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Variant rs6596140 of *Follistatin-like 4* Gene (*FSTL4*) May Be Associated with Poor Response to Angiotensin Receptor Blockers (ARBs) among Filipinos

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Constituting one of the most commonly used antihypertensive drug families are the angiotensin receptor blockers (ARBs). The aim of this study was to identify the variants associated with response to ARBs that may potentially be used as markers for designing a tailor-fit treatment strategy for hypertension. An unmatched case-control study was done among adult hypertensive Filipino patients maintained on ARBs. Genotypic analysis of blood DNA was conducted. Logistic regression analyses were performed to determine association of clinical and genetic variables with ARB response. A total of 69 poor responders and 126 normal responders were included in the study. After performing univariate logistic regression, five single nucleotide polymorphisms showed association with poor response to ARBs. The genetic variant rs6596140 remained significant (dominant model; OR 2.36, $p = 0.009$) after adjusting for female sex and age. Variant rs6596140 was found to be associated with poor response to ARBs among Filipinos. Prior to clinical application, verification is recommended prior to clinical application. As the function of this variant is presently unknown, an investigation to elucidate its role in ARB response in hypertension is also recommended.

Keywords: angiotensin receptor blockers, Filipinos, *FSTL4*, genetic polymorphism, hypertension, rs6596140

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INTRODUCTION

Angiotensin receptor blockers (ARBs) are one of the most widely used drug classes for hypertension in the Philippines. They act on the renin-angiotensin-aldosterone system (RAAS) through inhibition of angiotensin II AT1 receptor and by decreasing peripheral resistance (Abraham *et al.* 2015). It has also been demonstrated to be cardioprotective – preventing heart failure, atrial fibrillation, and myocardial infarction (Dézsi 2016).

Several studies have suggested a genetic predisposition of ARB response (Rimpelä *et al.* 2017; Johnson 2008; Hiltunen and Kontula 2012; Canzanello *et al.* 2008). Rimpelä *et al*. (2017) reported that rs3814995 of *NPHS1* (NPHS1 adhesion molecule or nephrin gene) was associated with favorable losartan response; those with homozygous variant alleles of rs3814995 have higher blood pressure (BP) reduction on losartan than those with homozygous wild alleles, but the mechanism has yet to be investigated. Similarly, the SILVHIA (Swedish Irbesartan Left Ventricular Hypertrophy Investigation versus Atenolol) trial showed that diastolic BP is effectively reduced by irbesartan among patients with two copies of the inserted A allele of an *ACE* (angiotensin-converting enzyme gene) variant (Kurland *et al*. 2001). By contrast, patients with variants near *SLC9A9* (solute carrier family 9 member A9 gene) and *MYO3B* (myosin IIIB gene) exhibited a poor response to candesartan (Turner *et al.* 2012).

Genetic variants vary across different ethnicities, and some of these variants may affect drug response. This highlights the importance of investigating these variants and how they affect drug response among populations. Ethnicity has been incorporated in hypertension guidelines to aid in the selection of antihypertensive drug therapy; for example, African Americans have been shown to reach their BP goals better using diuretics or calcium channel blockers (CCBs), while Caucasian Americans respond better to ACE inhibitors and beta blockers (Johnson 2008). However, no data have been published specifically among Filipinos, which warrants an investigation targeted to this population.

This study aimed to determine the association of candidate genetic variants with poor response to ARBs. Because ARBs are proven to have cardioprotective effects (Yancy *et al.* 2017), identifying associated genetic variants may also have implications on the established benefits of ARB therapy, such as in the prevention of long-term cardiac complications – including cardiac remodeling, fibrosis, and heart failure. The discovery of genetic markers may also be used to help manage patients for which ARBs are also indicated, such as diabetic nephropathy, metabolic syndrome, hyperuricemia, erectile dysfunction, and cognitive decline. Further, therapy guided by clinical and genetic markers may diminish unnecessary costs and ineffective chronic treatment in the presence of targeted medications.

MATERIALS AND METHODS

Study Design

This was an unmatched case-control study investigating the association of candidate variants with poor response to ARBs among Filipinos.

