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

The Harvard community has made this article openly available. Please share how this access benefits you. Your story matters

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

Citable link
http://nrs.harvard.edu/urn-3:HUL.InstRepos:10461887

Terms of Use
This article was downloaded from Harvard University’s DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA
Orthostatic hypotension and novel blood pressure-associated gene variants: Genetics of Postural Hemodynamics (GPH) Consortium

Artur Fedorowski1,2*, Nora Franceschini3, Jennifer Brody4,5,6, Chunyu Liu7,8, Germaine C. Verwoert9,10,11, Eric Boerwinkle12, David Couper13, Kenneth M. Rice14, Jerome I. Rotter15, Francesco Mattace-Raso9,10, Andre Uitterlinden9,10,11, Albert Hofman9, Peter Almgren2, Marketa Sjögren2, Bo Hedblad2, Martin G. Larson7,16, Christopher Newton-Cheh17,18,19,20, Thomas J. Wang7,17,18, Kathryn M. Rose3, Bruce M. Psaty4,5,6,21, Daniel Levy7,8, Jacqueline Witteman9,11, and Olle Melander1,2

1Center for Emergency Medicine, Skåne University Hospital, Entrance 35, Floor 2, 205 02 Malmö, Sweden; 2Department of Epidemiology, University of North Carolina, Chapel Hill, NC, USA; 3Department of Epidemiology, University of Washington, Seattle, WA, USA; 4Department of Epidemiology, University of Washington, Seattle, WA, USA; 5Department of Health Services, University of Washington, Seattle, WA, USA; 6Department of Epidemiology, University of Washington, Seattle, WA, USA; 7Department of Biostatistics, University of North Carolina, Chapel Hill, NC, USA; 8Department of Biostatistics, University of North Carolina, Chapel Hill, NC, USA; 9Department of Biostatistics, Erasmus Medical Center, Rotterdam, The Netherlands; 10Department of Biostatistics, University of North Carolina, Chapel Hill, NC, USA; 11Department of Clinical Sciences, Lund University, Clinical Research Center, Malmö, Sweden; 12Human Genetics Center, School of Public Health, University of Texas, Houston, TX, USA; 13Department of Biostatistics, University of North Carolina, Chapel Hill, NC, USA; 14Department of Epidemiology, University of North Carolina, Chapel Hill, NC, USA; 15Center for Emergency Medicine, Skaåne University Hospital, Entrance 35, Floor 2, 205 02 Malmö, Sweden; 16Department of Clinical Sciences, Lund University, Clinical Research Center, Malmö, Sweden; 17Netherlands Consortium for Healthy Aging (NCHA), Netherlands Genome Initiative (NGI), Den Haag, The Netherlands; 18Department of Medicine, Massachussets General Hospital, Boston, MA, USA; 19Center for Human Genetic Research, Cardiovascular Research Center, Massachusetts General Hospital, Boston, MA, USA; 20Program in Medical and Population Genetics, Broad Institute of Harvard and MIT, Cambridge, MA, USA; and 21Group Health Research Institute, Group Health Cooperative, Seattle, WA, USA

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 ≥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 $NPR3$–$CSorf23$ ($rs1173771$: 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, 1.24–1.43; $P = 0.01$). 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.

* Corresponding author. Tel: +46 40 33 10 00, Fax: +46 40 33 62 08, Email: artur.fedorowski@med.lu.se

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/3.0/), which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.
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. 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. However, OH is often asymptomatic and occurs in the general population, where it has been linked to advancing age, neurodegenerative diseases, diabetes, hypertension, and reduced renal function. Further, OH predicts mortality and cardiovascular events, independently of traditional risk factors.

In parallel, several authors have examined the genetic component of OH. Population-based studies have suggested that polymorphisms of G-protein-related genes GNAS1 and GNB3, influencing cardiovascular tone and reactivity, Insulin promoter factor 1 (PDX1) on chromosome 13, implicated in beta-cell function, 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, 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. 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.

