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Association of 77 Polymorphisms in 52 Candidate Genes with Blood Pressure Progression and Incident Hypertension: The Women's Genome Health Study

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Abstract

Objective—Genetic risk factors for essential hypertension are largely unknown. The aim of the present study was to assess the association of 77 previously characterized gene variants in 52 candidate genes from various biological pathways with blood pressure progression and incident hypertension.

Methods—We analyzed data from 18738 Caucasian women who participated in a prospective cohort study and were free of hypertension at baseline. Blood pressure progression at 48 months and incident hypertension during the entire follow-up according to the different genotypes were assessed by logistic regression and Cox proportional-hazards models, respectively.

Results—At 48 months of follow-up, 7889 of 16635 women (47.4%) had blood pressure progression. Only three of 70 polymorphisms with a minor allele frequency $\geq 2\%$ had a significant association with blood pressure progression. The odds ratio (95% confidence interval (CI)) for MTHFR rs1801133 (minor allele T), NPPA rs5063 (minor allele A) and NPPA rs5065 (minor allele C) were 1.05 (1.00–1.10), 0.84 (0.76–0.94) and 0.93 (0.88–1.00), respectively. After adjustment for multiple testing using the false discovery rate, only the NPPA rs5063 association remained significant. During a median follow-up of 9.8 years, 5540 of 18738 women developed incident hypertension. Only five of 70 polymorphisms were significantly associated with incident hypertension. The hazard ratio (95% CI) for IL6 rs1800795 (minor allele C), MTHFR rs1801133, NPPA rs5063, NOS3 rs1799983 (minor allele T) and TGFB1 rs1800469 (minor allele T) were 0.96 (0.92–1.00), 1.06 (1.02–1.10), 0.88 (0.80–0.96), 1.05 (1.01–1.09) and 1.05 (1.01–1.10), respectively. After adjustment for multiple testing, none of these associations remained significant.

Conclusion—NPPA gene polymorphisms may have a role in blood pressure progression and incident hypertension. Our data also provide moderate confirmatory evidence of association between MTHFR rs1801133 and hypertension.

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Disclosures

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Keywords

Blood pressure; Hypertension; Gene polymorphism; Natriuretic peptide precursor A; Methylenetetrahydrofolate Reductase

Introduction

Although obesity and other environmental factors substantially contribute to the high incidence of essential hypertension (1,2), several studies suggest that in human beings a significant part of the inter-individual variability of blood pressure is heritable (3,4). In a population based sample, Tobin et al estimated the heritability of mean 24-hour blood pressure to be about 65% (4).

The exploration of genetic risk factors of hypertension is an important research priority, due to the high prevalence of the disorder and the potential for improved risk prediction and novel antihypertensive drug targets. Consequently, a multitude of biological pathways of interest have been investigated in recent years (5). For example, natriuretic peptides and the renin angiotensin system play a significant role in the regulation of vascular tone and sodium homeostasis (6,7), making genetic polymorphisms within these pathways valid candidates to predict an individual's risk of blood pressure progression and incident hypertension. Because of the consistent association between elevated plasma levels of C-reactive protein and incident hypertension (8–10), inflammation-modulating polymorphisms might also be implicated in the pathogenesis of hypertension.

Unfortunately, prior studies assessing candidate genes for hypertension were predominantly small and provided inconsistent results. As demonstrated recently, population stratification and publication bias may explain an important part of this inconsistency (11,12). Therefore, information from large, prospective cohort studies is needed to elucidate the small effects of genetic variants in the pathogenesis of complex diseases. In this context, the Women's Genome Health Study (WGHS) provides a unique opportunity to prospectively assess the relationship between a multitude of candidate gene polymorphisms and the risk of blood pressure progression and incident hypertension.

Methods

Participants

All study subjects were participants of the WGHS (13). The WGHS comprises a large-scale genetic epidemiological study in initially healthy women participating in the National Institute of Health funded Women's Health Study (14–16) who provided a baseline blood sample for DNA analysis before randomization and were then prospectively followed for incident disease events.

Information on baseline variables was collected by mailed questionnaires. Follow-up questionnaires asking participants about study outcomes and other information were sent every six months during the first year and every 12 months thereafter. Follow-up information from randomization through the end of the trial, March 31, 2004 was used for this analysis. For the present study, we included 18738 Caucasian women who were free of hypertension, did not receive antihypertensive drugs at baseline, and who had complete information on all covariates included in the multivariable models. We recently showed within this cohort that the reporting of Caucasian ancestry was highly reliable and that there was no evidence of population sub-stratification (17). Median follow-up for this sample population was 9.8 years (interquartile range 6.6–10.5 years). Written informed consent was obtained from all participants. The study

was approved by the institutional review board of the Brigham and Women's Hospital, Boston, and was monitored by an external data and safety monitoring board.

Study variables

We assessed the relationship of blood pressure progression and incident hypertension with 77 previously described gene polymorphisms in 52 candidate genes. The findings for a small number of these polymorphisms have been published previously (18,19). The candidate genes examined were selected from biochemical pathways that have been implicated in the development and progression of cardiovascular disease (20,21). In addition to the biological relevance of the selected candidate genes, the polymorphisms were further selected based on prior evidence of potential functionality, validated allele frequency and heterozygosity, and sequence-proven allelic variation.

