^{-9}$	0.36	-0.28	0.53	$5.9 \times 10^{-1}$
1	s12405515	172357441	DNM3	E	T/G	0.56	-0.17	0.03	$1.4 \times 10^{-9}$	0.20	0.68	0.66	$3.0 \times 10^{-1}$
1	s12408022	217718789	GPATCH2	E	T/C	0.26	0.20	0.03	$2.4 \times 10^{-10}$	0.06	-0.43	1.14	$7.1 \times 10^{-1}$
1	rs10916082	227252626	CDC42BPA	E	A/G	0.73	-0.18	0.03	$8.4 \times 10^{-9}$	0.52	-0.06	0.52	$9.1 \times 10^{-1}$
1	rs2760061	228191075	WNT3A	E	A/T	0.47	0.23	0.03	$2.1 \times 10^{-16}$	0.62	-0.02	0.56	$9.7 \times 10^{-1}$
1	rs953492	243471192	SDCCAG8	E	A/G	0.46	0.22	0.03	$7.4 \times 10^{-16}$	0.68	-0.18	0.56	$7.5 \times 10^{-1}$
1	rs2004776	230848702	AGT	E	T/C	0.23	0.32	0.06	$5.0 \times 10^{-8}$	0.52	-0.45	0.52	$3.9 \times 10^{-1}$
1	rs1565716	29549216	MECR	E	A/G	0.07	0.21	0.03	$3.5 \times 10^{-10}$	0.09	0.66	1.02	$5.2 \times 10^{-1}$
1	rs35981664	218549354	TGFB2	E	A/T	0.69	-0.16	0.02	$2.0 \times 10^{-17}$	0.99	-0.58	3.69	$8.8 \times 10^{-1}$
1	rs12142296	46541679	PIK3R3	E	T/G	0.86	-0.16	0.03	$8.9 \times 10^{-11}$	0.98	1.09	1.66	$5.1 \times 10^{-1}$
1	rs72704264	145713305	CD160	E	C/G	0.21	0.12	0.02	$3.6 \times 10^{-8}$	0.03	0.58	1.44	$6.9 \times 10^{-1}$
2	rs1446468	164963486	FIGN-GRB14	E	T/C	0.53	-0.50	0.07	$6.9 \times 10^{-9}$	0.95	-0.61	1.17	$6.1 \times 10^{-1}$
2	rs16823124	183224127	PDE1A	E	A/G	0.42	0.26	0.04	$2.0 \times 10^{-10}$	0.11	-0.06	0.80	$9.4 \times 10^{-1}$
<b>2</b>	<b>rs55701159</b>	<b>25139596</b>	<b>ADCY3</b>	<b>E</b>	<b>T/G</b>	<b>0.89</b>	<b>0.29</b>	<b>0.04</b>	<b><math>7.2 \times 10^{-11}</math></b>	<b>0.89</b>	<b>-1.98</b>	<b>0.79</b>	<b><math>1.3 \times 10^{-2}</math></b>
2	rs4952611	40567743	SLC8A1	E	T/C	0.58	-0.16	0.03	$4.0 \times 10^{-8}$	0.72	-0.08	0.59	$9.0 \times 10^{-1}$
2	rs2579519	96675166	GPAT2-FAHD2CP	E	T/C	0.63	-0.20	0.03	$4.8 \times 10^{-12}$	0.72	0.01	0.61	$9.9 \times 10^{-1}$
2	rs7592578	191439591	TMEM194B	E	T/G	0.19	-0.24	0.04	$9.5 \times 10^{-12}$	0.27	-0.81	0.61	$1.8 \times 10^{-1}$
2	rs1063281	218668732	TNS1	E	T/C	0.60	-0.20	0.03	$1.3 \times 10^{-12}$	0.59	0.28	0.55	$6.1 \times 10^{-1}$
2	rs1975487	55809054	PNPT1	E	A/G	0.46	-0.16	0.03	$1.8 \times 10^{-9}$	0.68	0.02	0.55	$9.7 \times 10^{-1}$
2	rs1220128	158499902	ACVR1C	E	C/G	0.85	0.19	0.02	$6.2 \times 10^{-15}$	0.40	0.20	0.53	$7.1 \times 10^{-1}$
2	rs1996992	219651349	CYP27A1	E	T/G	0.05	-0.30	0.04	$4.7 \times 10^{-14}$	0.09	-1.00	0.93	$2.8 \times 10^{-1}$
2	rs13001283	127183454	GYPC	E	A/G	0.16	0.15	0.02	$1.9 \times 10^{-10}$	0.11	0.81	0.79	$3.1 \times 10^{-1}$
2	rs7606205	144146311	ARHGAP15	E	A/C	0.70	-0.13	0.02	$2.4 \times 10^{-11}$	0.49	-0.40	0.53	$4.5 \times 10^{-1}$
2	rs34570306	146272860	ZEB2	E	T/C	0.53	-0.12	0.02	$1.2 \times 10^{-11}$	0.07	-0.00	1.04	$1.0 \times 10^{-1}$
2	rs4851462	98357163	ZAP70	E	T/C	0.63	-0.12	0.02	$4.0 \times 10^{-11}$	0.90	-0.46	0.91	$6.2 \times 10^{-1}$
2	rs2707238	38094149	LINC00211	E	C/G	0.28	0.10	0.02	$6.8 \times 10^{-8}$	0.28	-0.42	0.60	$4.8 \times 10^{-1}$
3	rs11128722	14958126	FGD5	E	A/G	0.56	-0.17	0.03	$5.1 \times 10^{-10}$	0.32	0.55	0.53	$3.0 \times 10^{-1}$
3	rs918466	64710253	ADAMTS9	E	A/G	0.41	-0.18	0.03	$1.7 \times 10^{-11}$	0.90	0.57	0.86	$5.1 \times 10^{-1}$
3	rs36022378	49913705	CAMKV- ACTBP13	E	T/C	0.80	-0.20	0.03	$4.7 \times 10^{-9}$	0.98	-0.37	2.44	$8.8 \times 10^{-1}$
3	rs743757	50476378	CACNA2D2	E	C/G	0.14	0.25	0.04	$2.4 \times 10^{-10}$	0.55	-0.60	0.54	$2.7 \times 10^{-1}$
3	s9827472	56726646	FAM208A	E	T/C	0.37	-0.18	0.03	$4.3 \times 10^{-10}$	0.48	0.19	0.52	$7.0 \times 10^{-1}$
3	rs2306374	138119952	MRAS	E	T/C	0.84	-0.18	0.03	$7.4 \times 10^{-9}$	0.96	2.03	1.37	$1.4 \times 10^{-1}$
3	rs12374077	185317674	SEN2	E	C/G	0.35	0.16	0.03	$9.2 \times 10^{-9}$	0.47	0.52	0.52	$3.2 \times 10^{-1}$
3	rs143112823	154707967	RP11-439C8.2	E	A/G	0.09	-0.40	0.05	$1.4 \times 10^{-14}$	0.09	-0.41	0.99	$6.8 \times 10^{-1}$
3	rs419076	169100886	MECOM	E	T/C	0.47	0.24	—	$2.1 \times 10^{-12}$	0.57	-0.29	0.54	$5.8 \times 10^{-1}$
3	rs319690	47927484	MAP4	E	T/C	0.50	0.28	0.05	$1.8 \times 10^{-8}$	0.44	0.26	0.55	$6.3 \times 10^{-1}$
3	rs1706003	194299967	TMEM44	E	T/G	0.47	0.12	0.02	$5.8 \times 10^{-12}$	0.01	-3.51	2.17	$1.1 \times 10^{-1}$
3	rs11923667	101268080	TRMT10C	E	A/T	0.41	0.12	0.02	$3.1 \times 10^{-11}$	0.27	-1.06	0.57	$6.5 \times 10^{-2}$

(Continues)

TABLE 3 (Continued)

