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Orthostatic hypotension and novel blood pressure-associated gene variants: Genetics of Postural Hemodynamics (GPH) Consortium

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Aims
Orthostatic hypotension (OH), an independent predictor of mortality and cardiovascular events, strongly correlates with hypertension. Recent genome-wide studies have identified new loci influencing blood pressure (BP) in populations, but their impact on OH remains unknown.

Methods and results
A total of 38 970 men and women of European ancestry from five population-based cohorts were included, of whom 2656 (6.8%) met the diagnostic criteria for OH (systolic/diastolic BP drop $\geq$20/10 mmHg within 3 min of standing). Thirty-one recently discovered BP-associated single nucleotide polymorphisms (SNPs) were examined using an additive genetic model and the major allele as referent. Relations between OH, orthostatic systolic BP response, and genetic variants were assessed by inverse variance-weighted meta-analysis. We found Bonferroni adjusted ($P < 0.0016$) significant evidence for association between OH and the *EBF1* locus (rs11953630, per-minor-allele odds ratio, 95% confidence interval: 0.90, 0.85–0.96; $P = 0.001$), and nominal evidence ($P < 0.05$) for *CYP17A1* (rs11191548: 0.85, 0.75–0.95; $P = 0.005$), and NPR3-*C5orf23* (rs1173771: 0.92, 0.87–0.98; $P = 0.009$) loci. Among subjects not taking BP-lowering drugs, three SNPs within the *NPPA/NPPB* locus were nominally associated with increased risk of OH (rs17367504: 1.13, 1.02–1.24; $P = 0.02$, rs198358: 1.10, 1.01–1.20; $P = 0.04$, and rs5068: 1.22, 1.04–1.43; $P = 0.01$). Moreover, an *ADM* variant was nominally associated with continuous orthostatic systolic BP response in the adjusted model ($P = 0.04$).

Conclusion
The overall association between common gene variants in BP loci and OH was generally weak and the direction of effect inconsistent with resting BP findings. These results suggest that OH and resting BP share few genetic components.

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Keywords Orthostatic hypotension • Genetics • Single nucleotide polymorphism • Steroid 17-alpha-hydroxylase • Natriuretic peptides • Adrenomedullin

Introduction

As people spend much of their active time in the upright position, well-functioning cardiovascular reflexes are crucial for neutralizing the haemodynamic effects of gravity and maintaining adequate perfusion of the upper body.[1] Otherwise, disturbances of the haemodynamic response to postural change may result in orthostatic hypotension (OH), provoking signs of cerebral hypoperfusion, such as dizziness and syncope.[2] However, OH is often asymptomatic and occurs in the general population, where it has been linked to advancing age,[3] neurodegenerative diseases,[4] diabetes,[5] hypertension,[6] and reduced renal function.[7] Further, OH predicts mortality and cardiovascular events, independently of traditional risk factors.[8–13]

In parallel, several authors have examined the genetic component of OH.[14,15] Population-based studies have suggested that polymorphisms of G-protein-related genes *GNAS1* and *GNB3*, influencing cardiovascular tone and reactivity,[16] Insulin promoter factor 1 (*PDX1*) on chromosome 13, implicated in beta-cell function,[17] and the neural precursor cell expressed, developmentally down-regulated 4-like gene (*NEDD4L*) on chromosome 18, an essential regulator of sodium retention in the distal nephron,[18] may be associated with altered postural systolic blood pressure (SBP) response. However, the sample sizes were relatively small (varying from 415 to 3383 individuals).

Recently, in a series of genome-wide association studies (GWAS), we and others have identified nearly 30 new loci associated with resting BP and hypertension risk.[19–22] As physiological pathways involved in systemic BP control may impact the haemodynamic response to orthostasis, we proposed to study the relationship between the newly discovered BP-associated single nucleotide polymorphisms (SNPs), OH, and postural systolic BP response in five large population-based cohorts of European ancestry, all of which were part of The International Consortium for Blood Pressure GWAS.[22]

Methods

Study samples, baseline examination, and genetic analyses

A detailed description of study samples [The Atherosclerosis Risk in Communities Study (ARIC), The Cardiovascular Health Study (CHS), The Framingham Heart Study (FHS), The Malmö Preventive Project (MPP), and The Rotterdam Study], baseline examination, and genetic analyses are provided in the Supplementary material online, *Methods*.

Clinical characteristics

Orthostatic hypotension was defined according to international consensus as a decrease in mean SBP $\geq$20 mmHg and/or decrease in mean diastolic BP (DBP) $\geq$10 mmHg within 3 min of standing.[23] Postural change in SBP (ΔSBP) was calculated as supine SBP—standing SBP to match the directionality of the regression coefficients for OH in statistical analyses. Hypertension was defined as a mean supine SBP $\geq$140 mmHg and/or mean supine DBP $\geq$90 mmHg, or use of antihypertensive treatment.[24] Diabetes was defined as fasting plasma glucose (FPG) $\geq$7.0 mmol/L, or current pharmacological treatment of diabetes, or a self-reported history of diabetes.[25]