Blood pressure at randomization was self-reported by the female health professionals, a group where self-report of blood pressure has proven highly accurate (22–24). Participating women categorized their blood pressure levels into nine categories of systolic blood pressure and seven categories of diastolic blood pressure. For the purpose of this study, women were classified into three predefined blood pressure categories: below 120 mmHg for systolic and 75 mmHg for diastolic blood pressure; 120 to 129 mmHg for systolic or 75 to 84 mmHg for diastolic blood pressure; and 130 to 139 mmHg for systolic or 85 to 89 mmHg for diastolic blood pressure (25). Women with discordant systolic and diastolic blood pressure categories were classified into the higher category.

Other covariates of interest were ascertained at study entry and included age, smoking, history of hypercholesterolemia (self-reported cholesterol of at least 240 mg/dl (6.22 mmol/l)), body mass index (weight in kilograms divided by the square of height in meters), and history of diabetes.

Outcome assessment

First, we assessed blood pressure progression at 48 months. For this analysis, we created categories of self-reported blood pressure at 48 months of follow-up identical to those at baseline. Blood pressure progression was defined by progressing at least one blood pressure category compared to baseline, or by a new diagnosis of hypertension during the first 48 months of follow-up. Because of missing blood pressure information at 48 months, cardiovascular events or death during the first 48 months of follow-up, we excluded 2103 participants from these analyses.

Second, we assessed cases of incident hypertension during the entire follow-up period of 9.8 years. Incident cases of hypertension were defined by meeting at least one of the following criteria: self-report of a new physician diagnosis of hypertension assessed at years 1, 3 and yearly thereafter; self-report of antihypertensive treatment assessed at years 1, 3 and 4; or self-reported systolic blood pressure of at least 140 mmHg or diastolic blood pressure of at least 90 mmHg.

Women reporting a new physician diagnosis of hypertension also provided month and year of diagnosis. For a diagnosis defined by another criterion or a missing date for a physician diagnosis, a date between the current and the previous questionnaire was randomly assigned. Women who developed cardiovascular disease for which the management may affect blood pressure levels, were censored at the date of diagnosis and not considered at risk for incident hypertension thereafter. All 18738 women were included in the incident hypertension analyses.

Genotype determination

Genotyping was performed in the context of a multimarker assay using an immobilized probe approach, as previously described (Roche Molecular Systems, Alameda, CA) (20,21). In brief, each DNA sample was amplified by polymerase chain reaction (PCR) with pooled biotinylated primers. Each PCR product pool was then hybridized to a panel of sequence-specific oligonucleotide probes immobilized in a linear array. The colorimetric detection method was based on the use of streptavidin–horseradish peroxidase conjugate with hydrogen peroxide and 3,3',5,5'-tetramethylbenzidine as substrates. Genotype assignment was performed using proprietary Roche Molecular Systems image processing software. To confirm genotype assignment, scoring was carried out by two independent observers. Discordant results (<1% of all scoring) were resolved by a joint reading, and where necessary, a repeat genotyping. Genotyping completion rate was $\geq 95\%$ for all genetic variants assessed in this study.

Statistical analysis

We calculated allele frequencies and performed a Hardy–Weinberg equilibrium test using an exact method. To compare the risk of blood pressure progression and incident hypertension across genotype groups, we used logistic regression and Cox proportional hazards models, respectively. We pre-specified that polymorphisms with a minor allele frequency <2% would be excluded from the analyses. Separate models were constructed for each genotype, always assuming an additive model only. The common wild type was used as the reference group. In a first step, age-adjusted models were constructed. Thereafter, we fitted multivariable models adjusting for age, smoking, baseline blood pressure category, history of diabetes, body mass index, history of hypercholesterolemia, and randomized treatment assignments (aspirin, vitamin E and beta carotene). Given the similarity of the results, only multivariable adjusted models are presented in this manuscript. To adjust for multiple hypothesis testing, we applied the false discovery rate (FDR) using the PROC MULTTEST procedure in SAS (26). Although no universal FDR significance threshold has been defined, previous candidate gene studies used a value of 0.20 (27), meaning that one should expect at most 20% of declared discoveries to be false.

Categorical variables were entered in the regression models using binary indicator variables. Interactions were assessed by comparing the likelihood ratio with and without the interaction terms in the models. The proportional hazards assumption was examined for all models by including a genotype by logarithm of time interaction into the model (28). At the 0.05 level, this assumption was formally violated for two genetic polymorphisms, both p values being 0.04. Given the large number of polymorphisms tested and the large sample size of the cohort, we did not consider these p values as evidence for a significant violation of the proportional hazards assumption. All analyses were carried out using SAS version 9 (SAS Institute Inc, Cary, NC).

Results

Baseline characteristics of the 18738 non-hypertensive women are shown in Table 1. Mean age and body mass index were 54 ± 7 years and 25.1 ± 4.4 kg/m², respectively, 44.5% had a baseline systolic and diastolic blood pressure below 120 mmHg and 75 mmHg, respectively, 39.2% had a systolic and/or diastolic blood pressure between 120 and 129 mmHg and/or 75 and 84 mmHg, respectively and 16.3% had a systolic and/or diastolic blood pressure between 130 and 139 mmHg and/or 85 and 89 mmHg, respectively.