Chr	SNP	Position <sup>a</sup>	Nearest gene	Population	EA/ RA	Discovery sample				EMaBS sample			
						EAF	$\beta$	SE	p-value	EAF	$\beta^b$	SE	p-value
3	rs6777317	197070959	DLG1	E	A/G	0.92	0.12	0.02	$1.5 \times 10^{-10}$	0.90	0.76	0.92	$4.1 \times 10^{-1}$
3	rs4634143	23163749	UBE2E2	E	T/C	0.30	0.12	0.02	$7.9 \times 10^{-10}$	0.07	0.10	1.06	$9.3 \times 10^{-1}$
3	rs3774372	41877414	ULK4	E	T/C	0.83	-0.37	—	$9.0 \times 10^{-14}$	0.77	-0.72	0.59	$2.2 \times 10^{-1}$
4	rs13139571	156645513	GUCY1A3- GUCY1B3	E	C/A	0.76	0.26	—	$2.2 \times 10^{-10}$	0.86	0.89	0.75	$2.4 \times 10^{-1}$
4	rs6825911	111381638	ENPEP	AS	C/T	0.51	0.39	0.07	$9.0 \times 10^{-9}$	0.61	0.46	0.55	$4.0 \times 10^{-1}$
4	rs2291435	38387395	TBC1D1-FLJ13197	E/AA	T/C	0.52	-0.16	0.03	$4.3 \times 10^{-9}$	0.30	0.07	5.58	$9.0 \times 10^{-1}$
4	rs66887589	120509279	PDE5A	E	T/C	0.52	-0.22	0.03	$3.4 \times 10^{-15}$	0.62	-0.46	0.55	$4.0 \times 10^{-1}$
4	rs1458038	81164723	FGF5	E	T/C	0.29	0.46	—	$8.5 \times 10^{-25}$	0.04	0.98	1.35	$4.7 \times 10^{-1}$
4	rs223361	103769304	UBE2D3	E	T/C	0.66	0.17	0.02	$2.7 \times 10^{-20}$	0.48	-0.10	0.54	$8.5 \times 10^{-1}$
4	rs28667801	26785356	STIM2	E	A/T	0.59	-0.16	0.02	$1.9 \times 10^{-19}$	0.87	-0.01	0.78	$9.9 \times 10^{-1}$
4	rs55829085	2165493	POLN	E	A/C	0.95	-0.28	0.04	$3.0 \times 10^{-11}$	0.99	2.13	2.50	$4.0 \times 10^{-1}$
<b>4</b>	<b>rs7694000</b>	<b>95324968</b>	<b>PDLIM5</b>	<b>E</b>	<b>A/T</b>	<b>0.54</b>	<b>-0.10</b>	<b>0.02</b>	<b><math>3.5 \times 10^{-8}</math></b>	<b>0.21</b>	<b>2.03</b>	<b>0.63</b>	<b><math>1.3 \times 10^{-3}</math></b>
4	rs62312401	116987529	NDST4-TRAM1L1	AA	C/G	0.94	1.13	0.24	$3.5 \times 10^{-9}$	0.04	-2.14	1.39	$1.3 \times 10^{-1}$
5	rs12521868	131784393	C5orf56	E	T/G	0.37	-0.19	—	$6.1 \times 10^{-11}$	0.04	-0.06	1.44	$9.6 \times 10^{-1}$
5	rs1173771	32815028	NPR3-C5orf23	E	G/A	0.60	0.26	—	$9.1 \times 10^{-12}$	0.82	1.04	0.72	$1.5 \times 10^{-1}$
5	rs11953630	157845402	EBF1	E	T/C	0.37	-0.28	—	$3.8 \times 10^{-13}$	0.13	1.27	0.77	$9.9 \times 10^{-2}$
5	rs10077885	114390121	TRIM36	E	A/C	0.50	-0.17	0.03	$4.0 \times 10^{-11}$	0.65	-0.40	0.55	$4.7 \times 10^{-1}$
5	rs6891344	123136656	CSNK1G3	E	A/G	0.82	0.23	0.03	$1.6 \times 10^{-11}$	0.72	0.45	0.56	$4.1 \times 10^{-1}$
5	rs10078021	75038431	POC5	E	T/G	0.63	-0.16	0.03	$1.3 \times 10^{-8}$	0.15	-0.41	0.69	$5.5 \times 10^{-1}$
5	rs72812846	173377636	CPEB4	E	A/T	0.28	-0.21	0.03	$2.2 \times 10^{-11}$	0.04	-0.18	1.43	$9.0 \times 10^{-1}$
5	rs10062049	61553881	KIF2A	E	T/C	0.14	0.22	0.02	$4.5 \times 10^{-18}$	0.32	0.62	0.63	$3.2 \times 10^{-1}$
<b>5</b>	<b>rs954767</b>	<b>3706050</b>	<b>IRX1</b>	<b>E</b>	<b>A/C</b>	<b>0.74</b>	<b>-0.15</b>	<b>0.02</b>	<b><math>4.2 \times 10^{-14}</math></b>	<b>0.68</b>	<b>1.14</b>	<b>0.54</b>	<b><math>3.6 \times 10^{-2}</math></b>
5	rs55747751	132397351	HSPA4	E	A/G	0.08	-0.22	0.03	$1.4 \times 10^{-11}$	0.01	-0.17	2.43	$9.4 \times 10^{-1}$
<b>5</b>	<b>rs4286632</b>	<b>66291370</b>	<b>MAST4</b>	<b>E</b>	<b>A/G</b>	<b>0.73</b>	<b>0.12</b>	<b>0.02</b>	<b><math>1.9 \times 10^{-9}</math></b>	<b>0.84</b>	<b>1.50<sup>c</sup></b>	<b>0.74</b>	<b><math>4.3 \times 10^{-2}</math></b>
5	rs2188962	131770805	C5orf56	E/AA	T/C	0.37	-0.20	0.03	$3.0 \times 10^{-11}$	0.03	1.25	1.70	$4.6 \times 10^{-1}$
5	rs12515541	57095011	ACTBL2	E	T/G	0.61	0.12	0.02	$6.2 \times 10^{-11}$	0.49	0.08	0.54	$8.9 \times 10^{-1}$
6	rs926552	29548089	SNORD32B	E/AA	T/C	0.11	-0.26	0.05	$7.2 \times 10^{-8}$	0.21	-0.25	0.63	$7.0 \times 10^{-1}$
6	rs10943605	79655477	PHIP	E/AA	A/G	0.46	0.16	0.03	$3.3 \times 10^{-9}$	0.28	0.10	0.57	$8.6 \times 10^{-1}$
6	rs13205180	51832494	PKHD1	E	T/C	0.49	0.17	0.03	$7.0 \times 10^{-10}$	0.12	0.43	0.81	$6.0 \times 10^{-1}$
6	rs9372498	118572486	SLC35F1	E	A/T	0.08	0.33	0.05	$1.8 \times 10^{-11}$	0.10	0.11	0.87	$9.0 \times 10^{-1}$
6	rs147212971	166178451	PDE10A	E	T/C	0.06	-0.36	0.06	$1.6 \times 10^{-9}$	0.17	0.34	0.74	$6.5 \times 10^{-1}$
6	rs1799945	26091179	HFE	E	G/C	0.14	0.46	—	$1.5 \times 10^{-15}$	0.02	-0.43	1.90	$8.2 \times 10^{-1}$
<b>6</b>	<b>rs805303</b>	<b>31616366</b>	<b>BAT2-BAT5</b>	<b>E</b>	<b>G/A</b>	<b>0.61</b>	<b>0.23</b>	<b>—</b>	<b><math>3.0 \times 10^{-11}</math></b>	<b>0.40</b>	<b>1.75<sup>c</sup></b>	<b>0.54</b>	<b><math>1.0 \times 10^{-3}</math></b>
6	rs13209747	127115454	RSPO3	E/AA/AS	T/C	0.19	0.56	0.12	$2.4 \times 10^{-11}$	0.07	-0.50	0.96	$6.0 \times 10^{-1}$
6	rs17080102	151004770	PLEKHG1	E/AA/AS	C/G	0.10	-0.74	0.15	$1.9 \times 10^{-11}$	0.15	-1.21	0.70	$8.8 \times 10^{-2}$
6	rs9472135	43809802	VEGFA	E	T/C	0.70	0.15	0.02	$4.3 \times 10^{-16}$	0.77	0.58	0.62	$3.5 \times 10^{-1}$
6	rs668459	139835689	CITED2	E	T/C	0.59	-0.11	0.02	$1.0 \times 10^{-10}$	0.28	0.02	0.57	$9.7 \times 10^{-1}$
6	rs598682	154418759	OPRM1	E	A/G	0.25	-0.11	0.02	$7.2 \times 10^{-8}$	0.03	0.23	1.31	$8.6 \times 10^{-1}$
<b>7</b>	<b>rs17428471</b>	<b>27337867</b>	<b>EVX1-HOXA</b>	<b>E/AA/AS</b>	<b>T/G</b>	<b>0.14</b>	<b>0.61</b>	<b>0.14</b>	<b><math>1.6 \times 10^{-9}</math></b>	<b>0.13</b>	<b>2.01<sup>c</sup></b>	<b>0.79</b>	<b><math>1.1 \times 10^{-2}</math></b>
7	rs2969070	2512545	CHST12-LFNG	E	A/G	0.63	-0.18	0.03	$2.9 \times 10^{-11}$	0.97	-0.24	1.58	$8.8 \times 10^{-1}$
<b>7</b>	<b>rs11556924</b>	<b>129663496</b>	<b>ZC3HC1</b>	<b>E</b>	<b>T/C</b>	<b>0.38</b>	<b>-0.21</b>	<b>0.03</b>	<b><math>8.2 \times 10^{-15}</math></b>	<b>0.01</b>	<b>6.90</b>	<b>2.72</b>	<b><math>1.2 \times 10^{-2}</math></b>
7	rs6969780	27159136	HOXA3	E/AA	C/G	0.13	0.26	0.05	$1.1 \times 10^{-8}$	0.39	0.68	0.54	$2.1 \times 10^{-1}$
7	rs891511	150704843	NOS3	E/AA	A/G	0.37	-0.26	0.03	$2.0 \times 10^{-16}$	0.59	-0.55	0.52	$3.0 \times 10^{-1}$
7	rs1947228	96461649	SHFM1	E	T/C	0.42	-0.14	0.02	$2.6 \times 10^{-16}$	0.96	1.01	1.29	$4.4 \times 10^{-1}$
7	rs1722886	134215259	AKR1B10	E	A/T	0.57	0.12	0.02	$3.8 \times 10^{-12}$	0.29	-0.05	0.57	$9.3 \times 10^{-1}$