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 Malmo 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. 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 ≥140 mmHg and/or mean supine DBP ≥90 mmHg, or use of anti-hypertensive treatment. 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.

Statistical analyses

All non-European descent individuals were excluded prior to analysis. Thirty-one preselected SNPs, which previously showed significant association with BP and 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 (χ² heterogeneity, P ≥ 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.

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−  | OH + | OH−  | OH + | OH−  | OH + | OH−  | OH + | OH−  | OH + |
| 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/m²)    | 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 (%)| ≥140/90 mmHg | 12 | 24 | 52 | 55 | 27 | 30 | 35 | 52 | 53 | 65 |
| Antihypertensive treatment (%) | ≥160/100 mmHg | 2 | 6 | 36 | 40 | 7 | 8 | 7 | 20 | 31 | 42 |
| 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.

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    | Locus          | Chr | Model 1          | Model 2          | Model 3          |
|-----------|----------------|-----|------------------|------------------|------------------|
|           |                |     | Crude (n = 38 970) | Adjusted (n = 38 970) | No antihypertensive treatment (n = 32 679) |
|           |                |     | Regression coefficient | Regression coefficient | Regression coefficient |
|           |                |     | Est. coefficient 95% CI | Est. coefficient 95% CI | Est. coefficient 95% CI |
| rs10850411 | TBX5 -TBX3     | 12  | 0.021             | -0.047, 0.089     | 0.024             | -0.046, 0.094     | 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            |
| rs1294654  | PLC3D          | 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 -GUCYB3| 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             |
| rs       | Gene              | Chr | Est. Coefficient | Log10 p-Value | 95% CI          | Beta          | p-Value | 95% CI          | Beta          | p-Value |
|---------|-------------------|-----|------------------|--------------|----------------|---------------|---------|----------------|---------------|---------|
| 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(S')        | 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 | FLJ2810 - TEMEM133| 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.
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
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.
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.
Figure S2 online, one.29,30 An association between rs11191548 variance and synthase expression and a very low level of circulating aldosterone–angiotensin system, which causes a decreased aldosterone activity. Clinically, an inheritance and corticosterone excess. These two aldosterone precursors with reduced activity of CYP17A1 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,4 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 (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 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 variant 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

| SNP ID          | Gene locus            | Minor allele effect on | Blood pressure | Orthostatic hypotension | Orthostatic systolic blood pressure fall |
|-----------------|-----------------------|------------------------|---------------|-------------------------|----------------------------------------|
| rs11191548      | CYP17A1—NT5C2        | CYP17A1 †             | ↓             | ↓                       | ↓                                      |
| rs1173771       | NPR3—Csf23           | NPR-C ‡               | ↓             | ↓                       | —                                      |
| rs11953630      | EBF1                 | Autoimmune †          | ↓             | ↓                       | —                                      |
| rs17367504      | MTHFR—NPPB           | ANP/BNP †             | ↓             | ↑                       | —                                      |
| rs198358        | NPPA/NPPB            | ANP/BNP †             | ↓             | ↑                       | —                                      |
| rs5068          | NPPA/NPPB            | ANP/BNP †             | ↓             | ↑                       | —                                      |
| rs7129220       | ADM                  | ADM †                 | ↑             | —                       | ↑                                      |

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

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).
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. 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.

