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Citation

Fedorowski, Artur, Nora Franceschini, Jennifer Brody, Chunyu Liu, Germaine C. Verwoert, Eric Boerwinkle, David Couper, Kenneth M. Rice, Jerome I. Rotter, Francesco Mattace-Raso, Andre Uitterlinden, Albert Hofman, Peter Almgren, Marketa Sjögren, Bo Hedblad, Martin G. Larson, Christopher Newton-Cheh, Thomas J. Wang, Kathryn M. Rose, Bruce M. Psaty, Daniel Levy, Jacqueline Witteman, and Olle Melander. 2012. Orthostatic hypotension and novel blood pressure-associated gene variants: Genetics of Postural Hemodynamics (GPH) consortium. *European Heart Journal* 33(18): 2331-2341.

Published Version

doi:10.1093/eurheartj/ehs058

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

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Received 27 November 2011; revised 10 January 2012; accepted 16 February 2012; online publish-ahead-of-print 14 April 2012

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 ≥ 20 mmHg and/or decrease in mean diastolic BP (DBP) ≥ 10 mmHg within 3 min of standing.²³ Postural change in SBP (Δ SBP) 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 ≥ 140 mmHg and/or mean supine DBP ≥ 90 mmHg, or use of anti-hypertensive treatment.²⁴ Diabetes was defined as fasting plasma glucose (FPG) ≥ 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 (STATA Corp 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 ($\sim 4.5\%$), 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.

^aHypertension 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		
		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											
<i>NPPA -NPPB</i>	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											
<i>FURIN -FES</i>	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											
<i>ATP2B1</i>	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											
<i>MOV10</i>	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											
<i>SH2B3</i>	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											
<i>ULK4</i>	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											
<i>PLEKHA7</i>	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											
<i>MECOM</i>	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											
<i>CACNB2(5')</i>	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											
<i>NPPA -NPPB</i>	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											
<i>GNAS -EDN3</i>	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											
<i>FLJ32810 -TMEM133</i>	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											
<i>ADM</i>	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											
<i>BAT2 -BAT5</i>	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											
<i>PLCE1</i>	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.