(Continues)

**TABLE 3** (Continued)

Chr	SNP	Position <sup>a</sup>	Nearest gene	Population	EA/ RA	Discovery sample				EMaBS sample			
						EAF	$\beta$	SE	p-value	EAF	$\beta^b$	SE	p-value
7	rs9638084	156311745	LINC01006	E	A/G	0.40	0.12	0.02	$8.5 \times 10^{-11}$	0.55	-0.40	0.51	$4.3 \times 10^{-1}$
7	rs11563582	27351650	EVX1-HOXA	AA	A/G	0.13	1.02	0.17	$8.4 \times 10^{-10}$	0.17	0.80	0.71	$2.6 \times 10^{-1}$
8	rs78192203	142375073	GPR20	AA	T/A	0.80	0.77	0.14	$1.3 \times 10^{-8}$	0.79	-0.29	0.65	$6.5 \times 10^{-1}$
8	rs2978098	101676675	SNX31	E	A/C	0.54	0.17	0.03	$1.5 \times 10^{-9}$	0.03	-0.02	1.70	$9.9 \times 10^{-1}$
8	rs62524579	144060955	P11-273G15.2	E	A/G	0.53	-0.18	0.03	$3.8 \times 10^{-9}$	0.37	0.28	0.55	$6.2 \times 10^{-1}$
8	rs10087782	141858620	PTK2	E	T/C	0.45	0.13	0.02	$3.0 \times 10^{-14}$	0.82	0.32	0.67	$6.3 \times 10^{-1}$
8	rs1047030	22428708	SORBS3	E	A/G	0.81	0.13	0.02	$5.7 \times 10^{-8}$	0.96	-0.80	1.23	$5.2 \times 10^{-1}$
9	rs4364717	21801530	MTAP	E	A/G	0.55	-0.18	0.03	$1.3 \times 10^{-10}$	0.24	0.33	0.61	$5.8 \times 10^{-1}$
9	rs76452347	35906471	HRCT1	E/AA	T/C	0.19	-0.23	0.04	$6.8 \times 10^{-10}$	0.09	-0.16	0.92	$8.6 \times 10^{-1}$
9	rs7020564	109670016	ZNF462	E	A/C	0.70	-0.11	0.02	$6.7 \times 10^{-9}$	0.12	-0.54	0.82	$5.1 \times 10^{-1}$
10	rs4746172	75855842	VCL	E	C/T	—	0.23	0.04	$9.1 \times 10^{-8}$	0.23	-0.49	0.66	$4.6 \times 10^{-1}$
10	rs1801253	115805056	ADRB1	E	G/C	0.27	-0.36	0.06	$9.5 \times 10^{-10}$	0.34	-0.45	0.56	$4.2 \times 10^{-1}$
10	rs10995311	64564934	ADO	E/AA	G/C	0.38	-0.20	0.03	$2.1 \times 10^{-11}$	0.03	1.36	1.47	$3.6 \times 10^{-1}$
10	rs1530440	63524591	C10orf107	E	T/C	0.19	-0.39	0.06	$1.0 \times 10^{-9}$	0.03	-0.87	1.58	$5.8 \times 10^{-1}$
10	rs4590817	63467553	C10orf107	E	G/C	0.84	0.42	—	$1.3 \times 10^{-12}$	0.84	-0.81	0.68	$2.4 \times 10^{-1}$
10	rs2782980	115781527	ADRB1	E	T/C	0.20	-0.28	0.05	$9.6 \times 10^{-8}$	0.47	-0.76	0.53	$1.5 \times 10^{-1}$
10	rs1813353	18707448	CACNB2	E	T/C	0.68	0.42	—	$2.3 \times 10^{-15}$	0.84	0.16	0.73	$8.3 \times 10^{-1}$
10	rs603424	102075479	PKD2L1	E	A/G	0.18	0.18	0.02	$1.2 \times 10^{-14}$	0.75	0.36	0.63	$5.7 \times 10^{-1}$
10	rs10906391	13523937	BEND7	E	T/C	0.32	0.13	0.02	$7.6 \times 10^{-12}$	0.03	-0.27	1.65	$8.6 \times 10^{-1}$
10	rs4373814	18419972	CACNB2(5')	E	G/C	0.55	-0.22	—	$4.4 \times 10^{-10}$	0.39	-0.35	0.53	$5.1 \times 10^{-1}$
10	rs11191548	104846178	CYP17A1/NT5C2	E	T/C	0.91	0.46	—	$9.4 \times 10^{-13}$	0.98	1.23	1.42	$3.9 \times 10^{-1}$
11	rs4601790	65353906	EHBP1L1	E/AS	G/A	0.27	-0.02	0.04	$9.9 \times 10^{-9}$	0.06	-0.32	1.05	$7.6 \times 10^{-1}$
11	rs7103648	47461783	RAPSN-PSMC3- SLC39A13	E	A/G	0.61	-0.24	0.03	$9.0 \times 10^{-19}$	0.85	0.78	0.74	$3.0 \times 10^{-1}$
<b>11</b>	<b>rs751984</b>	<b>61278246</b>	<b>LRRC10B</b>	<b>E</b>	<b>T/C</b>	<b>0.88</b>	<b>0.38</b>	<b>0.04</b>	<b><math>4.2 \times 10^{-20}</math></b>	<b>0.79</b>	<b>1.56<sup>c</sup></b>	<b>0.63</b>	<b><math>1.4 \times 10^{-2}</math></b>
11	rs900145	13293905	ARNTL	E/AA	G/A	0.34	-0.20	0.03	$1.8 \times 10^{-8}$	0.52	0.97	0.54	$7.0 \times 10^{-2}$
11	rs11030119	27728102	BDNF	E	A/G	0.31	-0.16	0.03	$2.9 \times 10^{-8}$	0.35	-0.36	0.54	$5.1 \times 10^{-1}$
11	rs67330701	69079707	MYEOV	E	T/C	0.09	-0.37	0.05	$2.1 \times 10^{-12}$	0.01	0.92	2.27	$6.9 \times 10^{-1}$
<b>11</b>	<b>rs633185</b>	<b>100593538</b>	<b>FLJ32810- TMEM133</b>	<b>E</b>	<b>G/C</b>	<b>0.28</b>	<b>-0.33</b>	<b>—</b>	<b><math>2.0 \times 10^{-15}</math></b>	<b>0.23</b>	<b>-1.49<sup>c</sup></b>	<b>6.23</b>	<b><math>1.7 \times 10^{-2}</math></b>
11	rs381815	16902268	PLEKHA7	E	T/C	0.26	0.35	—	$5.3 \times 10^{-14}$	0.26	0.58	0.62	$3.4 \times 10^{-1}$
11	rs1401454	16250183	SOX6	E/AA/AS	T/C	0.46	0.45	0.10	$5.1 \times 10^{-10}$	0.46	-0.27	0.52	$6.1 \times 10^{-1}$
11	rs360153	9762274	SWAP70	E	T/C	0.42	-0.22	0.02	$4.4 \times 10^{-36}$	0.52	-0.30	0.52	$5.7 \times 10^{-1}$
11	rs11026586	22515533	RP11-34N19.1	E	A/G	0.07	0.29	0.03	$2.7 \times 10^{-17}$	0.06	0.43	1.21	$7.3 \times 10^{-1}$
11	rs875106	70005641	ANO1	E	A/G	0.52	-0.13	0.02	$1.7 \times 10^{-14}$	0.71	1.02	5.8	$7.7 \times 10^{-2}$
11	rs4420291	74374950	POLD3	E	A/G	0.51	0.10	0.02	$2.2 \times 10^{-8}$	0.33	0.08	0.58	$8.9 \times 10^{-1}$
<b>11</b>	<b>rs7129220</b>	<b>10350538</b>	<b>ADM</b>	<b>E</b>	<b>G/A</b>	<b>0.89</b>	<b>-0.30</b>	<b>—</b>	<b><math>6.4 \times 10^{-8}</math></b>	<b>0.92</b>	<b>-0.79<sup>c</sup></b>	<b>1.01</b>	<b><math>4.4 \times 10^{-3}</math></b>
12	rs17249754	90060586	ATP2B1	E	G/A	0.84	0.52	—	$1.2 \times 10^{-18}$	0.85	-1.89	0.69	$7.0 \times 10^{-1}$
12	rs10850411	115387796	TBX5/TBX3	E	T/C	0.70	0.25	—	$5.4 \times 10^{-10}$	0.61	0.32	0.53	$5.5 \times 10^{-1}$
12	rs1060105	123806219	SBNO1	E/AS	T/C	0.21	-0.18	—	$3.1 \times 10^{-8}$	0.05	-1.08	1.22	$3.8 \times 10^{-1}$
12	rs2384550	115352731	TBX5-TBX3	E	A/G	0.35	-0.35	0.06	$3.7 \times 10^{-8}$	0.35	-0.93	0.53	$7.9 \times 10^{-2}$
12	rs35444	115552437	TBX3	AS	A/G	0.75	0.50	0.05	$1.3 \times 10^{-10}$	0.56	-0.66	0.53	$2.1 \times 10^{-1}$
12	rs7302981	50537815	CERS5	E/AA	A/G	0.34	0.25	0.03	$9.4 \times 10^{-19}$	0.10	0.90	0.84	$2.8 \times 10^{-1}$
12	rs7132012	8832203	RP11-20D14.4	E	A/G	0.68	0.15	0.02	$3.2 \times 10^{-17}$	0.57	0.08	0.51	$8.8 \times 10^{-1}$
12	rs1271309	124820705	NCOR2	E	A/G	0.16	-0.20	0.02	$1.5 \times 10^{-16}$	0.08	0.22	0.92	$8.1 \times 10^{-1}$
12	rs7137749	57098040	NACA	E	T/C	0.37	0.14	0.02	$7.2 \times 10^{-15}$	0.52	-0.44	0.52	$4.1 \times 10^{-1}$