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) and delayed OH (after 3 min of standing) 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
1. Smith JJ, Parsh CM, Erickson M. Hemodynamic response to the upright posture. J Clin Pharmacol 1994;34:375–386.
2. Robertson D. The pathophysiology and diagnosis of orthostatic hypotension. Clin Auton Res 2008;18(Suppl 1):2–7.
3. Gupta V, Lipsitz LA. Orthostatic hypotension in the elderly: diagnosis and treatment. Am J Med 2007;120:841–847.
4. Low PA, Singer W. Management of neurogenic orthostatic hypotension: an update. Lancet Neurol 2008;7:451–458.
5. Vinik AI, Ziegler D. Diabetic cardiovascular autonomic neuropathy. Circulation 2001;105:387–397.
6. Fedorowski A, Burri P, Melander O. Orthostatic hypertension in genetically related hypertensive and normotensive individuals. J Hypertens 2009;27:976–982.
7. 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.
8. Masaki KH, Schatz JI, 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.
9. Eigenbrodt ML, Rose KM, Couper DJ, Amundsson DJ, Smith R, Jones D. Orthostatic hypotension as a risk factor for stroke: the atherosclerosis risk in communities (ARIC) study, 1987–1996. Stroke 2003;34:2307–2313.
10. Rose KM, Tyroler HA, Nando CJ, Amundsson DJ, Light KC, Rosamond W, Sherratt AR, Sakjo M. Orthostatic hypotension and the incidence of coronary heart disease: the Atherosclerosis Risk in Communities study. Am J Hypertens 2000;13:571–578.
11. Rose KM, Eigenbrodt ML, Biga RL, Couper DJ, Light KC, Sherratt AR, Heiss G. Orthostatic hypotension predicts mortality in middle-aged adults: the Atherosclerosis Risk In Communities (ARIC) Study. Circulation 2006;114:630–636.
12. Fedorowski A, Stavenow L, Hedblad B, Berglund N, Nilsson PM, Melander O. Orthostatic hypotension predicts all-cause mortality and coronary events in middle-aged individuals (The Malmo Preventive Project). Eur J Heart J 2010;31:85–91.
13. 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.
14. 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.
15. 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;26:2379–2385.
16. 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.
17. North KE, Rose KM, Borecki IB, Oberman A, Hunt SC, Miller MB, Blangero J, Almasy 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.
18. 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.
19. Newton-Cheh C, Larson MG, Vasan RS, Levy D, Bloch KD, Surti A, Guiducci C, Kathiresan S, Benjamin EJ, Struck J, Margenthalner NG, Bergmann A, Blankenberg S, Kee F, Nilsson P, Yin X, Peletan L, Vartiaen E, Salomaa V, Hirschhorn JN, Melander O, Wang TJ. Association of common variants in
Orthostatic hypotension and novel blood pressure-associated gene variants

NPPA and NPPB with circulating natriuretic peptides and blood pressure. Nat Genet 2009;41:348–353.

20. Newton-Chec C, Johnson T, Gateva V, Tobin MD, Bochud M, Coin L, Najjar SS, Zhao JH, Heath SC, Etteramendy S, Padapados K, Voight BF, Scott LJ, Zhang F, Farrall M, Tanaka T, Wallace C, Chambers JC, Khaw KT, Nilsson P, van der Harst P, Poidoro S, Grobbee DE, Onland-Moret NC, Bots ML, Wain LV, Elliott KS, Teumer A, Luan J, Lucas G, Kuusisto J, Burton PR, Hadley D, McAndle WL, Brown M, Dominiczak A, Newhouse SJ, Samani NJ, Webster J, Zeggini E, Beckmann JS, Bergman S, Lim N, Song K, Vollenweider P, Waeber G, Waterworth DM, Yuan X, Gropo L, Orho-Melander M, Allione A, Di Gregorio A, Guerrera S, Panico S, Ricci F, Romazani V, Sacerdoti C, Vines 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, Morbank M, Doring A, Gieger C, Illig T, Meitinger T, Org E, Pfeifer A, Wichmann HE, Kathiresan S, Mangat I, D’onnell CJ, Schwartz SM, Siscovick DS, Subbrana I, Freimer NB, Hartikainen AL, McCarthy MI, O’Reilly PF, Peltonen L, Pouta A, de Jong PE, Snieder H, van Gilster WH, Clarke R, Goel A, Hamsten A, Peden JF, Seedorf U, syvainen ac, Tognoni G, Lakatta EG, Sanna S, Scheet P, Schlessinger D, Scuteri A, Dorra M, Ernst F, Felix SB, Homuth G, Lorber 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, Velske H, Uterwall CS, van der Schouw YT, Numans ME, Matullo G, Navis G, Berglund B, Bragham SA, Kooper JN, Connell JMF, Bandinelli S, Ferrucci L, Watkins H, Spector TD, Tuomilehto J, Altshuler D, Strachan DP, Laan M, Meneton P, Wareham NJ, Uda M, Marjelin MR, Moozer 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, Laufer LJ, Dephhin A, Glazer NL, Morrison AC, Johnson AD, Aspelund T, Aulchenko Y, Lusmey T, Kottgen A, Vasan RS, Rivadecaniera E, Elikbodotir G, Guo X, Arking DE, Macttace-Raso FL, Smith AV, Taylor K, Scharpf RB, Hwang SJ, Sijbrands EJ, Bis J, Harris TB, Ganesh SK, D’onnell CJ, Hoffman A, Rotter J, Corin J, Benjamin EJ, Uiterlinden AG, Heiss G, Fox CS, Witteman JC, Boerwinkle E, Wang TJ, Gudnason V, Larson MG, Mahtaj S, Rast belt 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 Autonerv Syst 1996;58:123–124.