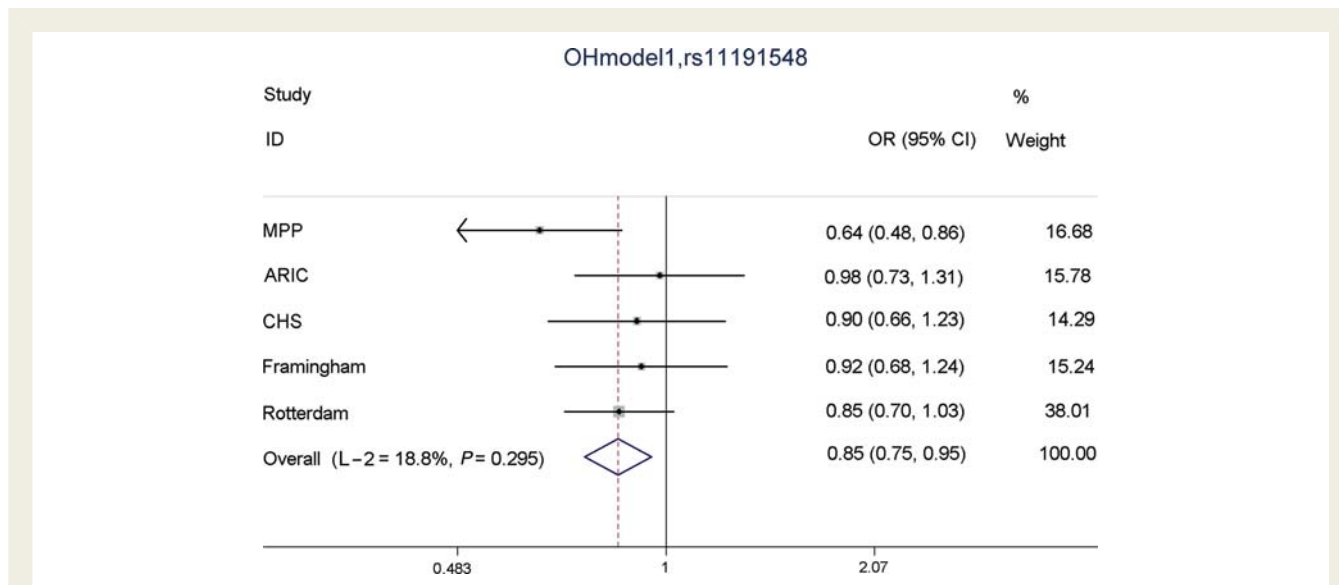


Figure 1 Forest plot for association between rs11191548 (C/T) and orthostatic hypotension (OH) according to unadjusted logistic regression model (Model 1) in meta-analysis of five cohorts. MPP, the Malmö Preventive Project; ARIC, the Atherosclerosis Risk in Communities Study; CHS, the Cardiovascular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

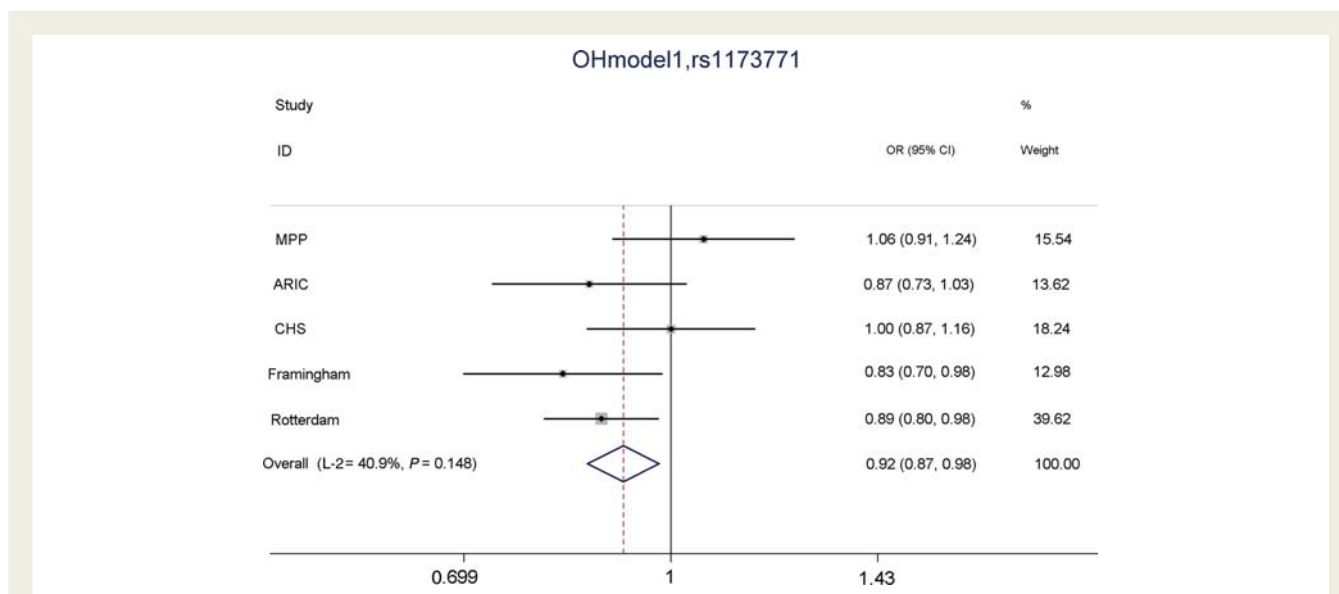


Figure 2 Forest plot for association between rs1173771 (A/G) and orthostatic hypotension (OH) according to unadjusted logistic regression model (Model 1) in meta-analysis of five cohorts. MPP, the Malmö Preventive Project; ARIC, the Atherosclerosis Risk in Communities Study; CHS, the Cardiovascular Health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