Statistical analyses

All non-European descent individuals were excluded prior to analysis. Thirty-one preselected SNPs, which previously showed significant association with BP and/or hypertension in GWAS of European descent individuals, were examined using additive models for increasing copy of the minor allele (i.e. major allele homozygote = 0, heterozygote = 1, and minor allele homozygote = 2). In a three-stage analysis within each cohort, we first performed logistic regression with OH as a binary variable, and linear regression using the orthostatic SBP response as a dependent continuous variable without adjusting for covariates. In the second stage, we adjusted for age at examination, gender, body mass index (BMI), current smoking, resting SBP and DBP, use of antihypertensive treatment, and diabetes as potential confounders. In the third stage, all individuals taking antihypertensive treatment were excluded. We combined the results of all five cohorts using inverse variance-weighted meta-analysis according to the regression models: unadjusted, multivariable-adjusted, and excluding those receiving antihypertensive treatment, respectively. The fixed effects model of meta-analysis was applied in the absence of significant between-study heterogeneity (χ^2 heterogeneity, $P \geq 0.05$); otherwise a random effects model was used. The meta-analytical approach was chosen based on a recent comparison of meta-analysis with joint analysis of individual participant data showing that these two methods are equivalent.[26]

Logistic and linear regressions were performed using IBM SPSS Statistics software version 19.0 (SPSS, Inc., Chicago, IL, USA) except for FHS (details provided in the see Supplementary material online), and for CHS (R Statistical Software, R Foundation for Statistical Computing, Vienna, Austria). Inverse-variance-weighted meta-analysis was performed using STATA 11 (STATACorp LP, College Station, TX, USA). Power calculations were done by PS Power and Sample Size Calculations software version 3.0 (Department of Biostatistics, Vanderbilt University, TN, USA). All tests were two-sided and $P < 0.05$ was considered as nominally significant. The nominally significant associations were then re-evaluated using the Bonferroni method for multiple testing ($P < 0.05/31$ tested variants).

Results

A total of 38 970 men and women were included; of these 2656 (6.8%) met the diagnostic criteria for OH. ARIC and MPP represented relatively younger cohorts (45–54 years) when compared with CHS, FHS, and Rotterdam Study (62–72 years) and had a lower prevalence of OH (*Table 1*). A small fraction of MPP participants were on anti-hypertensive treatment (~4.5%), whereas, in ARIC, the proportion did not substantially differ from other cohorts (~25 vs. 22–30%). Minor allele frequencies of the analysed SNPs were consistent across the cohorts (see Supplementary material online, *Table S1*).

Table 1 Characteristics of study participants by orthostatic hypotension status presented as means (SD) or percentage

Characteristic	ARIC		CHS		FHS		MPP		Rotterdam	
	OH− (*n* = 9171)	OH + (*n* = 446)	OH− (*n* = 2534)	OH + (*n* = 481)	OH− (*n* = 2773)	OH+ (*n* = 321)	OH− (*n* = 17 493)	OH+ (*n* = 383)	OH− (*n* = 4343)	OH+ (*n* = 1025)
Age (years)	54 (6)	58 (5)	72 (5)	73 (5)	62 (9)	65 (9)	45 (7)	50 (7)	68 (9)	73 (9)
Gender (male %)	47	51	39	40	43	40	65	45	43	33
BMI (kg/m^2)	27 (5)	27 (5)	26 (5)	26 (4)	28 (5)	27 (5)	24 (3)	24 (4)	26 (4)	27 (5)
Current smoking (%)	24	29	11	11	14	15	38	38	23	24
SBP supine (mmHg)	118 (17)	126 (19)	135 (21)	136 (23)	134 (18)	146 (19)	127 (14)	137 (19)	138 (22)	144 (23)
DBP supine (mmHg)	71 (10)	73 (11)	71 (11)	69 (12)	79 (9)	80 (9)	84 (9)	87 (11)	74 (11)	74 (12)
Hypertension[a] (%)										
≥140/90 mmHg	12	24	52	55	27	30	35	52	53	65
≥160/100 mmHg	2	6	36	40	7	8	7	20	31	42
Antihypertensive treatment (%)	24	48	30	31	30	41	4	12	21	27
Diabetes (%)	9	17	12	14	9	11	3	6	9	14
Prevalent CVD (%)	5	9	0	0	7	13	0	0	13	18

ARIC, the Atherosclerosis Risk in Communities Study; CHS, the Cardiovascular Health Study; FHS, the Framingham Heart Study; MPP, the Malmö Preventive Project; Rotterdam, the Rotterdam Study; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CVD, cardiovascular disease.

[a]Hypertension was defined according to supine or sitting (for CHS only) BP.

Table 2 Association between single nucleotide polymorphisms and orthostatic hypotension according to three different logistic regression models in meta-analysis of five cohorts