As shown in Table 2, seven of the 77 polymorphisms (9%) had a minor allele frequency <2% and were therefore excluded from further analysis. After Bonferroni correction, four of the remaining polymorphisms were not in Hardy–Weinberg equilibrium (ACE rs1799752

$p < 0.0001$, CSF2 rs25882 $p < 0.0001$, FGB rs1800790 $p < 0.0001$, and MS4A2 rs569108 $p < 0.0001$). Based on our stringent genotyping criteria, we believe that genotyping error is unlikely and that the most likely reason for these findings is chance in association with a large sample size. Moreover, the observed allele frequencies of the four genetic variants correspond to those reported elsewhere (29,30).

At 48 months of follow-up, 7889 of 16635 women (47.4%) had blood pressure progression. Multivariable regression analyses are shown in Table 3. Overall, only three of the 70 polymorphisms (4%) were statistically significant at the 0.05 level. The odds ratios (95% confidence intervals) for MTHFR rs1801133, NPPA rs5063 and NPPA rs5065 were 1.05 (1.00–1.10), 0.84 (0.76–0.94) and 0.93 (0.88–1.00), respectively. The FDR values for these three polymorphisms were 0.70, 0.10 and 0.70, respectively.

During a median follow-up of 9.8 years, 5540 of 18738 women developed incident hypertension. As shown in Table 4, the multivariable Cox proportional hazards models revealed that only five of 70 polymorphisms (7%) were significantly associated with incident hypertension at the 0.05 level. The hazard ratios (95% confidence interval) for IL6 rs1800795, MTHFR rs1801133, NPPA rs5063, NOS3 rs1799983 and TGFB1 rs1800469 were 0.96 (0.92–1.00), 1.06 (1.02–1.10), 0.88 (0.80–0.96), 1.05 (1.01–1.09) and 1.05 (1.01–1.10), respectively. The corresponding FDR values for these five polymorphisms were 0.50, 0.22, 0.22, 0.44 and 0.40, respectively.

Taken together, only the NPPA rs5063 and MTHFR rs1801133 gene variants were consistently associated with both blood pressure progression at 48 months and incident hypertension over the entire follow-up period. While statistically significant for blood pressure progression, the association between incident hypertension and NPPA rs5065 was of borderline statistical significance ($p = 0.06$). We previously published detailed results of the association between these two NPPA polymorphisms and blood pressure progression or incident hypertension (18). With regard to MTHFR rs1801133, the association with blood pressure progression and incident hypertension was consistent and independent of baseline blood pressure. After stratification according to baseline blood pressure, the relative risk (95% confidence interval) for each minor allele copy across increasing blood pressure categories was 1.10 (1.02–1.18), 0.98 (0.91–1.06) and 1.08 (0.96–1.21) for blood pressure progression, and 1.07 (0.99–1.17), 1.05 (0.99–1.12), and 1.05 (0.98–1.12) for incident hypertension. Accordingly, genotype by baseline blood pressure interactions in the non-stratified regression models were not statistically significant ($p = 0.73$ and $p = 0.89$, respectively).

Discussion

In this prospective study, we assessed the relationship of 70 candidate polymorphisms with blood pressure progression and incident hypertension. After adjustment for multiple testing, only the NPPA rs5063 polymorphism remained significantly associated with blood pressure progression (odds ratio (95% confidence interval) 0.84 (0.76–0.94); FDR=0.10). The association between this polymorphism and risk of incident hypertension was of borderline significance after adjustment for multiple testing (hazard ratio (95% confidence interval) 0.88 (0.80–0.96); FDR=0.22). As we pointed out in our previous publication, replication of this finding in a different cohort is needed to confirm the implication of the NPPA gene in the pathogenesis of hypertension (18).

Out of the remaining 69 polymorphisms, the MTHFR rs1801133 variant was the only one that was consistently associated with both blood pressure progression and incident hypertension before adjustment for multiple testing. In this context, it is important to note that the present study had enough power to detect small-to-moderate associations. For incident hypertension,

assuming a univariate-additive model, a power of 80%, and an alpha level of 0.05, the study had the ability to detect a relative risk of more than 1.10 if the minor allele frequency is 0.50 and of more than 1.30 if the minor allele frequency is 0.01. A relative risk of 1.30 for a single polymorphism seems to be unrealistic and we empirically decided to use a minor allele frequency of 2% as our cut-off for inclusion. The relative risk estimate (95% confidence interval) for incident hypertension per additional minor allele was 1.06 (1.02–1.10). The FDR of 0.22 was of borderline significance. Interestingly, a recent meta-analysis of several small case control studies suggested a relationship between the T-allele of rs1801133 and hypertension (31), with a summary relative risk estimate of 1.24 (1.02–1.50) among minor allele homozygotes. Taken together, the present report in combination with the recent meta-analysis suggest that the MTHFR rs1801133 gene variant may be involved in the pathogenesis of hypertension, despite the fact that in the present study the association was not statistically significant after adjustment for multiple testing.