Study Population and Inclusion/Exclusion Criteria

Participants were enrolled from the Philippine General Hospital, communities in Metro Manila, and private clinics from July 2013 to March 2017. The inclusion criteria were as follows: >18 yr of age; evidence of systolic BP ≥ 140 and/or diastolic BP ≥ 90 mmHg on at least two occasions; on treatment with ARB for one month or more; and able to independently provide consent. Study subjects who reported taking ARBs for at least a month prior to the start of the study were included. There were no further measures done to record the duration of drug intake. Participants stratified as ARB poor responders were those who still had readings of systolic BP ≥ 140 and/or diastolic BP ≥ 90 mmHg on monitoring or on follow-up despite being on the maximum dose of ARBs (Appendix Table I), while ARB responders were those whose BP measurements were less than 140/90 mm Hg on monitoring or follow-up on ARB monotherapy. All enrolled participants with co-existing medical conditions were continuously managed with other medications throughout the duration of the study.

The exclusion criteria were as follows: decompensated heart failure, decompensated chronic lung disease, decompensated chronic liver disease, end-stage renal disease, active malignancy, secondary hypertension, secondary dyslipidemia, pregnancy during enrollment, and relatedness to the third degree of consanguinity.

Clinical Data Collection

Demographic data and clinical characteristics of the participants were obtained from their patient records and from verbal interviews. Serum lipid profile and creatinine were obtained and recorded.

DNA Extraction and Quantification

Blood samples collected were stored in EDTA tubes on ice, and DNA was extracted using the QiaAmp DNA mini kit following the spin protocol for blood buffy coat, as specified in the manufacturer's instruction manual. DNA was quantified using a spectrometer at 260nm and stored at –20 °C until use prior to genotyping.

Genotyping

A customized beadchip was designed in 2012 using candidate SNPs, which have shown evidence of association with hypertension and ARB response. These were selected after a comprehensive search was done in the following databases: PharmGKB (Pharmacogenomics Knowledgebase) database, GWAS catalog of the National Human Genome Research Institute, PubMED, and public patent databases (Patentscope of World Intellectual Property Office and Espacenet of European Patent Office). The selected SNPs were submitted to Illumina Inc. for scoring to determine the suitability of the SNPs for genotyping. Note, however, that while the microarray platform used is optimally designed to detect bi-allelic SNPs, some tri- or quad-allelic SNPs have been correlated especially if such have strong empirical evidence.

Customized genotyping of candidate SNPs was performed using DNA microarray technology following the GGGT (GoldenGate Genotyping) assay protocol as specified in the manufacturer's manual. After microarray processing, the beadchip was imaged on the HiScan System, and data from these images were analyzed using GenomeStudio software.

Data Analyses

Genotyping data were analyzed using GenomeStudio 2.0 and PLINK version 2.05.10. Genotype data with call rates > 95% and with individual missingness < 0.05 were included. The following inclusion thresholds were further used: minor allele frequency of 0.01, genotype missingness of 0.05, and Hardy-Weinberg equilibrium (HWE) of controls of $p < 0.001$.

The association of genotypes with ARB response was analyzed by univariate and multiple logistic regression analyses with clinical parameters according to their construed model, as determined by the chi-squared test or Fisher exact test, with a cut-off p-value set at 0.05.

Ethical Considerations

All procedures have been reviewed in compliance with ethical standards of the University of the Philippines Manila Research Ethics Board (UPMREB 2012-186-01).

RESULTS

The study included 197 participants: 71 poor responders and 126 responders. Two poor responders were excluded due to low call rates (Figure 1A). Among the 98 candidate SNPs (Appendix Table II), 16 were removed (Figure 1B; Appendix Table III).

The clinical characteristics and laboratory profiles of the participants are summarized in Tables 1 and 2. Poor responders have significantly higher mean systolic and diastolic BPs than responders (Table 2). The poor responders are significantly older (mean = 59 yr old) compared to responders (mean = 55 yr old; Student's t-test p-value = 0.005). There were more females who were poor responders as compared to males ($p = 0.003$). Additionally, most of the participants were on losartan (68.72%), while others were on telmisartan, irbesartan, and olmesartan (Appendix Table IV).