SNP ID	Chr	Model 1			Model 2			Model 3		
Locus		Crude (n = 38 970)			Adjusted (n = 38 970)			No antihypertensive treatment (n = 32 679)		
		Regression coefficient		*P*-value	Regression coefficient		*P*-value	Regression coefficient		*P*-value
		Est. coefficient	95% CI		Est. coefficient	95% CI		Est. coefficient	95% CI	
rs10850411 *TBX5 -TBX3*	12	0.021	−0.047, 0.089	0.55	0.024	−0.046, 0.094	0.50	0.006	−0.079, 0.090	0.89
rs11191548 *CYP17A1 -NT5C2*	10	−0.167	−0.284, −0.051	0.005	−0.173	−0.294, −0.052	0.005	−0.168	−0.313, −0.024	0.022
rs1173771 *NPR3 -C5orf23*	5	−0.082	−0.144, −0.020	0.009	−0.081	−0.145, −0.017	0.012	−0.057	−0.134, 0.019	0.14
rs11953630 *EBF1*	5	−0.103	−0.167, −0.040	0.001	−0.096	−0.161, −0.030	0.004	−0.107	−0.186, −0.029	0.007
rs12946454 *PLCD3*	17	0.070	−0.045, 0.185	0.23	0.068	−0.047, 0.183	0.25	0.022	−0.063, 0.107	0.61
rs13082711 *SLC4A7*	3	−0.005	−0.080, 0.070	0.89	0.002	−0.075, 0.080	0.95	−0.011	−0.104, 0.082	0.82
rs13107325 *SLC39A8*	4	0.045	−0.078, 0.167	0.47	0.042	−0.084, 0.167	0.52	−0.014	−0.168, 0.141	0.86
rs13139571 *GUCY1A3 -GUCY1B3*	4	0.016	−0.055, 0.087	0.66	0.027	−0.047, 0.100	0.48	0.000	−0.088, 0.089	0.99
rs1327235 *JAG1*	20	0.049	−0.013, 0.110	0.12	0.039	−0.025, 0.103	0.24	0.068	−0.009, 0.145	0.082
rs1378942 *CYP1A1 -ULK3*	15	0.037	−0.027, 0.101	0.26	0.027	−0.039, 0.093	0.42	0.069	−0.010, 0.147	0.088
rs1530440 *C10orf107*	10	−0.034	−0.114, 0.045	0.40	−0.033	−0.115, 0.049	0.44	−0.039	−0.137, 0.058	0.43
rs16948048 *ZNF652*	17	−0.009	−0.072, 0.053	0.77	0.008	−0.056, 0.072	0.81	0.004	−0.073, 0.081	0.92
rs16998073 *PRDM8 -FGF5*	4	0.066	−0.068, 0.200	0.34	0.0634	−0.083, 0.210	0.40	−0.001	−0.094, 0.092	0.99
rs17367504 *MTHFR -NPPB*	1	0.045	−0.036, 0.126	0.28	0.054	−0.030, 0.138	0.20	0.121	0.022, 0.219	0.016
rs17608766 *GOSR2*	17	0.064	−0.029, 0.158	0.18	0.057	−0.039, 0.154	0.25	0.069	−0.048, 0.185	0.25
rs1799945 *HFE*	6	−0.057	−0.146, 0.032	0.21	−0.049	−0.140, 0.043	0.30	−0.037	−0.148, 0.075	0.52

rs198358										
NPPA -NPPB	1	0.038	−0.033, 0.109	0.29	0.048	−0.025, 0.122	0.20	0.093	0.006, 0.179	0.036
rs2521501										
FURIN -FES	15	0.025	−0.049, 0.100	0.51	0.030	−0.047, 0.107	0.45	0.019	−0.072, 0.111	0.68
rs2681492										
ATP2B1	12	−0.034	−0.114, 0.045	0.40	−0.031	−0.114, 0.051	0.46	−0.046	−0.144, 0.053	0.36
rs2932538										
MOV10	1	0.030	−0.040, 0.101	0.40	0.038	−0.034, 0.111	0.30	0.028	−0.060, 0.115	0.53
rs3184504										
SH2B3	12	−0.003	−0.063, 0.056	0.91	−0.006	−0.067, 0.055	0.84	−0.022	−0.095, 0.051	0.56
rs3774372										
ULK4	3	−0.002	−0.083, 0.079	0.96	0.008	−0.076, 0.091	0.86	0.011	0.089, 0.112	0.83
rs381815										
PLEKHA7	11	−0.010	−0.079, 0.058	0.77	0.007	−0.063, 0.078	0.84	−0.015	−0.100, 0.070	0.73
rs419076										
MECOM	3	−0.005	−0.065, 0.056	0.88	−0.004	−0.067, 0.058	0.89	0.000	−0.075, 0.075	1.00
rs4373814										
CACNB2(5′)	10	0.014	−0.047, 0.075	0.66	−0.001	−0.064, 0.062	0.97	0.011	−0.065, 0.088	0.77
rs5068										
NPPA -NPPB	1	0.074	−0.060, 0.208	0.28	0.081	−0.058, 0.220	0.25	0.198	0.041, 0.355	0.014
rs6015450										
GNAS -EDN3	20	0.030	−0.063, 0.122	0.53	0.043	−0.052, 0.138	0.38	0.061	−0.054, 0.176	0.30
rs633185										
FLJ32810 -TMEM133	11	−0.038	−0.105, 0.030	0.28	−0.021	−0.092, 0.049	0.55	−0.015	−0.098, 0.069	0.73
rs7129220										
ADM	11	0.062	−0.039, 0.162	0.23	0.068	−0.036, 0.172	0.20	0.046	−0.079, 0.172	0.47
rs805303										
BAT2 -BAT5	6	0.010	−0.053, 0.072	0.76	0.009	−0.055, 0.073	0.79	−0.022	−0.169, 0.125	0.77
rs932764										
PLCE1	10	−0.013	−0.074, 0.048	0.68	−0.016	−0.079, 0.048	0.63	0.003	−0.133, 0.139	0.97

Chr, chromosome; Est. coefficient, estimate coefficient.