From a functional perspective, the MTHFR rs1801133 polymorphism leads to an alanine-to-valine substitution at position 677 (677 C>T). As a consequence, a thermolabile enzyme with decreased activity is produced, TT homozygotes having a 50% reduction in enzyme activity (32). In this cohort, we recently demonstrated different homocysteine levels across MTHFR rs1801133 genotypes, supporting the possibility of a true association with blood pressure progression and incident hypertension (33). However, more studies are needed to assess the potential role of the MTHFR metabolism in the pathogenesis of hypertension.

The candidate gene approach relies on prior knowledge of biological pathways and its associations with disease. Therefore, this approach makes discoveries within new or unknown pathways unlikely. In recent years, genome-wide association studies of common complex diseases using 300,000 to 500,000 polymorphisms per individual have become available. These studies have elucidated consistent risk loci for several cardiovascular risk factors, such as type 2 diabetes (34–36) and dyslipidemia (37–39), and have provided interesting insights in the pathophysiology of these disorders. Unfortunately, the only large genome wide association study for hypertension published so far failed to identify polymorphisms that are significantly associated with hypertension after adjustment for multiple testing (36), highlighting the need for more large scale, carefully designed studies in this important area. In this context, participants of the WGHS are currently undergoing genotyping for more than 360'000 polymorphisms, and more detailed results concerning the association between genetic polymorphisms and hypertension are expected in future analyses (13).

Strengths and limitations

Strengths of the present study are the large sample size, the number of polymorphisms considered, the prospective design and the long-term follow-up with a large number of incident cases. Potential limitations of our study also require discussion. First, this study included only Caucasian female health professionals, and our findings may not be generalizable to other populations. Second, we used self-reported blood pressure and hypertension status. However, the prognostic value of self-reported blood pressure in cohort studies involving US health professionals is similar compared to directly measured blood pressure values in participants of other cohort studies (22). Furthermore, the validity of this approach has been examined in the comparable Nurses' Health Study, where 99% of the women who reported high blood pressure levels had their diagnosis confirmed based on medical record review (23). Moreover in this cohort, self-reported blood pressure, total cholesterol and body mass index have previously been shown to be strong predictors of cardiovascular risk, with relative risks consistent in magnitude with those observed in other major studies (24,40,41). However, given the limited precision of blood pressure assessment in categories at baseline, it has to be emphasized that we cannot exclude a small blood pressure effect of the genotypes evaluated

in the current study. Another limitation of this study is the lack of information on dietary intake and renal function, two important factors in development of hypertension. Furthermore, hypertension may be a heterogeneous entity and this study does not exclude the possibility that some of the genetic variants assessed are associated with a more homogeneous form of hypertension. This study also relied on the assumption that common genetic variants have a significant role in the pathogenesis of blood pressure progression and incident hypertension, an as yet unproven hypothesis. Finally, the assessment of gene-gene and gene-environment interactions was beyond the scope of this study. Future studies are needed to explore in detail this important issue.

Conclusion

This large, prospective study among initially healthy women indicates that NPPA gene polymorphisms may have a role in blood pressure progression and incident hypertension. Although the MTHFR rs1801133 polymorphism failed to meet the criteria for association after adjustment for multiple testing, this study validates findings from previous small studies and implicates a potential involvement of the MTHFR rs1801133 gene variant in the risk of developing hypertension. Future large scale studies using comprehensive genome wide analysis techniques are needed to further elucidate the genetics of hypertension.

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Table 1

Baseline characteristics

Characteristic	N=18738
Age, years	54 ± 7
Body mass index, kg/m ²	25.1 ± 4.4
History of diabetes (%)	1.2
History of hypercholesterolemia (%)	24.9
Smoking (%)	
Current	11.8
Former	37.0
Never	51.2
Exercise, times/week (%)	
Rarely/never	35.1
<1	19.8
1–3	33.1
>3	12.0
Alcohol consumption (%)	
Rarely/never	41.6
1–3 drinks per month	13.4
1–6 drinks per week	34.4
≥1 drink per day	10.6
Highest education level (%)	
Less than a bachelor's degree	53.9
Bachelor's degree	24.8
Master's degree or doctorate	21.4
Baseline blood pressure category (%)	
<120/75 mmHg	44.5
120–129/75–84 mmHg	39.2
130–139/85–89 mmHg	16.3