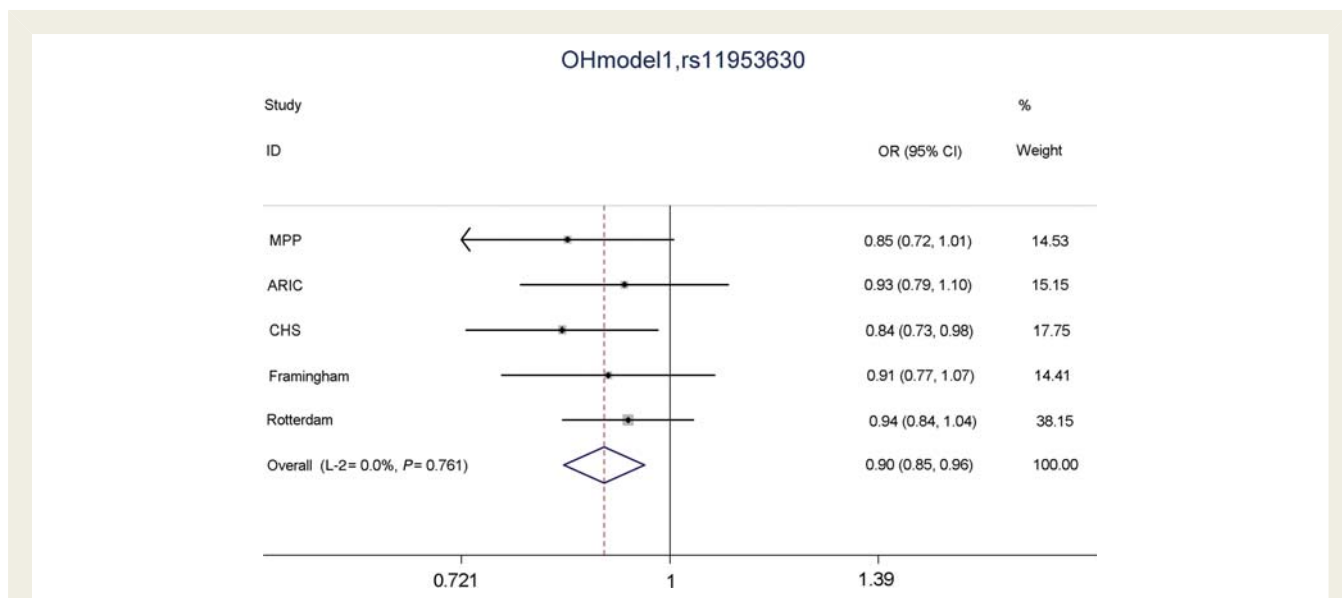


Figure 3 Forest plot for association between rs11953630 (T/C) and orthostatic hypotension (OH) according to unadjusted logistic regression model (Model 1) in meta-analysis of five cohorts. MPP, the Malmö Preventive Project; ARIC, the Atherosclerosis Risk in Communities Study; CHS, the Cardiovascular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