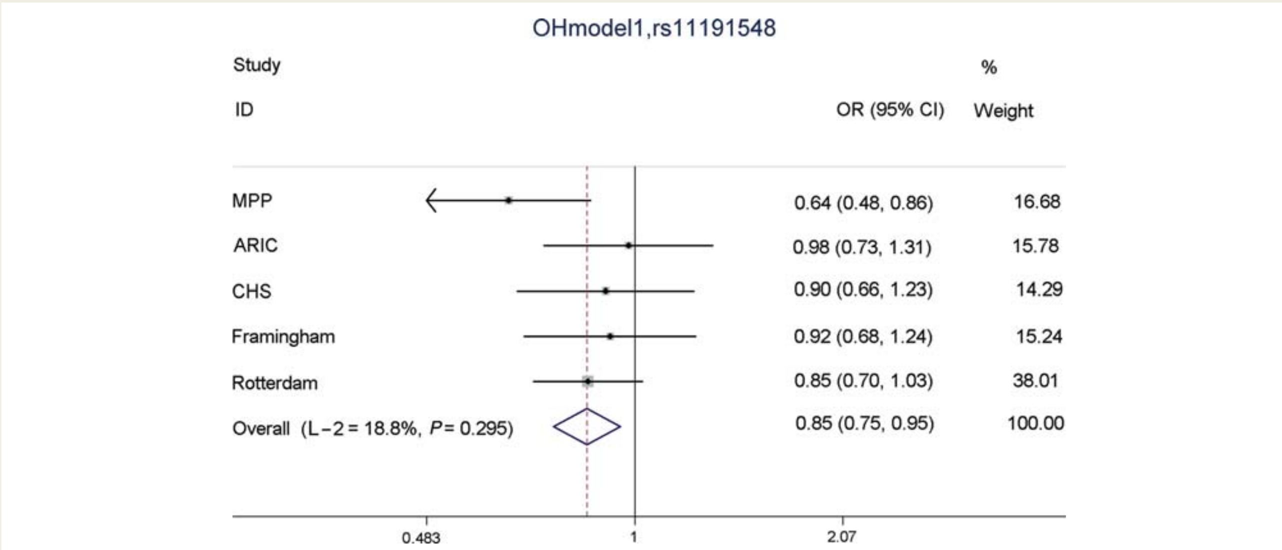

Figure 1 Forest plot for association between rs11191548 (C/T) and orthostatic hypotension (OH) according to unadjusted logistic regression model (Model 1) in meta-analysis of five cohorts. MPP, the Malmö Preventive Project; ARIC, the Atherosclerosis Risk in Communities Study; CHS, the Cardiovascular Health Study; Framingham, the Framingham Heart Study; Rotterdam, the Rotterdam Study; OR, odds ratio; CI, confidence interval.

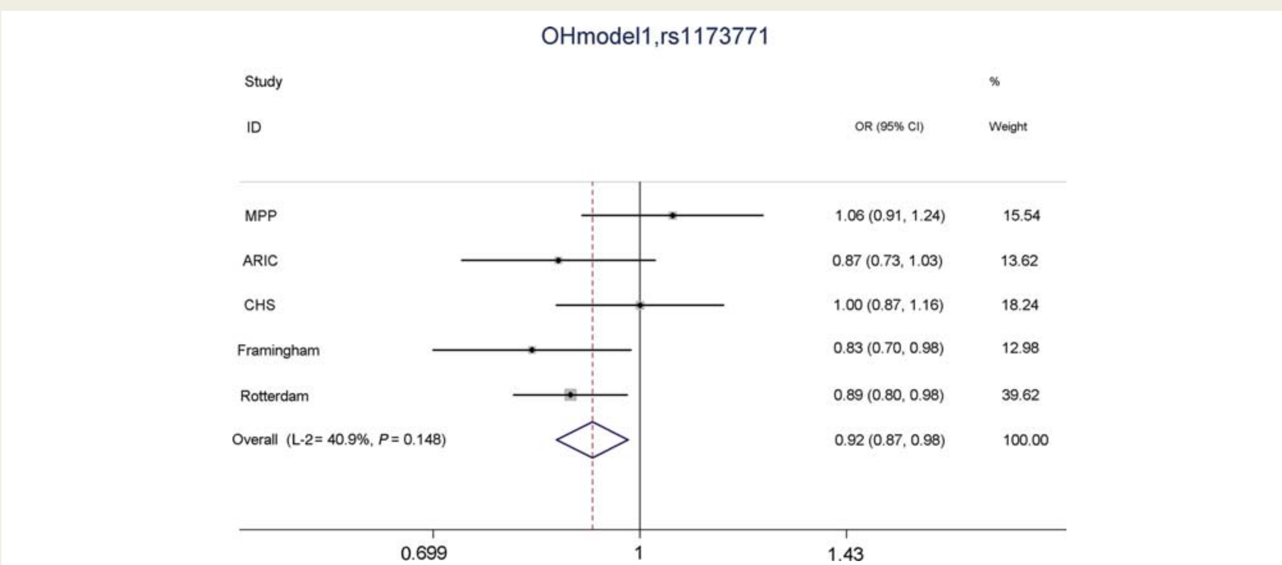

Figure 2 Forest plot for association between rs1173771 (A/G) and orthostatic hypotension (OH) according to unadjusted logistic regression model (Model 1) in meta-analysis of five cohorts. MPP, the Malmö Preventive Project; ARIC, the Atherosclerosis Risk in Communities Study; CHS, the Cardiovascular Health Study; Framingham, the Framingham Heart Study; Rotterdam, the Rotterdam Study; OR, odds ratio; CI, confidence interval.