Data are mean ± standard deviation or percentages

Table 2

Genetic polymorphisms evaluated in the study

Gene	Symbol	Polymorphism	Chromosome	Minor allele	MAF	HWE*
Adducin 1 (alpha)	<i>ADD1</i>	<i>rs4961</i>	4p16.3	T	0.196	0.63
Angiotensin II receptor type 1	<i>AGTR1</i>	<i>rs5186</i>	3q21-25	C	0.305	0.77
Angiotensinogen	<i>AGT</i>	<i>rs699</i>	1q42-43	C	0.412	0.40
Angiotensin-converting enzyme 1	<i>ACE</i>	<i>rs1799752</i>	17q23	I	0.477	<0.0001
Beta-2 adrenergic receptor	<i>ADRB2</i>	<i>rs1042713</i>	5q31-32	A	0.368	0.65
		<i>rs1042714</i>		G	0.438	0.10
		<i>rs1800888</i>		T	0.013	0.07
Beta-3 guanine nucleotide-binding protein	<i>GNB3</i>	<i>rs5443</i>	12p13	T	0.309	0.24
CD14 molecule	<i>CD14</i>	<i>rs2569190</i>	5q31.1	T	0.473	0.15
Chemokine ligand 12	<i>CXCL12</i>	<i>rs1801157</i>	10q11.1	A	0.196	0.18
Chemokine receptor 2	<i>CCR2</i>	<i>rs1799864</i>	3p21	A	0.089	0.17
Chemokine receptor 3	<i>CCR3</i>	<i>rs5742906</i>	3p21.3	T	0.004	1.00
Chemokine receptor 5	<i>CCR5</i>	<i>rs333</i>	3p21	Del	0.104	0.004
		<i>rs1799987</i>		G	0.446	0.86
Colony stimulating factor 2	<i>CSF2</i>	<i>rs25882</i>	5q31.1	C	0.198	<0.0001
Complement component 3	<i>C3</i>	<i>rs2230199</i>	19p13.3-p13.2	G	0.210	0.004
Complement component 5	<i>C5</i>	<i>rs17611</i>	9q33-q34	A	0.441	0.27
Cystathionine-beta-synthase	<i>CBS</i>	<i>rs12329790</i>	21q22.3	T	0.002	1.00
Cytotoxic T-lymphocyte-associated protein 4	<i>CTLA4</i>	<i>rs5742909</i>	2q33	T	0.094	0.69
		<i>rs231775</i>		G	0.383	0.71
Chemokine ligand 11	<i>CCL11</i>	<i>rs3744508</i>	7q21.1-21.2	A	0.175	0.80
		<i>rs4795895</i>		A	0.188	0.92
Coagulation factor II	<i>F2</i>	<i>rs1799963</i>	11p11-q12	A	0.014	0.001
Coagulation factor V	<i>F5</i>	<i>rs6025</i>	1q23	A	0.028	0.04
Coagulation factor VII	<i>F7</i>	<i>rs5742910</i>	13q34	I	0.120	1.00
		<i>rs6046</i>		A	0.110	0.97
Fibrinogen beta	<i>FGB</i>	<i>rs1800790</i>	4q28	A	0.212	<0.0001
Group-specific component (vitamin D binding protein)	<i>GC</i>	<i>rs7041</i>	4q12-q13	T	0.439	0.15
		<i>rs4588</i>		A	0.284	0.02

Gene	Symbol	Polymorphism	Chromosome	Minor allele	MAF	HWE [*]
Integrin, alpha 2	<i>ITGA2</i>	<i>rs1062535</i>	5q23-31	A	0.394	0.95
Integrin, beta 3	<i>ITGB3</i>	<i>rs5918</i>	17q21.32	C	0.152	0.75
Intercellular adhesion molecule 1	<i>ICAM1</i>	<i>rs5491</i>	19p13.3-13.2	T	0.003	1.00
		<i>rs1799969</i>		A	0.116	0.61
Interleukin 1 alpha	<i>IL1A</i>	<i>rs1800587</i>	2q14	T	0.301	0.39
Interleukin 1 beta	<i>IL1B</i>	<i>rs16944</i>	2q14	T	0.331	0.75
		<i>rs1143634</i>		T	0.234	0.84
Interleukin 4	<i>IL4</i>	<i>rs2243250</i>	5q31.1	T	0.149	0.87
Interleukin 4 receptor	<i>IL4R</i>	<i>rs1805010</i>	16p11.2-12.1	G	0.450	0.83
		<i>rs1805015</i>		C	0.165	0.50
Interleukin 5 receptor, alpha	<i>IL5RA</i>	<i>rs1801275</i>		G	0.209	0.97
Interleukin 6	<i>IL6</i>	<i>rs2290608</i>	3p26-24	A	0.257	0.84
		<i>rs1800796</i>	7p21	C	0.053	0.59
		<i>rs1800795</i>		C	0.422	0.28
Interleukin 9	<i>IL9</i>	<i>rs2069885</i>	5q31.1	T	0.135	0.85
Interleukin 10	<i>IL10</i>	<i>rs1800872</i>	1q31-32	A	0.232	0.17
Interleukin 13	<i>IL13</i>	<i>rs1295686</i>	5q31	T	0.202	0.60
Leukotriene C4 synthase	<i>LTC4S</i>	<i>rs730012</i>	5q35	C	0.285	0.59
Lymphotoxin alpha	<i>LTA</i>	<i>rs1041981</i>	6p21.3	A	0.340	0.68
		<i>rs909253</i>		G	0.335	0.53
Matrix metalloproteinase 3	<i>MMP3</i>	<i>rs3025058</i>	11q22.3	6A	0.491	0.05
Membrane-spanning 4-domains, subfamily A, member 2	<i>MS4A2</i>	<i>rs569108</i>	11q13	G	0.025	<0.0001
5,10-methylenetetrahydrofolate reductase	<i>MTHFR</i>	<i>rs1801133</i>	1p36.3	T	0.327	0.15
Natriuretic peptide precursor A	<i>NPPA</i>	<i>rs5063</i>	1p36.21	A	0.049	0.38
		<i>rs5065</i>		C	0.148	0.65
Nitric oxide synthase 2A	<i>NOS2A</i>	<i>rs1137933</i>	17q11.2-q12	T	0.223	0.16
Nitric oxide synthase 3	<i>NOS3</i>	<i>rs1800779</i>	7q36	G	0.373	0.17
		<i>rs3918226</i>		T	0.078	0.12
Secretoglobin, family 1A, member 1	<i>SCGB1A1</i>	<i>rs1799983</i>		T	0.327	0.64
Selectin E	<i>SELE</i>	<i>rs3741240</i>	11q12.3-13.1	A	0.351	0.52
		<i>rs5361</i>	1q22-25	C	0.105	0.55