(Continues)

TABLE 3 (Continued)

Chr	SNP	Position <sup>a</sup>	Nearest gene	Population	EA/ RA	Discovery sample				EMaBS sample			
						EAF	$\beta$	SE	<i>p</i> -value	EAF	$\beta^b$	SE	<i>p</i> -value
12	rs7134060	96717095	CDK17	E	A/G	0.45	-0.11	0.02	$1.1 \times 10^{-9}$	0.26	-0.93	0.60	$1.2 \times 10^{-1}$
12	rs75507123	5417856	RP11-1038A11.3	E	T/G	0.13	-0.14	0.03	$3.9 \times 10^{-8}$	0.02	-0.66	1.70	$7.0 \times 10^{-1}$
12	rs1098708	27321112	STK38L	E	A/G	0.28	-0.10	0.02	$4.6 \times 10^{-8}$	0.82	1.08	0.67	$1.1 \times 10^{-1}$
13	rs55684003	97988689	MBNL2	E	A/G	0.70	0.12	0.02	$1.0 \times 10^{-10}$	0.95	-1.83	1.14	$1.1 \times 10^{-1}$
13	rs9563529	58316637	PCDH17	E	T/G	0.21	0.12	0.02	$1.4 \times 10^{-8}$	0.26	0.56	0.59	$3.4 \times 10^{-1}$
14	rs11628933	60700903	PPM1A	E	C/G	0.23	-0.12	0.02	$3.1 \times 10^{-9}$	0.40	-0.41	0.54	$4.5 \times 10^{-1}$
14	rs4424827	35110857	SNX6	E	T/C	0.57	-0.10	0.02	$2.1 \times 10^{-8}$	0.94	-0.38	7.20	$9.6 \times 10^{-1}$
<b>15</b>	<b>rs7178615</b>	<b>66869072</b>	<b>RP11-321F6.1</b>	<b>E</b>	<b>A/G</b>	<b>0.37</b>	<b>-0.18</b>	<b>0.03</b>	<b><math>2.6 \times 10^{-10}</math></b>	<b>0.19</b>	<b>1.42</b>	<b>0.69</b>	<b><math>4.1 \times 10^{-2}</math></b>
15	rs62012628	79070000	ADAMTS7	E	T/C	0.29	-0.24	0.03	$5.1 \times 10^{-12}$	0.31	-0.03	0.58	$9.6 \times 10^{-1}$
15	rs12906962	95312071	chr15mb95	E	T/C	0.68	-0.22	0.03	$5.6 \times 10^{-14}$	0.21	-0.73	0.64	$2.5 \times 10^{-1}$
<b>15</b>	<b>rs1378942</b>	<b>75077367</b>	<b>CYP11A1-ULK3</b>	<b>E</b>	<b>C/A</b>	<b>0.36</b>	<b>0.48</b>	<b>0.09</b>	<b><math>6.0 \times 10^{-8}</math></b>	<b>0.97</b>	<b>2.99<sup>c</sup></b>	<b>1.48</b>	<b><math>4.4 \times 10^{-2}</math></b>
15	rs2521501	91437388	FURIN-FES	E	T/A	0.31	0.36	—	$1.9 \times 10^{-15}$	0.21	-1.11	0.66	$9.5 \times 10^{-2}$
15	rs873122	92702020	SLCO3A1	E	C/G	0.72	0.12	0.02	$6.5 \times 10^{-10}$	0.94	2.00	1.16	$8.5 \times 10^{-2}$
15	rs7180952	85162551	ZSCAN2	E	T/C	0.54	-0.10	0.02	$9.8 \times 10^{-9}$	0.75	0.02	0.61	$9.8 \times 10^{-1}$
<b>15</b>	<b>rs62004794</b>	<b>68454523</b>	<b>PIAS1</b>	<b>E</b>	<b>A/G</b>	<b>0.44</b>	<b>-0.10</b>	<b>0.02</b>	<b><math>3.4 \times 10^{-8}</math></b>	<b>0.60</b>	<b>-1.16<sup>c</sup></b>	<b>0.55</b>	<b><math>3.6 \times 10^{-2}</math></b>
16	rs12921187	4943019	PPL	E	T/G	0.43	-0.17	0.03	$2.5 \times 10^{-10}$	0.96	-2.36	1.23	$5.5 \times 10^{-2}$
16	rs72799341	30936743	FBXL19	E	A/G	0.24	0.19	0.03	$5.8 \times 10^{-9}$	0.09	0.03	0.90	$9.8 \times 10^{-1}$
16	rs8059962	81574197	CMIP	E	T/C	0.42	-0.17	0.03	$1.3 \times 10^{-9}$	0.61	0.37	0.52	$4.8 \times 10^{-1}$
16	rs1126464	89704365	DPEPI	E/AA	C/G	0.22	0.24	0.03	$2.4 \times 10^{-13}$	0.06	-0.90	1.10	$4.2 \times 10^{-1}$
16	rs45474499	66914492	PDP2	E	T/C	0.05	0.36	0.04	$8.5 \times 10^{-18}$	0.07	0.85	1.09	$4.3 \times 10^{-1}$
16	rs7185555	69131281	HAS3	E	C/G	0.15	-0.15	0.02	$2.3 \times 10^{-10}$	0.31	0.42	0.56	$4.6 \times 10^{-1}$
<b>16</b>	<b>rs9932866</b>	<b>706067</b>	<b>WDR90</b>	<b>E</b>	<b>A/G</b>	<b>0.37</b>	<b>0.12</b>	<b>0.02</b>	<b><math>2.9 \times 10^{-10}</math></b>	<b>0.90</b>	<b>-1.61</b>	<b>0.80</b>	<b><math>4.5 \times 10^{-2}</math></b>
17	rs4308	61559625	ACE	E	A/G	0.37	0.21	0.03	$6.8 \times 10^{-14}$	0.03	-1.29	1.73	$4.5 \times 10^{-1}$
17	rs12940887	47402807	ZNF652	E	T/C	0.38	0.27	—	$2.3 \times 10^{-14}$	0.07	0.41	1.25	$7.4 \times 10^{-1}$