Association between blood pressure gene variants and orthostatic hypotension

As can be seen in *Table 2*, minor alleles of rs11191548, rs1173771, and rs11953630, all of which are associated with lower resting BP, were also nominally associated with lower probability of OH in both the crude and adjusted model (*Figures 1–3*). Of these, only rs11953630 met the Bonferroni significance level ($P < 0.05/31$, model 1). After exclusion of all subjects taking anti-hypertensive drugs, the relationship between OH and rs1173771 was attenuated, while it remained substantially unchanged for rs11191548 and rs11953630 (*Table 2*). In the human genome, rs11191548

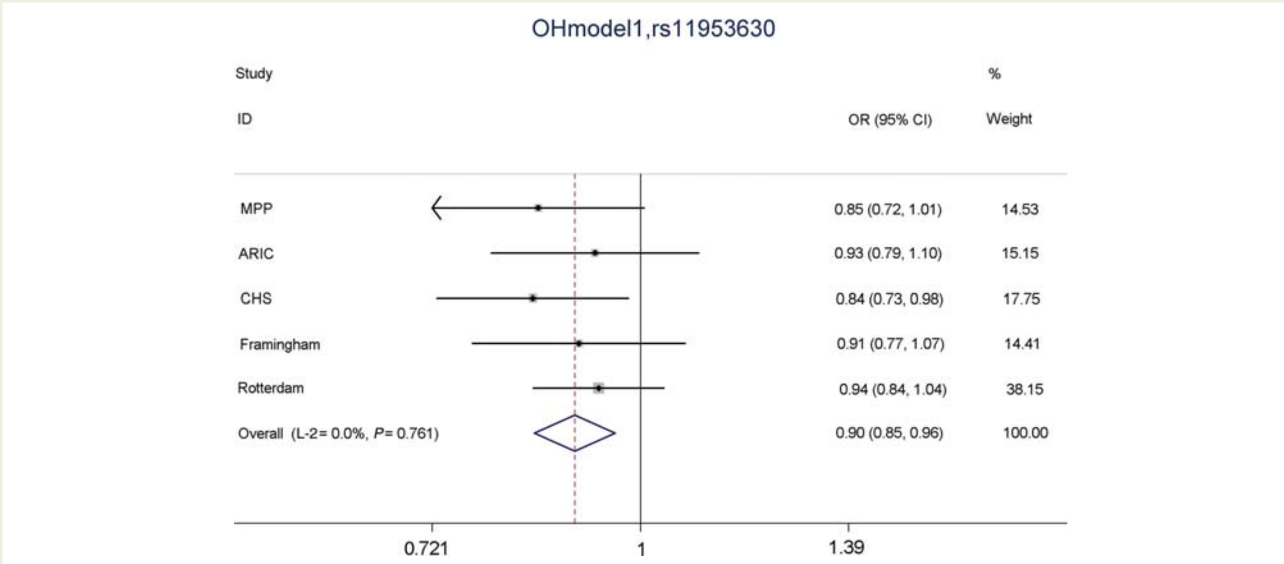

Figure 3 Forest plot for association between rs11953630 (T/C) and orthostatic hypotension (OH) according to unadjusted logistic regression model (Model 1) in meta-analysis of five cohorts. MPP, the Malmö Preventive Project; ARIC, the Atherosclerosis Risk in Communities Study; CHS, the Cardiovascular Health Study; Framingham, the Framingham Heart Study; Rotterdam, the Rotterdam Study; OR, odds ratio; CI, confidence interval.