24. Marrio G, De Basker G, Dominicza A, Cifera R, Fagard R, Gemanno G, Grassi G, Hegemy AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruzolpe L, Rynkieczka A, Schermer R, Boudier H, Zanchetti A, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filgainos F, Funkl-Orentano C, Hellemans I, Kristensen SD, McGregor G, Sechim E, Silber S, Tendera M, Widimsky P, Zamorano JL, Erdine S, Kowalski W, Abaghi-Rose E, Ambrosioni E, Lindholm LH, Vigama M, Adamopoulos S, Abaghi-Rose E, Ambrosioni E, Bertomeu V, Clement D, Erdine S, Farsang C, Gaita D, Lip G, Mallon J, Manolis AJ, Nilsson P, O’Brien E, Ponikowski P, Redon J, Ruschitzka F, Tamargo J, van Zwielen 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. Albers 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, Popatti G, Naso D, Magnino C, Testa E, Vieglio F. Orthostatic hypotension: evaluation and treatment. Cardiovasc Hematol Disord Drug Targets 2007;7:63–70.

29. Ferrari P, Bianchetti M, Frey F. Juvenile hypertension, the role of genetically altered steroid metabolism. Harm Res 2001;5:213–223.

30. Martin RM, Lin CJ, Costa EM, de Oliveira ML, Camila A, Villar H, Longa CI, Mendonca BB. P450c17 deficiency in Brazilian patients: biochemical diagnosis through progesterone levels confirmed by CYP17 genotyping. J Clin Endocrinol Metab 2003;88:579–574.

31. Uljan 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, Danieli D, Maimatining S, Guillerou G, Prugnard X, Maitre MH, Ramon E, Maubert D. Impact of natriuretic peptide clearance receptor (NPR3) gene variants on blood pressure tolerance in type 2 diabetes. Diabetes Care 2011;34:1199–1204.

33. Nordmark G, Kristjansdottir G, Theander E, Appel S, Eriksson P, Vasaitis L, Kvastrum M, Delate V, Lundmark P, Lundmark A, Spowall C, Brun JG, Jonsson MV, Harboe E, Goransson LG, Johnsen SJ, Soderkvist P, Eriksdal ML, Alm G, Boeklund E, Wahren-Herlenius M, Omdal R, Rannbloom L, Jonsson R, Syvonen AC. Association of EF1, FAM167A(CBor113) and TNF5F4 gene variants with primary Sjogren’s syndrome. Genes Immun 2015;12:100–109.

34. Kundt 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, Kim K. Prevalence and correlates of orthostatic hypotension in middle-aged and young women in Korea: the Korean Health and Nutrition Study. J Hum Hypertens 2004;18:717–723.

36. Daniels LB, Maisel AS. Natriuretic peptides. J Am Coll Cardiol 2007;50:2357–2368.

37. McKNag 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;66:28–32.