Gene	Symbol	Polymorphism	Chromosome	Minor allele	MAF	HWE*
Selectin P	<i>SELP</i>	<i>rs5355</i> <i>rs6131</i> <i>rs6133</i>	1q22-25	T A T	0.042 0.187 0.118	0.22 0.96 0.08
Serpin peptidase inhibitor, clade E, member 1	<i>SERPINE1</i>	<i>rs1799768</i> <i>rs7242</i>	7q21.3-22	G G	0.457 0.436	0.17 0.77
Sodium channel, nonvoltage-gated 1 alpha	<i>SCNN1A</i>	<i>rs5742912</i> <i>rs2228576</i>	12p13	C A	0.023 0.330	0.29 0.98
Transcription factor 7	<i>TCF7</i>	<i>rs5742913</i> <i>rs244656</i>	5q31.1	A T	0.106 0.137	0.79 0.88
Transforming growth factor, beta 1	<i>TGFB1</i>	<i>rs1800469</i>	19q13.1	T	0.300	0.55
Tumor necrosis factor	<i>TNF</i>	<i>rs1800750</i> <i>rs1800629</i> <i>rs673</i>	6p21.3	A A A	0.015 0.173 0.003	0.003 0.03 <0.0001
Vascular cell adhesion molecule 1	<i>VCAM1</i>	<i>rs361525</i> <i>rs1041163</i>	1p32-31	A C	0.051 0.161	0.04 0.98
Vitamin D (1,25-dihydroxyvitamin D3) receptor	<i>VDR</i>	<i>rs2228570</i> <i>rs1544410</i>	12q13.11	T A	0.388 0.409	0.82 0.69

MAF Minor allele frequency

HWE Hardy-Weinberg equilibrium

Del Deletion

* p value for HWE using Fisher probability test

Table 3
Gene variants and risk of blood pressure progression

Polymorphism	Odds ratio [*]	95% CI	P value	FDR
<i>ADD1</i> rs4961	0.996	0.941–1.053	0.88	1.00
<i>AGTR1</i> rs5186	1.033	0.984–1.085	0.19	0.78
<i>AGT</i> rs699	1.033	0.988–1.081	0.16	0.70
<i>ACE</i> rs1799752	0.963	0.923–1.006	0.09	0.70
<i>ADRB2</i> rs1042713	0.978	0.934–1.025	0.36	0.93
<i>ADRB2</i> rs1042714	1.003	0.959–1.049	0.89	1.00
<i>GNB3</i> rs5443	0.976	0.930–1.024	0.32	0.93
<i>CD14</i> rs2569190	0.986	0.942–1.033	0.55	0.99
<i>CXCL12</i> rs1801157	1.027	0.970–1.088	0.36	0.93
<i>CCR2</i> rs1799864	1.020	0.941–1.104	0.63	1.00
<i>CCR5</i> rs333	1.055	0.979–1.136	0.16	0.70
<i>CCR5</i> rs1799987	0.992	0.947–1.038	0.73	1.00
<i>CSF2</i> rs25882	1.044	0.986–1.104	0.14	0.70
<i>C3</i> rs2230199	1.052	0.995–1.112	0.08	0.70
<i>C5</i> rs17611	0.991	0.946–1.037	0.69	1.00
<i>CTLA4</i> rs5742909	0.929	0.858–1.004	0.06	0.70
<i>CTLA4</i> rs231775	1.036	0.988–1.086	0.14	0.70
<i>CCL11</i> rs3744508	1.020	0.960–1.083	0.52	0.96
<i>CCL11</i> rs4795895	1.050	0.990–1.114	0.10	0.70
<i>F5</i> rs6025	1.062	0.927–1.216	0.39	0.93
<i>F7</i> rs5742910	0.974	0.910–1.044	0.46	0.95
<i>F7</i> rs6046	0.955	0.889–1.026	0.21	0.82
<i>FGB</i> rs1800790	1.047	0.993–1.104	0.09	0.70
<i>GC</i> rs7041	1.004	0.959–1.052	0.85	1.00
<i>GC</i> rs4588	1.011	0.961–1.065	0.67	1.00
<i>ITGA2</i> rs1062535	0.985	0.941–1.031	0.52	0.96
<i>ITGB3</i> rs5918	0.969	0.911–1.031	0.32	0.93
<i>ICAM1</i> rs1799969	0.975	0.910–1.046	0.48	0.96
<i>IL1A</i> rs1800587	1.011	0.962–1.063	0.67	1.00
<i>IL1B</i> rs16944	0.990	0.943–1.039	0.68	1.00
<i>IL1B</i> rs1143634	1.040	0.985–1.098	0.16	0.70
<i>IL4</i> rs2243250	1.027	0.963–1.095	0.41	0.93
<i>IL4R</i> rs1805010	1.004	0.959–1.051	0.85	1.00
<i>IL4R</i> rs1805015	1.031	0.970–1.097	0.33	0.93
<i>IL4R</i> rs1801275	1.049	0.991–1.109	0.10	0.70
<i>IL5RA</i> rs2290608	0.998	0.946–1.051	0.93	1.00
<i>IL6</i> rs1800796	1.001	0.903–1.109	0.99	1.00
<i>IL6</i> rs1800795	0.980	0.936–1.027	0.40	0.93
<i>IL9</i> rs2069885	1.042	0.974–1.114	0.23	0.85
<i>IL10</i> rs1800872	1.015	0.961–1.071	0.60	1.00
<i>IL13</i> rs1295686	1.006	0.950–1.065	0.83	1.00