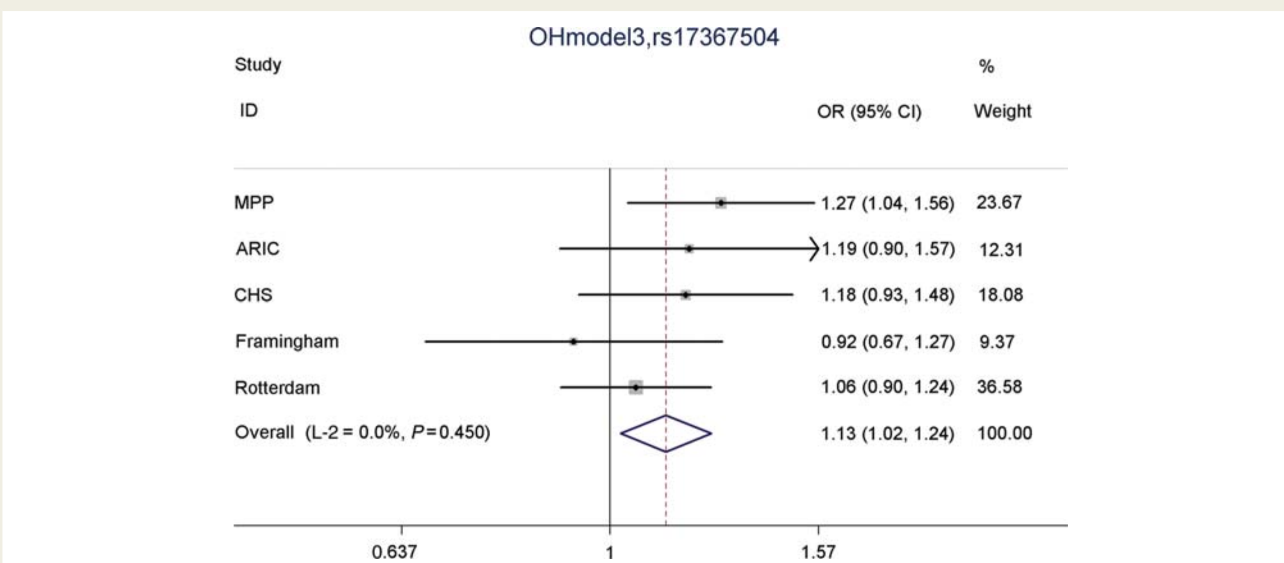

Figure 4 Forest plot for association between rs17367504 (G/A) and orthostatic hypotension (OH) according to the adjusted logistic regression model after exclusion of participants taking antihypertensive drugs (Model 3) in meta-analysis of five cohorts. MPP, the Malmö Preventive Project; ARIC, the Atherosclerosis Risk in Communities Study; CHS, the Cardiovascular Health Study; Framingham, the Framingham Heart Study; Rotterdam, the Rotterdam Study; OR, odds ratio; CI, confidence interval.

resides at a locus that contains *CYP17A1*, rs11953630 is situated in the vicinity of *CLINT1/EBF1*, and rs1173771 is located near *NPR3*, a gene coding for natriuretic peptide clearance receptor (*NPR3*). Furthermore, when participants taking BP-lowering drugs were excluded, we noted nominally significant association between OH and rs17367504, rs198358, and rs5068 (*Figures 4–6*). These three SNPs are located in the *NPPA/NPPB* region and are associated with lower BP, but higher odds for OH. Among those genetic variants, which were associated with OH, there was no significant ($P < 0.10$) SNP–SNP interactions on OH.

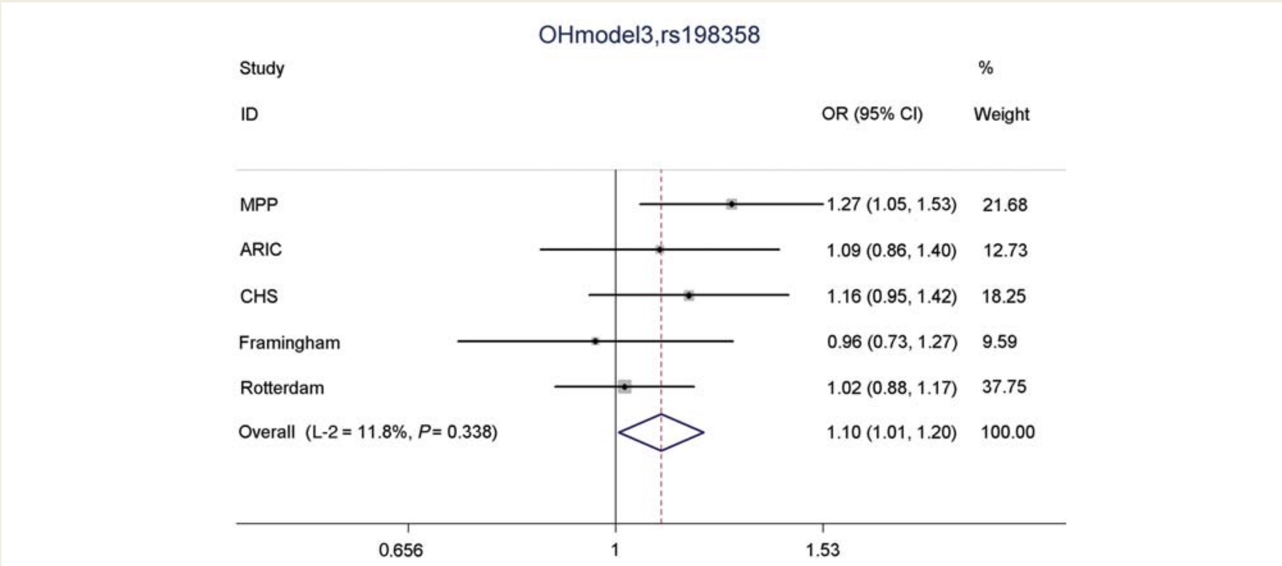

Figure 5 Forest plot for association between rs198358 (C/T) and orthostatic hypotension (OH) according to the adjusted logistic regression model after exclusion of participants taking antihypertensive drugs (Model 3) in meta-analysis of five cohorts. MPP, the Malmö Preventive Project; ARIC, the Atherosclerosis Risk in Communities Study; CHS, the Cardiovascular Health Study; Framingham, the Framingham Heart Study; Rotterdam, the Rotterdam Study; OR, odds ratio; CI, confidence interval.