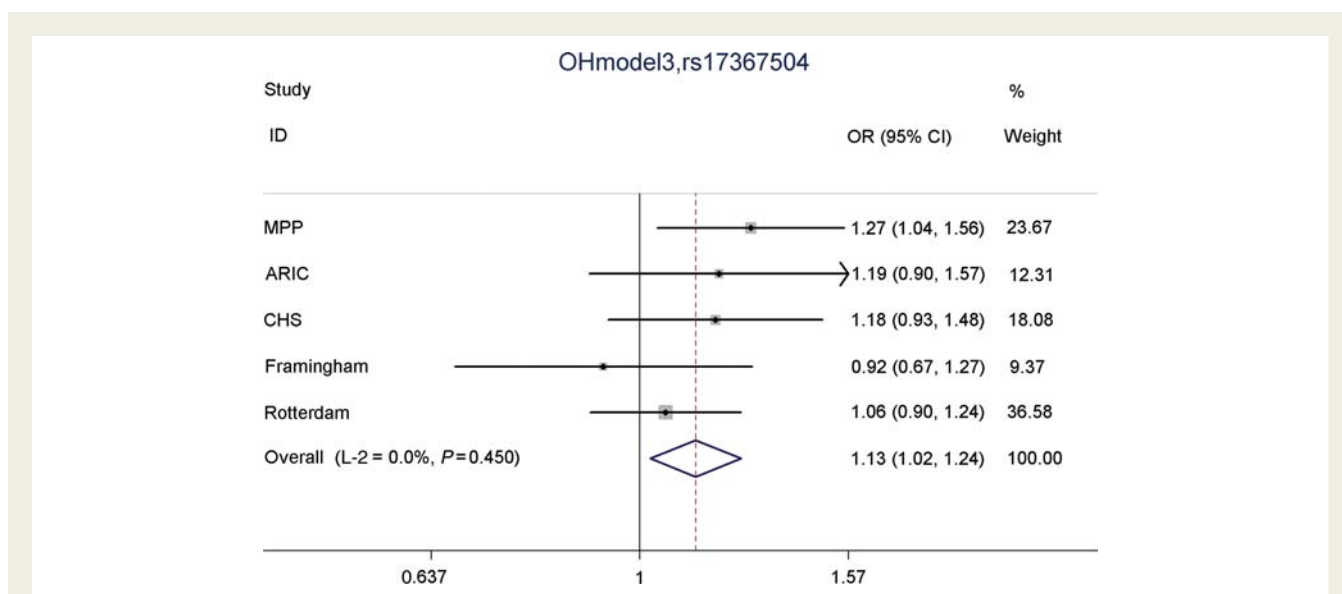


Figure 4 Forest plot for association between rs17367504 (G/A) and orthostatic hypotension (OH) according to the adjusted logistic regression model after exclusion of participants taking antihypertensive drugs (Model 3) in meta-analysis of five cohorts. MPP, the Malmö Preventive Project; ARIC, the Atherosclerosis 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.

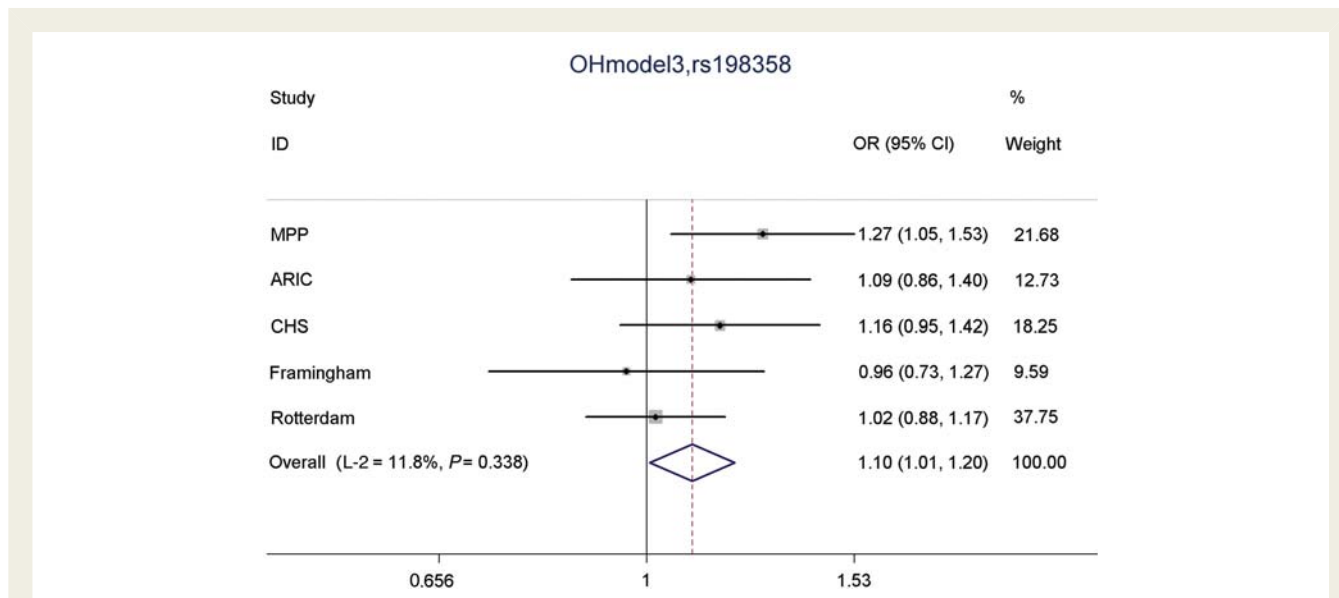


Figure 5 Forest plot for association between rs198358 (C/T) and orthostatic hypotension (OH) according to the adjusted logistic regression model after exclusion of participants taking antihypertensive drugs (Model 3) in meta-analysis of five cohorts. MPP, the Malmö Preventive Project; ARIC, the Atherosclerosis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