18	rs12958173	42141977	SETBP1	E	A/C	0.31	0.18	0.03	$5.8 \times 10^{-10}$	0.31	0.68	0.56	$2.2 \times 10^{-1}$
18	rs745821	48142854	MAPK4	E	T/G	0.76	0.19	0.03	$1.4 \times 10^{-9}$	0.70	0.21	0.58	$7.1 \times 10^{-1}$
18	rs34163044	51851616	STARD6	E	A/C	0.42	0.15	0.02	$9.6 \times 10^{-17}$	0.31	-0.13	0.59	$8.3 \times 10^{-1}$
18	rs11665020	10879503	PIEZO2	E	C/G	0.32	-0.14	0.02	$2.8 \times 10^{-14}$	0.14	-0.18	0.72	$8.1 \times 10^{-1}$
18	rs4800420	20158965	CTAGE1	E	A/G	0.29	0.12	0.02	$5.2 \times 10^{-10}$	0.17	-0.63	0.70	$3.7 \times 10^{-1}$
19	rs167479	11526765	RLG3	E/AA	T/G	0.45	-0.30	0.03	$4.2 \times 10^{-28}$	0.17	-0.23	0.71	$7.4 \times 10^{-1}$
19	rs62104477	30294991	CCNE1	E	T/G	0.33	0.18	0.03	$1.2 \times 10^{-9}$	0.25	0.47	0.61	$4.4 \times 10^{-1}$
19	rs4247374	7252756	INSR	E	T/C	0.14	-0.39	0.03	$2.1 \times 10^{-22}$	0.02	-1.85	1.96	$3.5 \times 10^{-1}$
19	rs2304130	19789528	ZNF101	E/AS	A/G	0.91	-0.29	—	$2.0 \times 10^{-8}$	0.74	-0.63	0.59	$2.9 \times 10^{-1}$
19	rs9710247	40760449	AKT2	E	A/G	0.45	0.16	0.03	$1.6 \times 10^{-9}$	0.90	-1.29	0.92	$1.6 \times 10^{-1}$
19	rs1821295	32590773	AC011518.1	E	T/C	0.70	-0.14	0.02	$3.1 \times 10^{-13}$	0.92	-0.06	1.14	$9.6 \times 10^{-1}$
20	rs6095241	47308798	PREX1	E/AS	A/G	0.45	-0.17	—	$4.8 \times 10^{-9}$	0.60	-0.42	0.53	$4.4 \times 10^{-1}$
20	rs6108168	8626271	PLCB1	E	A/C	0.25	-0.21	0.03	$1.1 \times 10^{-11}$	0.62	-0.08	0.53	$8.8 \times 10^{-1}$
20	rs1327235	10969030	JAG1	E	G/A	0.46	0.30	—	$1.4 \times 10^{-15}$	0.59	-0.09	0.52	$8.6 \times 10^{-1}$
20	rs6015450	57751117	GNAS-EDN3	E	G/A	0.12	0.56	—	$5.6 \times 10^{-23}$	0.18	0.74	0.65	$2.6 \times 10^{-1}$
20	rs1232482	11886643	BTBD3	E	T/C	0.40	-0.12	0.02	$6.1 \times 10^{-12}$	0.18	-1.26	0.70	$7.3 \times 10^{-2}$
<b>21</b>	<b>rs12627651</b>	<b>44760603</b>	<b>CRYAA-SIK1</b>	<b>E</b>	<b>A/G</b>	<b>0.29</b>	<b>0.20</b>	<b>0.03</b>	<b><math>1.4 \times 10^{-11}</math></b>	<b>0.07</b>	<b>2.55<sup>c</sup></b>	<b>1.12</b>	<b><math>2.3 \times 10^{-2}</math></b>

Note: Bold indicate  $p < 5.0 \times 10^{-2}$  for replication analysis.

Abbreviations: AA, African ancestry; AS, Asian ancestry; Chr, chromosomes; E, European ancestry; EA, effect allele; EAF, effect allele frequency; RA, reference allele; SE, standard error; SNP, single nucleotide polymorphism;  $\beta$ , Effect size estimates correspond to mean difference in mmHg per effect allele for systolic or diastolic blood pressure, adjusted for age and body mass index.

<sup>a</sup>Given with respect to Build 37 (GRCh37/hg19).

<sup>b</sup>Adjusted for age and body mass index.

<sup>c</sup>Indicate same  $\beta$  direction in both the discovery and EMaBS populations.

trait influenced by the simultaneous presence of several gene variants each with a small effect size and contributing in an additive manner to BP expression. Thus, the large effect sizes that this study had good power to detect, may not be realistic. For example, the present study had 80% power to detect a 3.2 mmHg change in mean systolic BP for a minor allele frequency of 20% at genome-wide significance level,  $p < 5 \times 10^{-8}$ . Many of the variants reliably associated with BP in adults have an effect size of 0.5 mmHg or less (Evangelou et al., 2018). In addition to the limitation caused by the relatively small sample size, imputation did not allow inference for rare variants not included in the imputation SNP panel.