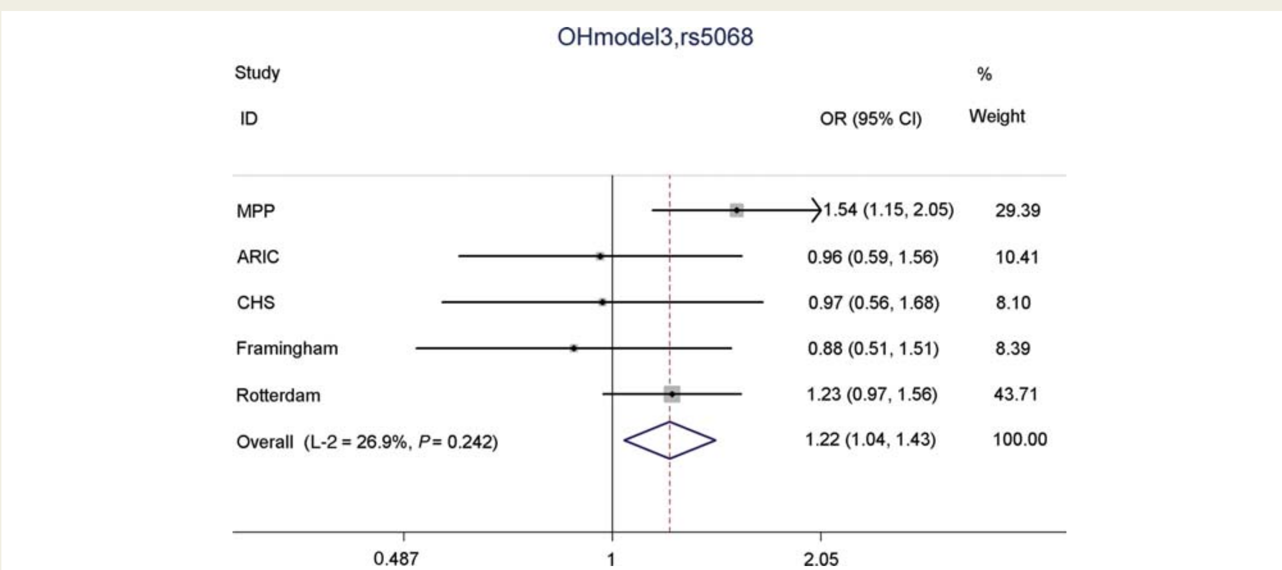

Figure 6 Forest plot for association between rs5068 (G/A) and orthostatic hypotension (OH) according to the adjusted logistic regression model after exclusion of participants taking antihypertensive drugs (Model 3) in meta-analysis of five cohorts. MPP, the Malmö Preventive Project; ARIC, the Atherosclerosis Risk in Communities Study; CHS, the Cardiovascular Health Study; Framingham, the Framingham Heart Study; Rotterdam, the Rotterdam Study; OR, odds ratio; CI, confidence interval.

Association between blood pressure gene variants and orthostatic systolic blood pressure response

Two BP-associated gene variants demonstrated a nominal association with orthostatic SBP response (see Supplementary material online, *Table S2*): rs11191548 in the crude model (est. coefficient = −0.269, −0.484 to −0.055; $P = 0.014$) and rs7129220 in the adjusted model (est. coefficient = 0.222, 0.011–0.433; $P = 0.039$) (see Supplementary material online, *Figure S1*). The minor allele of the latter, which is associated with higher resting BP, confers a more pronounced decrease in SBP on standing. The most plausible gene candidate in the vicinity of rs7129220 is *ADM* coding for a precursor of vasodilatory peptide adrenomedullin.

Table 3 Summary of potential common genetic polymorphism effects on blood pressure, orthostatic hypotension and orthostatic systolic blood pressure response

SNP ID	Gene locus	Minor allele effect on			
		Postulated biological mechanism	Blood pressure	Orthostatic hypotension	Orthostatic systolic blood pressure fall
rs11191548	*CYP17A1—NT5C2*	CYP17A1 ↑?	↓	↓	↓
rs1173771	*NPR3—C5orf23*	NPR-C ↓	↓	↓	—
*rs11953630**	*EBF1*	Autoimmune ↓?	↓	↓	—
rs17367504	*MTHFR—NPPB*	ANP/BNP ↑?	↓	↑	—
rs198358	*NPPA/NPPB*	ANP/BNP ↑	↓	↑	—
rs5068	*NPPA/NPPB*	ANP/BNP ↑	↓	↑	—
rs7129220	*ADM*	ADM ↓?	↑	—	↑

SNP, single nucleotide polymorphism; CYP17A1, cytochrome P450 enzyme CYP17A1; NPR-C, natriuretic peptide clearance receptor; ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; ADM, adrenomedullin.
*Statistically significant after Bonferroni adjustment ($P < 0.0016$).

Discussion

A marked BP decline in response to postural change can be due to such aetiological factors as disorders of the autonomic nervous system, volume status, cardiac function, use of pharmacological agents, and advancing age.[27,28] In parallel, it is not clear to what extent propensity towards OH is heritable. Here, we report that several of the newly discovered loci involved in the regulation of resting BP may be potentially implicated in the pathogenesis of OH. Although the overall association between common BP gene variants and OH was weak (24 of 31 SNPs showing no association at all), we identified one significant and four nominally associated loci (*Table 3*) on four chromosomes (see Supplementary material online, *Figure S2*).