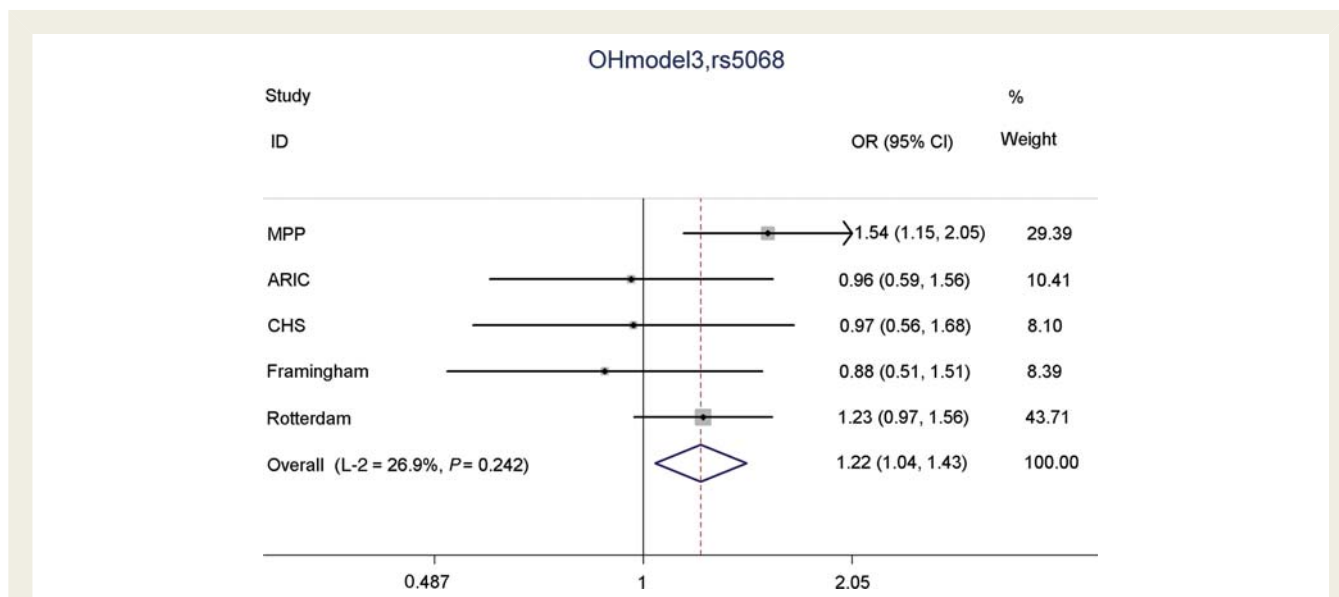


Figure 6 Forest plot for association between rs5068 (G/A) and orthostatic hypotension (OH) according to the adjusted logistic regression model after exclusion of participants taking antihypertensive drugs (Model 3) in meta-analysis of five cohorts. MPP, the Malmö Preventive Project; ARIC, the Atherosclerosis 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	<i>CYP17A1—NT5C2</i>	<i>CYP17A1</i> ↑?	↓	↓	↓
rs1173771	<i>NPR3—C5orf23</i>	<i>NPR-C</i> ↓	↓	↓	—
rs11953630*	<i>EBF1</i>	Autoimmune ↓?	↓	↓	—
rs17367504	<i>MTHFR—NPPB</i>	<i>ANP/BNP</i> ↑?	↓	↑	—
rs198358	<i>NPPA/NPPB</i>	<i>ANP/BNP</i> ↑	↓	↑	—
rs5068	<i>NPPA/NPPB</i>	<i>ANP/BNP</i> ↑	↓	↑	—
rs7129220	<i>ADM</i>	<i>ADM</i> ↓?	↑	—	↑

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 17 α -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 17 α -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 homeostasis. 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.

Funding

Detailed information on the sources of funding can be found in the Supplementary material online (Funding and Acknowledgements Section). Funding to pay the Open Access publication charges for this article was provided by Lund University.

Conflict of interest: B.M.P. serves on a DSMB for a clinical trial of a device funded by the manufacturer (Zoll).