Few GWAS “top SNPs” from non-African populations have been replicated in populations of African ancestry (Adeyemo et al., 2009; Franceschini et al., 2013; Kayima et al., 2017). Variants associated with BP in populations of African origin might be different from variants that influence BP in Caucasian populations or not in LD with the BP causing variants. Our replication study was limited to variants associated with BP from previous GWAS of BP in other populations. Thirty-three SNPs identified from previous BP GWAS were replicated, most of these were previously identified in populations of non-African origins. Of the identified loci, *PAX2* is essential in the development of the renal epithelium (Dressler & Woolf, 1999) and plays a critical role in kidney development (Hou, Chen, & Wang, 2011). The kidneys are critical in BP regulation. Two of the replicated SNPs are located on *ATP2B1*. *ATP2B1* is involved in calcium homeostasis (Hirawa, Fujiwara, & Umemura, 2013). The *ATP2B1* rs2681492, *MDM4* rs2169137, *EVX1/HOXA* rs17428471 SNPs previously associated with BP in transethnic populations (African, Caucasian and Asian) were associated with adolescent BP in the present study. These genes most likely influence BP across different ethnic groups.

Replication studies in diverse populations have returned mixed results. This current study conducted 370 tests using 330 SNPs, of which 33 SNPs (one SNP for both traits) were associated with BP. Failure to replicate most variants associated with BP in other populations could be due to differences in minor allele frequencies across populations or differences in LD patterns combined with a poor understanding of the causative variants or due to spurious initial findings. Blood pressure is likely to be influenced by the simultaneous presence of several genetic variants, each conferring a small change in BP.

Although none of the variants reached Bonferroni level of significance more associated variants were identified than expected under the null suggesting that some of these variants found to be associated could be worthy of further follow-up. Fourteen variants more than those expected by chance (19 variants) under the null hypothesis were associated with BP in this study.

Of the 40 SNPs tested for association with both traits, only *BAT2/BAT5* rs805303 was associated with both traits in the adolescents, suggesting that not many genetic loci have influence on both systolic and diastolic BP. Similar to an earlier replication study among adult Ugandans (Kayima et al., 2017), the *ATP2B1* rs2681492 was associated with BP in these Ugandan adolescents, but with an opposite effect direction to the discovery population (Hoffmann et al., 2017) and Ugandan adults (Kayima et al., 2017). The G allele of the *ATP2B1* rs2681492 was associated with lower systolic BP in Ugandans adults (Kayima et al., 2017) but with higher systolic BP in the present study.

Some loci may have varying roles in BP regulation across different populations. A European study investigated SNPs associated with BP at different age epochs (using independent samples for each age group): prepuberty (age 4–7 years), pubertal (8–12 years), and postpubertal (13–20 years). The A allele of *TGAI1* rs1563894 was associated with lower systolic BP in prepuberty while the T allele of *SMARCA2/VLDLR* rs872256 was associated with higher systolic BP during puberty (Parmar et al., 2016). No SNP was associated with BP in the postpubertal period, and no SNP was consistently associated with BP across all three age groups. The *TGAI1* rs1563894 and *SMARCA2/VLDLR* rs872256 were not replicated in this present study.

The present study has several strengths. This is the first BP GWAS of an African population and the first candidate gene analysis among adolescents residing in Africa. Participants in this study were similar to nonparticipants with respect to most baseline characterizes. Rigorous quality control procedures were used during the measurement of the various variables including BP and genotyping. Data from this study can contribute to future BP GWAS meta-analyses. Key limitations of this study were that it was underpowered to detect effects of rare variants and to enable testing for effect modification by sex and other environmental variables, and the lack of a replication sample from a similar setting with which to confirm our GWAS findings.

Future work should take advantage of various African cohorts to form consortia that can enable the conduct of GWAS meta-analysis well powered to identify rare and low-frequency variants that may be associated with BP in African populations. Future candidate gene analysis using a sample from a different geographical region or ethnic background should investigate for interactions between variants, this might help our understanding of the etiology of BP. It is possible that multiple interacting variants (rare and common) are influencing BP levels in this population. Although we did not formally allow for multiple testing in the replication analysis, the current study had 33 associated SNPs 14 more than expected by chance. Polygenic scores analysis of variants associated with BP among African populations may explain the missing BP heritability.

In summary, we conducted the first genetic study of BP phenotypes among Ugandan adolescents. Although this study did not identify novel BP variants, replication of some previously identified variants suggests that some genetic variants may universally influence BP susceptibility. Large scale studies in African populations are required to identify novel and evaluate previously reported loci.

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## CONFLICT OF INTEREST

None declared.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study will be available through the European Genome-Phenome Archive (EGA) upon lifting of the embargo for the VaccGene paper.

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## REFERENCES

- Addo, J., Smeeth, L., & Leon, D. A. (2007). Hypertension in sub-Saharan Africa: A systematic review. *Hypertension*, *50*(6), 1012–1018. <https://doi.org/10.1161/HYPERTENSIONAHA.107.093336>
- Adeyemo, A., Gerry, N., Chen, G., Herbert, A., Doumatey, A., Huang, H., ... Rotimi, C. (2009). A genome-wide association study of hypertension and blood pressure in African Americans. *PLoS Genetics*, *5*(7), e1000564. <https://doi.org/10.1371/journal.pgen.1000564>
- Genomes Project Consortium; Auton, A., Brooks, L. D., Durbin, R. M., Garrison, E. P., Kang, H. M., ... Abecasis, G. R. (2015). A global reference for human genetic variation. *Nature*, *526*(7571), 68–74. <https://doi.org/10.1038/nature15393>
- Biron, P., Mongeau, J. G., & Bertrand, D. (1976). Familial aggregation of blood pressure in 558 adopted children. *Canadian Medical Association Journal*, *115*(8), 773–774.
- Cho, Y. S., Go, M. J., Kim, Y. J., Heo, J. Y., Oh, J. H., Ban, H.-J., ... Kim, H.-L. (2009). A large-scale genome-wide association study of Asian populations uncovers genetic factors influencing eight quantitative traits. *Nature Genetics*, *41*(5), 527–534. <https://doi.org/10.1038/ng.357>
- Dressler, G. R., & Woolf, A. S. (1999). Pax2 in development and renal disease. *International Journal of Developmental Biology*, *43*(5), 463–468.
- Ehret, G. B., & Caulfield, M. J. (2013). Genes for blood pressure: An opportunity to understand hypertension. *European Heart Journal*, *34*(13), 951–961. <https://doi.org/10.1093/eurheartj/ehs455>
- Ehret, G. B., Ferreira, T., Chasman, D. I., Jackson, A. U., Schmidt, E. M., Johnson, T., ... Munroe, P. B. (2016). The genetics of blood pressure regulation and its target organs from association studies in 342,415 individuals. *Nature Genetics*, *48*(10), 1171–1184. <https://doi.org/10.1038/ng.3667>
- International Consortium for Blood Pressure Genome-Wide Association; Ehret, G. B., Munroe, P. B., Rice, K. M., Bochud, M., Johnson, A. D., ... Johnson, T. (2011). Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. *Nature*, *478*(7367), 103–109. <https://doi.org/10.1038/nature10405>
- Elliott, A. M., Kizza, M., Quigley, M. A., Ndibazza, J., Nampijja, M., Muhangi, L., ... Whitworth, J. A. (2007). The impact of helminths on the response to immunization and on the incidence of infection and disease in childhood in Uganda: Design of a randomized, double-blind, placebo-controlled, factorial trial of deworming interventions delivered in pregnancy and early childhood [ISRCTN32849447]. *Clinical Trials*, *4*(1), 42–57. <https://doi.org/10.1177/1740774506075248>
- Evangelou, E., Warren, H. R., Mosen-Ansorena, D., Mifsud, B., Pazoki, R., Gao, H., ... Caulfield, M. J. (2018). Genetic analysis of over 1 million people identifies 535 new loci associated with blood pressure traits. *Nature Genetics*, *50*(10), 1412–1425. <https://doi.org/10.1038/s41588-018-0205-x>
- Fox, E. R., Young, J. H., Li, Y., Dreisbach, A. W., Keating, B. J., Musani, S. K., ... Levy, D. (2011). Association of genetic variation with systolic and diastolic blood pressure among African Americans: The Candidate Gene Association Resource study. *Human Molecular Genetics*, *20*(11), 2273–2284. <https://doi.org/10.1093/hmg/ddr092>
- Franceschini, N., Fox, E., Zhang, Z., Edwards, T. L., Nalls, M. A., Sung, Y. J., ... Zhu, D. (2013). Genome-wide association analysis of blood-pressure traits in African-ancestry individuals reveals common associated genes in African and non-African populations. *American Journal of Human Genetics*, *93*(3), 545–554. <https://doi.org/10.1016/j.ajhg.2013.07.010>
- Ganesh, S. K., Chasman, D. I., Larson, M. G., Guo, X., Verwoert, G., Bis, J. C., ... Munroe, P. B. (2014). Effects of long-term averaging of quantitative blood pressure traits on the detection of genetic associations. *American Journal of Human Genetics*, *95*(1), 49–65. <https://doi.org/10.1016/j.ajhg.2014.06.002>
- Ganesh, S. K., Tragante, V., Guo, W., Guo, Y., Lanktree, M. B., Smith, E. N., ... Asselbergs, F. W. (2013). Loci influencing blood