Polymorphism	Odds ratio [*]	95% CI	P value	FDR
<i>LTC4S rs730012</i>	1.006	0.956–1.058	0.83	1.00
<i>LTA rs1041981</i>	1.018	0.971–1.067	0.46	0.95
<i>LTA rs909253</i>	1.016	0.968–1.067	0.51	0.96
<i>MMP3 rs3025058</i>	0.993	0.950–1.039	0.77	1.00
<i>MS4A2 rs569108</i>	1.010	0.874–1.167	0.89	1.00
<i>MTHFR rs1801133</i>	1.050	1.001–1.101	0.04	0.70
<i>NPPA rs5063</i>	0.844	0.760–0.937	0.001	0.10
<i>NPPA rs5065</i>	0.934	0.877–0.995	0.03	0.70
<i>NOS2A rs1137933</i>	0.977	0.925–1.032	0.41	0.93
<i>NOS3 rs1800779</i>	1.000	0.954–1.047	0.99	1.00
<i>NOS3 rs3918226</i>	0.990	0.912–1.075	0.81	1.00
<i>NOS3 rs1799983</i>	0.993	0.947–1.041	0.76	1.00
<i>SCGB1A1 rs3741240</i>	0.967	0.922–1.014	0.16	0.70
<i>SELE rs5361</i>	1.013	0.942–1.089	0.73	1.00
<i>SELE rs5355</i>	0.993	0.888–1.111	0.90	1.00
<i>SELP rs6131</i>	1.015	0.957–1.077	0.61	1.00
<i>SELP rs6133</i>	0.965	0.899–1.035	0.32	0.93
<i>SERPINE1 rs1799768</i>	1.002	0.958–1.048	0.93	1.00
<i>SERPINE1 rs7242</i>	1.004	0.960–1.051	0.85	1.00
<i>SCNN1A rs5742912</i>	0.943	0.812–1.096	0.45	0.95
<i>SCNN1A rs2228576</i>	0.976	0.931–1.024	0.32	0.93
<i>TCF7 rs5742913</i>	1.001	0.929–1.077	0.99	1.00
<i>TCF7 rs244656</i>	1.000	0.935–1.069	1.00	1.00
<i>TGFB1 rs1800469</i>	1.010	0.961–1.061	0.70	1.00
<i>TNF rs1800629</i>	0.995	0.938–1.056	0.87	1.00
<i>TNF rs361525</i>	0.998	0.903–1.103	0.97	1.00
<i>VCAM1 rs1041163</i>	0.956	0.898–1.018	0.16	0.70
<i>VDR rs2228570</i>	1.012	0.965–1.061	0.62	1.00
<i>VDR rs1544410</i>	0.978	0.933–1.024	0.34	0.93

CI Confidence interval

FDR False discovery rate

* Adjusted for age, body mass index, smoking, history of diabetes, history of hypercholesterolemia, blood pressure, and randomized treatment assignments.