References

- Smith JJ, Porth CM, Erickson M. Hemodynamic response to the upright posture. *J Clin Pharmacol* 1994;**34**:375–386.
- Robertson D. The pathophysiology and diagnosis of orthostatic hypotension. *Clin Auton Res* 2008;**18**(Suppl 1):2–7.
- Gupta V, Lipsitz LA. Orthostatic hypotension in the elderly: diagnosis and treatment. *Am J Med* 2007;**120**:841–847.
- Low PA, Singer W. Management of neurogenic orthostatic hypotension: an update. *Lancet Neurol* 2008;**7**:451–458.
- Vinik AI, Ziegler D. Diabetic cardiovascular autonomic neuropathy. *Circulation* 2007;**115**:387–397.
- Fedorowski A, Burri P, Melander O. Orthostatic hypotension in genetically related hypertensive and normotensive individuals. *J Hypertens* 2009;**27**:976–982.
- Franceschini N, Rose KM, Astor BC, Couper D, Vupputuri S. Orthostatic hypotension and incident chronic kidney disease: the atherosclerosis risk in communities study. *Hypertension* 2010;**56**:1054–1059.
- Masaki KH, Schatz IJ, Burchfiel CM, Sharp DS, Chiu D, Foley D, Curb JD. Orthostatic hypotension predicts mortality in elderly men: the Honolulu Heart Program. *Circulation* 1998;**98**:2290–2295.
- Eigenbrodt ML, Rose KM, Couper DJ, Arnett DK, Smith R, Jones D. Orthostatic hypotension as a risk factor for stroke: the atherosclerosis risk in communities (ARIC) study, 1987–1996. *Stroke* 2000;**31**:2307–2313.
- Rose KM, Tyroler HA, Nardo CJ, Arnett DK, Light KC, Rosamond W, Sharrett AR, Szklo M. Orthostatic hypotension and the incidence of coronary heart disease: the Atherosclerosis Risk in Communities study. *Am J Hypertens* 2000;**13**:571–578.
- Rose KM, Eigenbrodt ML, Biga RL, Couper DJ, Light KC, Sharrett AR, Heiss G. Orthostatic hypotension predicts mortality in middle-aged adults: the Atherosclerosis Risk In Communities (ARIC) Study. *Circulation* 2006;**114**:630–636.
- Fedorowski A, Stavenow L, Hedblad B, Berglund G, Nilsson PM, Melander O. Orthostatic hypotension predicts all-cause mortality and coronary events in middle-aged individuals (The Malmo Preventive Project). *Eur Heart J* 2010;**31**:85–91.
- Fedorowski A, Engstrom G, Hedblad B, Melander O. Orthostatic hypotension predicts incidence of heart failure: the Malmo preventive project. *Am J Hypertens* 2010;**23**:1209–1215.
- Harrap SB, Cui JS, Wong ZY, Hopper JL. Familial and genomic analyses of postural changes in systolic and diastolic blood pressure. *Hypertension* 2004;**43**:586–591.
- Scurrah KJ, Zaloumis SG, Hopper JL, Harrap SB. Contribution of genes and environment to variation in postural changes in mean arterial and pulse pressure. *J Hypertens* 2008;**26**:2319–2325.
- Tabara Y, Kohara K, Miki T. Polymorphisms of genes encoding components of the sympathetic nervous system but not the renin-angiotensin system as risk factors for orthostatic hypotension. *J Hypertens* 2002;**20**:651–656.
- North KE, Rose KM, Borecki IB, Oberman A, Hunt SC, Miller MB, Blangero J, Almsy L, Pankow JS. Evidence for a gene on chromosome 13 influencing postural systolic blood pressure change and body mass index. *Hypertension* 2004;**43**:780–784.
- Pankow JS, Dunn DM, Hunt SC, Leppert MF, Miller MB, Rao DC, Heiss G, Oberman A, Lalouel JM, Weiss RB. Further evidence of a quantitative trait locus on chromosome 18 influencing postural change in systolic blood pressure: the Hypertension Genetic Epidemiology Network (HyperGEN) Study. *Am J Hypertens* 2005;**18**:672–678.
- Newton-Cheh C, Larson MG, Vasani RS, Levy D, Bloch KD, Surti A, Guiducci C, Kathiresan S, Benjamin EJ, Struck J, Morgenthaler NG, Bergmann A, Blankenberg S, Kee F, Nilsson P, Yin X, Peltonen L, Vartiainen E, Salomaa V, Hirschhorn JN, Melander O, Wang TJ. Association of common variants in