- pressure identified using a cardiovascular gene-centric array. *Human Molecular Genetics*, 22(8), 1663–1678. <https://doi.org/10.1093/hmg/dd555>
- Gurdasani, D., Carstensen, T., Tekola-Ayele, F., Pagani, L., Tachmazidou, I., Hatzikotoulas, K., ... Sandhu, M. S. (2015). The African genome variation project shapes medical genetics in Africa. *Nature*, 517(7534), 327–332. <https://doi.org/10.1038/nature13997>
- Hirawa, N., Fujiwara, A., & Umemura, S. (2013). ATP2B1 and blood pressure: From associations to pathophysiology. *Current Opinion in Nephrology and Hypertension*, 22(2), 177–184. <https://doi.org/10.1097/MNH.0b013e32835da4ca>
- Ho, J. E., Levy, D., Rose, L., Johnson, A. D., Ridker, P. M., & Chasman, D. I. (2011). Discovery and replication of novel blood pressure genetic loci in the Women's Genome Health Study. *Journal of Hypertension*, 29(1), 62–69. <https://doi.org/10.1097/HJH.0b013e3283406927>
- Hoffmann, T. J., Ehret, G. B., Nandakumar, P., Ranatunga, D., Schaefer, C., Kwok, P.-Y., ... Risch, N. (2017). Genome-wide association analyses using electronic health records identify new loci influencing blood pressure variation. *Nature Genetics*, 49(1), 54–64. <https://doi.org/10.1038/ng.3715>
- Hou, X. M., Chen, X., & Wang, Y. L. (2011). The role of Pax2 in regulation of kidney development and kidney disease. *Yi Chuan*, 33(9), 931–938.
- Johnson, A. D., Newton-Cheh, C., Chasman, D. I., Ehret, G. B., Johnson, T., Rose, L., ... Levy, D. (2011). Association of hypertension drug target genes with blood pressure and hypertension in 86,588 individuals. *Hypertension*, 57(5), 903–910. <https://doi.org/10.1161/HYPERTENSIONAHA.110.158667>
- Johnson, T., Gaunt, T. R., Newhouse, S. J., Padmanabhan, S., Tomaszewski, M., Kumari, M., ... Munroe, P. B. (2011). Blood pressure loci identified with a gene-centric array. *American Journal of Human Genetics*, 89(6), 688–700. <https://doi.org/10.1016/j.ajhg.2011.10.013>
- Kato, N., Loh, M., Takeuchi, F., Verweij, N., Wang, X. U., Zhang, W., ... Chambers, J. C. (2015). Trans-ancestry genome-wide association study identifies 12 genetic loci influencing blood pressure and implicates a role for DNA methylation. *Nature Genetics*, 47(11), 1282–1293. <https://doi.org/10.1038/ng.3405>
- Kato, N., Takeuchi, F., Tabara, Y., Kelly, T. N., Go, M. J., Sim, X., ... He, J. (2011). Meta-analysis of genome-wide association studies identifies common variants associated with blood pressure variation in east Asians. *Nature Genetics*, 43(6), 531–538. <https://doi.org/10.1038/ng.834>
- Kayima, J., Liang, J., Natanzon, Y., Nankabirwa, J., Ssinabulya, I., Nakibuuka, J., ... Zhu, X. (2017). Association of genetic variation with blood pressure traits among East Africans. *Clinical Genetics*, 92(5), 487–494. <https://doi.org/10.1111/cge.12974>
- Kidambi, S., Ghosh, S., Kotchen, J. M., Grim, C. E., Krishnaswami, S., Kaldunski, M. L., ... Kotchen, T. A. (2012). Non-replication study of a genome-wide association study for hypertension and blood pressure in African Americans. *BMC Medical Genetics*, 13, 27. <https://doi.org/10.1186/1471-2350-13-27>
- Levy, D., Ehret, G. B., Rice, K., Verwoert, G. C., Launer, L. J., Dehghan, A., ... van Duijn, C. M. (2009). Genome-wide association study of blood pressure and hypertension. *Nature Genetics*, 41(6), 677–687. <https://doi.org/10.1038/ng.384>
- Li, C., Kim, Y. K., Dorajoo, R., Li, H., Lee, I.-T., Cheng, C.-Y., ... Kelly, T. N. (2017). Genome-wide association study meta-analysis of long-term average blood pressure in East Asians. *Circulation: Cardiovascular Genetics*, 10(2), e001527. <https://doi.org/10.1161/CIRCGENETICS.116.001527>
- Liang, J., Le, T. H., Edwards, D. R. V., Tayo, B. O., Gaulton, K. J., Smith, J. A., ... Franceschini, N. (2017). Single-trait and multi-trait genome-wide association analyses identify novel loci for blood pressure in African-ancestry populations. *PLoS Genetics*, 13(5), e1006728. <https://doi.org/10.1371/journal.pgen.1006728>
- Liu, C., Kraja, A. T., Smith, J. A., Brody, J. A., Franceschini, N., Bis, J. C., ... Chasman, D. I. (2016). Meta-analysis identifies common and rare variants influencing blood pressure and overlapping with metabolic trait loci. *Nature Genetics*, 48(10), 1162–1170. <https://doi.org/10.1038/ng.3660>
- Lule, S. A., Namara, B., Akurut, H., Lubyayi, L., Nampijja, M., Akello, F., ... Webb, E. L. (2019). Blood pressure risk factors in early adolescents: Results from a Ugandan birth cohort. *Journal of Human Hypertension*. <https://doi.org/10.1038/s41371-019-0178-y>
- Lule, S. A., Namara, B., Akurut, H., Muhangi, L., Lubyayi, L., Nampijja, M., ... Webb, E. L. (2019). Are birthweight and postnatal weight gain in childhood associated with blood pressure in early adolescence? Results from a Ugandan birth cohort. *International Journal of Epidemiology*, 48(1), 148–156. <https://doi.org/10.1093/ije/dyy118>
- Luoni, G., Forton, J., Jallow, M., Akha, E. S., Sisay-Joof, F., Pinder, M., ... Kwiatkowski, D. (2005). Population-specific patterns of linkage disequilibrium in the human 5q31 region. *Genes and Immunity*, 6(8), 723–727. <https://doi.org/10.1038/sj.gene.6364250>
- Maher, B. (2008). Personal genomes: The case of the missing heritability. *Nature*, 456(7218), 18–21. <https://doi.org/10.1038/456018a>
- Manolio, T. A., Collins, F. S., Cox, N. J., Goldstein, D. B., Hindorf, L. A., Hunter, D. J., ... Visscher, P. M. (2009). Finding the missing heritability of complex diseases. *Nature*, 461(7265), 747–753. <https://doi.org/10.1038/nature08494>
- Marchini, J., Howie, B., Myers, S., McVean, G., & Donnelly, P. (2007). A new multipoint method for genome-wide association studies by imputation of genotypes. *Nature Genetics*, 39(7), 906–913. <https://doi.org/10.1038/ng2088>
- Newton-Cheh, C., Johnson, T., Gateva, V., Tobin, M. D., Bochud, M., Coin, L., ... Munroe, P. B. (2009). Genome-wide association study identifies eight loci associated with blood pressure. *Nature Genetics*, 41(6), 666–676. <https://doi.org/10.1038/ng.361>
- Newton-Cheh, C., Larson, M. G., Vasani, R. S., Levy, D., Bloch, K. D., Surti, A., ... Wang, T. J. (2009). Association of common variants in NPPA and NPPB with circulating natriuretic peptides and blood pressure. *Nature Genetics*, 41(3), 348–353. <https://doi.org/10.1038/ng.328>
- Noubiap, J. J., Essouma, M., Bigna, J. J., Jingi, A. M., Aminde, L. N., & Nansseu, J. R. (2017). Prevalence of elevated blood pressure in children and adolescents in Africa: A systematic review and meta-analysis. *The Lancet Public Health*, 2(8), e375–e386. [https://doi.org/10.1016/s2468-2667\(17\)30123-8](https://doi.org/10.1016/s2468-2667(17)30123-8)
- O'Connell, J., Gurdasani, D., Delaneau, O., Pirastu, N., Ulivi, S., Cocca, M., ... Marchini, J. (2014). A general approach for haplotype phasing across the full spectrum of relatedness. *PLoS Genetics*, 10(4), e1004234. <https://doi.org/10.1371/journal.pgen.1004234>
- Parmar, P. G., Taal, H. R., Timpson, N. J., Thiering, E., Lehtimäki, T., Marinelli, M., ... Palmer, L. J. (2016). International genome-wide association study consortium identifies novel loci associated with blood pressure in children and adolescents. *Circulation:*