The first locus is indicated by rs11191548, which is situated in the 3′untranslated region near the gene encoding cytochrome P450 enzyme *CYP17A1*. This enzyme is responsible for steroid 17α-hydroxylase and 17, 20-lyase activity, necessary for both dehydroepiandrosterone and cortisol synthesis. Mutations associated with reduced activity of *CYP17A1* result in 11-deoxycorticosterone and corticosterone excess. These two aldosterone precursors demonstrate a weak mineralocorticoid activity. Clinically, an inherited 17α-hydroxylase deficiency leads to adrenal hyperplasia, hypertension, hypokalaemic alkalosis, and suppression of the renin–angiotensin system, which causes a decreased aldosterone synthase expression and a very low level of circulating aldosterone.[29,30] An association between rs11191548 variance and *CYP17A1* activity has not yet been established. However, the minor allele of this SNP is associated with lower supine BP (and lower odds for OH), which could be compatible with higher enzymatic activity of CYP17A1 (*Table 3*). Thus, higher CYP17A1 activity could result in a normally responsive synthesis of aldosterone, whereas the adrenal cortex could have a relatively greater capacity of cortisol production. Consequently, the minor allele of rs 11191548 would be associated with a more effective adrenal response (i.e. a relatively higher production of both aldosterone and cortisol) on orthostatic challenge, thus reducing OH risk by augmenting vascular tone and intravascular volume.[31] Additional experimental work would be required to support this hypothesis. The second locus indicated by rs1173771, which is situated in the intergenic region, encompasses the gene coding for *NPR3*. Genetic variant in this locus may reduce production of NPR-C or reduce clearance of natriuretic peptides by altering the function of NPR-C, thus lowering the resting BP, as suggested by a recent study.[32] As hypertension is a strong correlate of OH,[6] this mechanism may protect from an orthostatic BP fall. The third identified genetic variant, rs11953630, was the only one to remain statistically significant after the Bonferroni adjustment. This SNP is situated in the intergenic region between *CLINT1* and *EBF1*, for which a plausible physiological mechanism has not been yet proposed. However, the genetic polymorphism within the EBF1 locus has been recently linked to primary Sjögren's syndrome,[33] which is frequently associated with autonomic dysfunction and OH.[34] The fourth nominally associated with OH locus, *NPPA/NPPB*, encompasses genes coding for the natriuretic peptides, ANP and BNP. The minor alleles of rs198358 and rs5068, both situated in the 3′untranslated region, have previously been associated with higher levels of circulating ANP and BNP and lower supine BP.[19] In parallel, the minor allele of rs17367504, which is localized in an intron of *MTHFR* gene in the vicinity of *NPPA/NPPB*, was associated with lower BP in a recent GWAS.[20] The uncoupling of the directionality between supine BP and OH is interesting in the light of previously published data suggesting that hypertension (or higher SBP) is one of the strongest determinants of OH.[6,35] Natriuretic peptides are known for their vasodilatory and extracellular volume-reducing properties.[36] These effects can be partially explained by their negative action on renin and aldosterone release, in addition to direct effects on the kidney and vasculature. Moreover, natriuretic peptides exert effects on ANS-related compensatory reflexes by reducing the sensitivity of cardiac and pulmonary chemo- and baroreceptors, and by attenuating renal sympathetic activity.[37] Thus, the main regulatory mechanisms responsible for cardiac output, vascular tone, and intravascular volume control, which are crucial for maintenance of BP on standing, may be negatively influenced by chronically elevated levels of natriuretic peptides. More interestingly, the effects of *NPPA/NPPB* variants were observed only among those subjects who were not on anti-hypertensive treatment. Taking into account that most study participants were recruited during 'the diuretics era,' it seems very likely that pharmacologically potentiated urine production might blunt the impact of genetically altered natriuretic peptides levels on orthostatic response. The fifth locus implied by rs7129220 encompasses the gene encoding precursor of adrenomedullin, a potent direct vasodilator with natriuretic and diuretic properties secreted predominantly by endothelium.[38] The minor allele at this position, associated with higher resting BP, increases the risk of a BP fall on standing (*Table 3*), which is concordant with previous studies on the relationship between OH and hypertension.[6,35]

Study limitations

Our study has several limitations. Firstly, the discovery populations for genetic BP associations were partially the same as cohorts, which were included in this study. Secondly, orthostatic BP measurements were taken on one occasion and we were not able to identify participants with temporary vs. persistent OH. Thirdly, the OH phenotype differed slightly between cohorts (supine rest ranged from 5 to 20 min and standing BP was taken after 1–3 min). Thus, the overall OH prevalence may have been underestimated as patients with initial (within the first minute of standing)[39] and delayed OH (after 3 min of standing)[40] could not be detected. Moreover, CYP17A1 activity, NPR-C function, and concentration as well as the adrenomedullin-circulating level were not determined in the study sample. Finally, out of five identified loci, only one (EBF1) was significantly associated with OH after the Bonferroni adjustment. However, we had a specific hypothesis behind each of the genotype–phenotype tests performed. Given the strong physiological and epidemiological link between BP and OH, we cannot exclude that any SNP indisputably associated with resting BP and nominally with orthostatic BP response represents a valid finding limited by the statistical power of studied populations. For the assumed significance level of 0.0016 and a minor allele frequency of 25%, if the true per-minor-allele odds ratio for OH was 1.1, we would need to study 9392 cases and 131 488 controls to be able to reject the null hypothesis with a probability of 0.8. On the other hand, the size of the studied sample allowed correctly excluding effects, which exceeded the odds ratio of 1.20 per minor allele.

In summary, although we generally observed weak associations between BP gene variants and OH, we identified five loci potentially involved in disorders of orthostatic homoeostasis. Interestingly, alleles associated with higher resting BP translated into both higher (CYP17A1, NPR3-*C5orf23*, and EBF1 loci) and lower (NPPA/NPPB locus) risk of OH. These findings need validation in cohorts with more accurate or standardized phenotyping of orthostatic BP response; however, they may be helpful in understanding mechanisms leading to OH.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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