- NPPA and NPPB with circulating natriuretic peptides and blood pressure. *Nat Genet* 2009;**41**:348–353.
20. Newton-Cheh C, Johnson T, Gateva V, Tobin MD, Bochud M, Coin L, Najjar SS, Zhao JH, Heath SC, Eyheramendy S, Papadakis K, Voight BF, Scott LJ, Zhang F, Farrall M, Tanaka T, Wallace C, Chambers JC, Khaw KT, Nilsson P, van der Harst P, Polidoro S, Grobbee DE, Onland-Moret NC, Bots ML, Wain LV, Elliott KS, Teumer A, Luan J, Lucas G, Kuusisto J, Burton PR, Hadley D, McArdle WL, Brown M, Dominiczak A, Newhouse SJ, Samani NJ, Webster J, Zeggini E, Beckmann JS, Bergmann S, Lim N, Song K, Vollenweider P, Waeber G, Waterworth DM, Yuan X, Groop L, Orho-Melander M, Allione A, Di Gregorio A, Guarrera S, Panico S, Ricceri F, Romanazzi V, Sacerdote C, Vineis P, Barroso I, Sandhu MS, Luben RN, Crawford GJ, Jousilahti P, Perola M, Boehnke M, Bonnycastle LL, Collins FS, Jackson AU, Mohlke KL, Stringham HM, Valle TT, Willer CJ, Bergman RN, Morken MA, Doring A, Gieger C, Illig T, Meitinger T, Org E, Pfeufer A, Wichmann HE, Kathiresan S, Marrugat J, O'Donnell CJ, Schwartz SM, Siscovick DS, Subirana I, Freimer NB, Hartikainen AL, McCarthy MI, O'Reilly PF, Peltonen L, Pouta A, de Jong PE, Snieder H, van Gilst WH, Clarke R, Goel A, Hamsten A, Peden JF, Seedorf U, Syvanen AC, Tognoni G, Lakatta EG, Sanna S, Scheet P, Schlessinger D, Scuteri A, Dorr M, Ernst F, Felix SB, Homuth G, Lorbeer R, Reffelmann T, Rettig R, Volker U, Galan P, Gut IG, Hercberg S, Lathrop GM, Zelenika D, Deloukas P, Soranzo N, Williams FM, Zhai G, Salomaa V, Laakso M, Elosua R, Forouhi NG, Volzke H, Uitterwaal CS, van der Schouw YT, Numans ME, Matullo G, Navis G, Berglund G, Bingham SA, Kooner JS, Connell JM, Bandinelli S, Ferrucci L, Watkins H, Spector TD, Tuomilehto J, Altshuler D, Strachan DP, Laan M, Meneton P, Wareham NJ, Uda M, Jarvelin MR, Mooser V, Melander O, Loos RJ, Elliott P, Abecasis GR, Caulfield M, Munroe PB. Genome-wide association study identifies eight loci associated with blood pressure. *Nat Genet* 2009;**41**:666–676.
 21. Levy D, Ehret GB, Rice K, Verwoert GC, Launer LJ, Dehghan A, Glazer NL, Morrison AC, Johnson AD, Aspelund T, Aulchenko Y, Lumley T, Kottgen A, Vasan RS, Rivadeneira F, Eiriksdottir G, Guo X, Arking DE, Mitchell GF, Mattace-Raso FU, Smith AV, Taylor K, Scharpf RB, Hwang SJ, Sijbrands EJ, Bis J, Harris TB, Ganesh SK, O'Donnell CJ, Hofman A, Rotter JJ, Coresh J, Benjamin EJ, Uitterlinden AG, Heiss G, Fox CS, Witteman JC, Boerwinkle E, Wang TJ, Gudnason V, Larson MG, Chakravarti A, Psaty BM, van Duijn CM. Genome-wide association study of blood pressure and hypertension. *Nat Genet* 2009;**41**:677–687.
 22. The International Consortium for Blood Pressure Genome-Wide Association Studies. Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. *Nature* 2011;**478**:103–109.
 23. The definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. *J Auton Nerv Sys* 1996;**58**:123–124.