- Cardiovascular Genetics*, 9(3), 266–278. <https://doi.org/10.1161/CIRCGENETICS.115.001190>
- Peprah, E., Xu, H., Tekola-Ayele, F., & Royal, C. D. (2015). Genome-wide association studies in Africans and African Americans: Expanding the framework of the genomics of human traits and disease. *Public Health Genomics*, 18(1), 40–51. <https://doi.org/10.1159/000367962>
- Purcell, S., Neale, B., Todd-Brown, K., Thomas, L., Ferreira, M. A. R., Bender, D., ... Sham, P. C. (2007). PLINK: A tool set for whole-genome association and population-based linkage analyses. *American Journal of Human Genetics*, 81(3), 559–575. <https://doi.org/10.1086/519795>
- Qian, X., Lu, Z., Tan, M., Liu, H., & Lu, D. (2007). A meta-analysis of association between C677T polymorphism in the methylenetetrahydrofolate reductase gene and hypertension. *European Journal of Human Genetics*, 15(12), 1239–1245. <https://doi.org/10.1038/sj.ejhg.5201914>
- Salfati, E., Morrison, A. C., Boerwinkle, E., & Chakravarti, A. (2015). Direct estimates of the genomic contributions to blood pressure heritability within a population-based cohort (ARIC). *PLoS ONE*, 10(7), e0133031. <https://doi.org/10.1371/journal.pone.0133031>
- Simino, J., Shi, G., Bis, J. C., Chasman, D. I., Ehret, G. B., Gu, X., ... Wijmenga, C. (2014). Gene-age interactions in blood pressure regulation: A large-scale investigation with the CHARGE, Global BPgen, and ICBP Consortia. *American Journal of Human Genetics*, 95(1), 24–38. <https://doi.org/10.1016/j.ajhg.2014.05.010>
- Surendran, P., Drenos, F., Young, R., Warren, H., Cook, J. P., Manning, A. K., ... Munroe, P. B. (2016). Trans-ancestry meta-analyses identify rare and common variants associated with blood pressure and hypertension. *Nature Genetics*, 48(10), 1151–1161. <https://doi.org/10.1038/ng.3654>
- Takeuchi, F., Isono, M., Katsuya, T., Yamamoto, K., Yokota, M., Sugiyama, T., ... Kato, N. (2010). Blood pressure and hypertension are associated with 7 loci in the Japanese population. *Circulation*, 121(21), 2302–2309. <https://doi.org/10.1161/CIRCULATIONAHA.109.904664>
- Tishkoff, S. A., Reed, F. A., Friedlaender, F. R., Ehret, C., Ranciaro, A., Froment, A., ... Williams, S. M. (2009). The genetic structure and history of Africans and African Americans. *Science*, 324(5930), 1035–1044. <https://doi.org/10.1126/science.1172257>
- Tragante, V., Barnes, M. R., Ganesh, S. K., Lanktree, M. B., Guo, W., Franceschini, N., ... Keating, B. J. (2014). Gene-centric meta-analysis in 87,736 individuals of European ancestry identifies multiple blood-pressure-related loci. *American Journal of Human Genetics*, 94(3), 349–360. <https://doi.org/10.1016/j.ajhg.2013.12.016>
- Wain, L. V., Vaez, A., Jansen, R., Joehanes, R., van der Most, P. J., Erzurumluoglu, A. M., ... Ehret, G. B. (2017). Novel blood pressure locus and gene discovery using genome-wide association study and expression data sets from blood and the kidney. *Hypertension*, 70(3), e4–e14. <https://doi.org/10.1161/HYPERTENSIONAHA.117.09438>
- Wain, L. V., Verwoert, G. C., O'Reilly, P. F., Shi, G., Johnson, T., Johnson, A. D., ... van Duijn, C. M. (2011). Genome-wide association study identifies six new loci influencing pulse pressure and mean arterial pressure. *Nature Genetics*, 43(10), 1005–1011. <https://doi.org/10.1038/ng.922>
- Warren, H. R., Evangelou, E., Cabrera, C. P., Gao, H., Ren, M., Mifsud, B., ... Wain, L. V. (2017). Genome-wide association analysis identifies novel blood pressure loci and offers biological insights into cardiovascular risk. *Nature Genetics*, 49(3), 403–415. <https://doi.org/10.1038/ng.3768>
- Williams, R. R., Hunt, S. C., Hasstedt, S. J., Hopkins, P. N., Wu, L. L., Berry, T. D., ... Lifton, R. P. (1991). Are there interactions and relations between genetic and environmental factors predisposing to high blood pressure? *Hypertension*, 18(3 Suppl), I29–37. [https://doi.org/10.1161/01.HYP.18.3\\_Suppl.I29](https://doi.org/10.1161/01.HYP.18.3_Suppl.I29)
- Xi, B., Shen, Y., Zhao, X., Chandak, G. R., Cheng, H., Hou, D., ... Mi, J. (2014). Association of common variants in/near six genes (ATP2B1, CSK, MTHFR, CYP17A1, STK39 and FGF5) with blood pressure/hypertension risk in Chinese children. *Journal of Human Hypertension*, 28(1), 32–36. <https://doi.org/10.1038/jhh.2013.50>
- Yako, Y. Y., Balti, E. V., Matsha, T. E., Dzudie, A., Kruger, D., Sobngwi, E., ... Kengne, A. P. (2018). Genetic factors contributing to hypertension in African-based populations: A systematic review and meta-analysis. *J Clin Hypertens (Greenwich)*, 20(3), 485–495. <https://doi.org/10.1111/jch.13225>
- Yang, J., Lee, S. H., Goddard, M. E., & Visscher, P. M. (2011). GCTA: A tool for genome-wide complex trait analysis. *American Journal of Human Genetics*, 88(1), 76–82. <https://doi.org/10.1016/j.ajhg.2010.11.011>

## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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