Table 4
Gene variants and risk of incident hypertension

Polymorphism	Hazard ratio *	95% CI	P value	FDR
<i>ADD1</i> rs4961	1.012	0.965–1.061	0.62	0.96
<i>AGTR1</i> rs5186	0.997	0.957–1.038	0.87	0.99
<i>AGT</i> rs699	1.001	0.964–1.040	0.95	0.99
<i>ACE</i> rs1799752	0.986	0.950–1.023	0.45	0.96
<i>ADRB2</i> rs1042713	0.989	0.951–1.028	0.57	0.96
<i>ADRB2</i> rs1042714	1.000	0.963–1.039	1.00	1.00
<i>GNB3</i> rs5443	0.963	0.924–1.003	0.07	0.50
<i>CD14</i> rs2569190	1.022	0.983–1.063	0.26	0.68
<i>CXCL12</i> rs1801157	1.006	0.959–1.056	0.80	0.97
<i>CCR2</i> rs1799864	1.016	0.950–1.087	0.64	0.96
<i>CCR5</i> rs333	1.054	0.990–1.122	0.10	0.50
<i>CCR5</i> rs1799987	0.991	0.953–1.030	0.64	0.96
<i>CSF2</i> rs25882	1.044	0.996–1.096	0.08	0.50
<i>C3</i> rs2230199	1.042	0.994–1.092	0.08	0.50
<i>C5</i> rs17611	0.993	0.955–1.033	0.72	0.96
<i>CTLA4</i> rs5742909	0.969	0.906–1.037	0.36	0.84
<i>CTLA4</i> rs231775	1.010	0.971–1.051	0.62	0.96
<i>CCL11</i> rs3744508	1.019	0.968–1.072	0.47	0.96
<i>CCL11</i> rs4795895	1.030	0.980–1.082	0.25	0.68
<i>F5</i> rs6025	1.002	0.894–1.123	0.97	0.99
<i>F7</i> rs5742910	0.989	0.933–1.050	0.72	0.96
<i>F7</i> rs6046	0.994	0.935–1.056	0.84	0.99
<i>FGB</i> rs1800790	1.026	0.981–1.073	0.27	0.68
<i>GC</i> rs7041	1.000	0.961–1.040	1.00	1.00
<i>GC</i> rs4588	0.993	0.951–1.037	0.76	0.96
<i>ITGA2</i> rs1062535	1.012	0.973–1.052	0.55	0.96
<i>ITGB3</i> rs5918	0.967	0.918–1.020	0.22	0.68
<i>ICAM1</i> rs1799969	0.999	0.941–1.059	0.96	0.99
<i>IL1A</i> rs1800587	1.007	0.965–1.051	0.74	0.96
<i>IL1B</i> rs16944	0.989	0.949–1.031	0.61	0.96
<i>IL1B</i> rs1143634	1.020	0.974–1.067	0.40	0.90
<i>IL4</i> rs2243250	0.955	0.904–1.009	0.10	0.50
<i>IL4R</i> rs1805010	0.989	0.951–1.028	0.58	0.96
<i>IL4R</i> rs1805015	1.035	0.983–1.089	0.19	0.68
<i>IL4R</i> rs1801275	1.046	0.997–1.096	0.06	0.50
<i>IL5RA</i> rs2290608	0.991	0.947–1.036	0.69	0.96
<i>IL6</i> rs1800796	1.015	0.930–1.107	0.74	0.96
<i>IL6</i> rs1800795	0.960	0.923–0.999	0.04	0.50
<i>IL9</i> rs2069885	0.998	0.943–1.056	0.94	0.99
<i>IL10</i> rs1800872	0.969	0.926–1.015	0.18	0.68
<i>IL13</i> rs1295686	1.002	0.955–1.051	0.93	0.99

Polymorphism	Hazard ratio *	95% CI	P value	FDR
<i>LTC4S rs730012</i>	0.998	0.956–1.042	0.93	0.99
<i>LTA rs1041981</i>	0.994	0.955–1.035	0.77	0.96
<i>LTA rs909253</i>	0.987	0.947–1.028	0.53	0.96
<i>MMP3 rs3025058</i>	0.979	0.942–1.017	0.27	0.68
<i>MS4A2 rs569108</i>	1.086	0.964–1.224	0.17	0.68
<i>MTHFR rs1801133</i>	1.057	1.016–1.100	0.006	0.22
<i>NPPA rs5063</i>	0.875	0.800–0.958	0.004	0.22
<i>NPPA rs5065</i>	0.950	0.900–1.002	0.06	0.50
<i>NOS2A rs1137933</i>	0.977	0.933–1.024	0.33	0.80
<i>NOS3 rs1800779</i>	1.012	0.972–1.053	0.56	0.96
<i>NOS3 rs3918226</i>	1.062	0.991–1.138	0.09	0.50
<i>NOS3 rs1799983</i>	1.047	1.006–1.089	0.03	0.44
<i>SCGB1A1 rs3741240</i>	0.968	0.930–1.009	0.12	0.56
<i>SELE rs5361</i>	0.977	0.918–1.040	0.48	0.96
<i>SELE rs5355</i>	1.017	0.927–1.115	0.73	0.96
<i>SELP rs6131</i>	0.999	0.950–1.050	0.96	0.99
<i>SELP rs6133</i>	1.009	0.951–1.071	0.77	0.96
<i>SERPINE1 rs1799768</i>	0.995	0.958–1.033	0.79	0.97
<i>SERPINE1 rs7242</i>	1.012	0.974–1.052	0.53	0.96
<i>SCNN1A rs5742912</i>	1.082	0.956–1.224	0.21	0.68
<i>SCNN1A rs2228576</i>	0.977	0.938–1.017	0.25	0.68
<i>TCF7 rs5742913</i>	1.010	0.949–1.075	0.75	0.96
<i>TCF7 rs244656</i>	1.001	0.947–1.059	0.97	0.99
<i>TGFB1 rs1800469</i>	1.052	1.009–1.098	0.02	0.40
<i>TNF rs1800629</i>	0.994	0.945–1.046	0.82	0.68
<i>TNF rs361525</i>	0.940	0.861–1.027	0.17	0.68
<i>VCAM1 rs1041163</i>	0.970	0.920–1.023	0.26	0.68
<i>VDR rs2228570</i>	1.038	0.997–1.080	0.07	0.50
<i>VDR rs1544410</i>	0.987	0.949–1.027	0.53	0.96

CI Confidence interval

FDR False discovery rate

* Adjusted for age, body mass index, smoking, history of diabetes, history of hypercholesterolemia, blood pressure, and randomized treatment assignments.