 24. Mancina G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L, Rynkiewicz A, Schmieder RE, Boudier HA, Zanchetti A, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemsans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Erdine S, Kiowski W, Agabiti-Rosei E, Ambrosioni E, Lindholm LH, Viigimaa M, Adamopoulos S, Agabiti-Rosei E, Ambrosioni E, Bertomeu V, Clement D, Erdine S, Farsang C, Gaita D, Lip G, Mallion JM, Manolis AJ, Nilsson PM, O'Brien E, Ponikowski P, Redon J, Ruschitzka F, Tamargo J, van Zwieten P, Waeber B, Williams B. 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2007;**25**:1105–1187.
 25. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998;**15**:539–553.
 26. Lin DY, Zeng D. Meta-analysis of genome-wide association studies: no efficiency gain in using individual participant data. *Genet Epidemiol* 2010;**34**:60–66.
 27. Hajjar I. Postural blood pressure changes and orthostatic hypotension in the elderly patient: impact of antihypertensive medications. *Drugs Aging* 2005;**22**:55–68.
 28. Maule S, Papotti G, Naso D, Magnino C, Testa E, Veglio F. Orthostatic hypotension: evaluation and treatment. *Cardiovasc Hematol Disord Drug Targets* 2007;**7**:63–70.
 29. Ferrari P, Bianchetti M, Frey FJ. Juvenile hypertension, the role of genetically altered steroid metabolism. *Horm Res* 2001;**55**:213–223.
 30. Martin RM, Lin CJ, Costa EM, de Oliveira ML, Carrilho A, Villar H, Longui CA, Mendonca BB. P450c17 deficiency in Brazilian patients: biochemical diagnosis through progesterone levels confirmed by CYP17 genotyping. *J Clin Endocrinol Metab* 2003;**88**:5739–5746.
 31. Ullian ME. The role of corticosteroids in the regulation of vascular tone. *Cardiovasc Res* 1999;**41**:55–64.
 32. Saulnier PJ, Roussel R, Halimi JM, Lebrec J, Dardari D, Maimaitiming S, Guilloteau G, Prugnard X, Marechaud R, Ragot S, Marre M, Hadjadj S. Impact of natriuretic peptide clearance receptor (NPR3) gene variants on blood pressure in type 2 diabetes. *Diabetes Care* 2011;**34**:1199–1204.
 33. Nordmark G, Kristjansdottir G, Theander E, Appel S, Eriksson P, Vasaitis L, Kvarnstrom M, Delaleu N, Lundmark P, Lundmark A, Sjowall C, Brun JG, Jonsson MV, Harboe E, Goransson LG, Johnsen SJ, Soderkvist P, Eloranta ML, Alm G, Baecklund E, Wahren-Herlenius M, Omdal R, Ronnblom L, Jonsson R, Syvanen AC. Association of EBF1, FAM167A(C8orf13)-BLK and TNFSF4 gene variants with primary Sjogren's syndrome. *Genes Immun* 2011;**12**:100–109.
 34. Mandl T, Wollmer P, Manthorpe R, Jacobsson LT. Autonomic and orthostatic dysfunction in primary Sjogren's syndrome. *J Rheumatol* 2007;**34**:1869–1874.
 35. Shin C, Abbott RD, Lee H, Kim J, Kimm K. Prevalence and correlates of orthostatic hypotension in middle-aged men and women in Korea: the Korean Health and Genome Study. *J Hum Hypertens* 2004;**18**:717–723.
 36. Daniels LB, Maisel AS. Natriuretic peptides. *J Am Coll Cardiol* 2007;**50**:2357–2368.
 37. McGrath MF, de Bold ML, de Bold AJ. The endocrine function of the heart. *Trends Endocrinol Metab* 2005;**16**:469–477.
 38. Kato J, Tsuruda T, Kita T, Kitamura K, Eto T. Adrenomedullin: a protective factor for blood vessels. *Arterioscler Thromb Vasc Biol* 2005;**25**:2480–2487.
 39. Wieling W, Krediet CT, van Dijk N, Linzer M, Tschakovsky ME. Initial orthostatic hypotension: review of a forgotten condition. *Clin Sci (Lond)* 2007;**112**:157–165.
 40. Gibbons CH, Freeman R. Delayed orthostatic hypotension: a frequent cause of orthostatic intolerance. *Neurology* 2006;**67**:28–32.