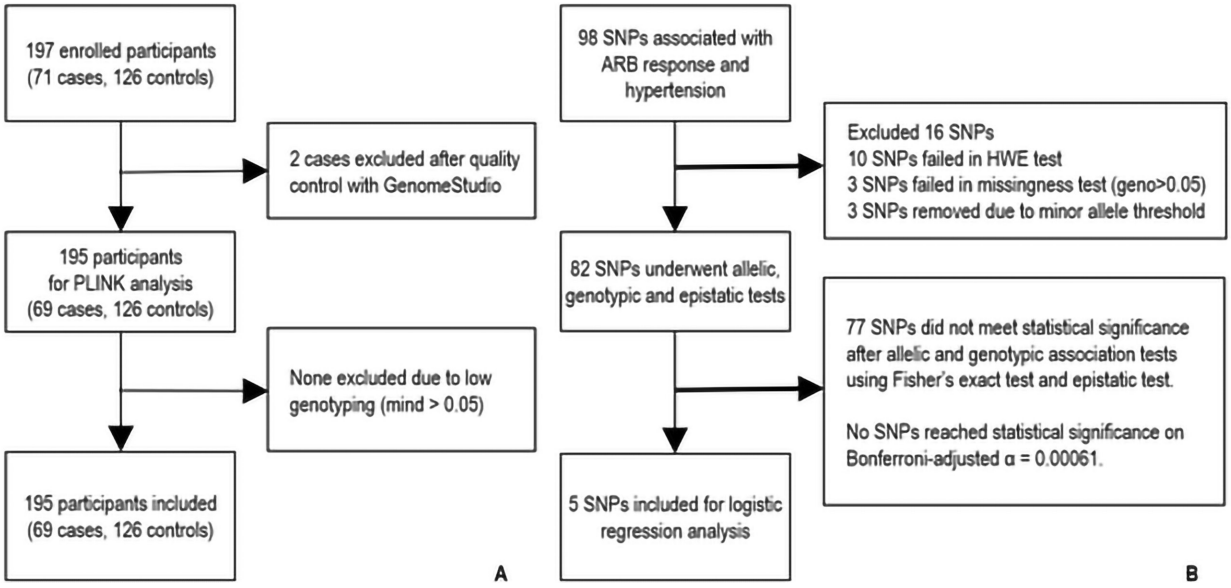

Figure 1. Overview of data processing and analysis. A total of 195 participants (A) and 82 SNPs (B) were analyzed to determine the association of genetic variants with ARB poor response. Abbreviations: SNP – single nucleotide polymorphism; HWE – Hardy-Weinberg equilibrium; geno – genotypic missingness; maf – minor allele frequency.

Table 1. Clinical characteristics of the study participants (n = 195). Data are given as percentage.

Characteristics	Poor responders (n = 69)	Responders (n = 126)	Crude OR (95% CI)	*p*-value*
Age ≥ 60 yr	52.17	33.33	2.18 (1.20, 3.98)	0.011
Female sex	56.52	34.13	2.51 (1.37, 4.58)	0.003
Abnormal BMI (≥ 25 kg/m^2)	48.53	62.30	0.57 (0.31, 1.04)	0.067
Diabetes mellitus	30.43	34.13	0.84 (0.45, 1.59)	0.600
Dyslipidemia	88.41	88.89	0.95 (0.38, 2.40)	0.919
Smoking	39.13	40.48	0.95 (0.52, 1.72)	0.854
Alcohol use	71.01	64.29	1.36 (0.72, 2.57)	0.341

OR – odds ratio; CI – confidence interval; BMI – body mass index
*Statistical significance set at $p < 0.05$ using simple logistic regression

Table 2. Laboratory parameters of the study participants (n = 195). Data are given as mean (SD).

Parameters	Poor responders (n = 69)	Responders (n = 126)	*p*-value*
Systolic BP, mmHg	144.35 (18.03)	119.52 (10.72)	< 0.0001
Diastolic BP, mmHg	84.78 (9.00)	77.46 (7.15)	< 0.0001
Serum creatinine, mg/dl	1.00 (0.34)	0.91 (0.32)	0.0574
Total cholesterol, mg/dl	195.97 (50.27)	194.92 (46.91)	0.8844
Triglycerides, mg/dl	130.93 (60.15)	123.76 (65.52)	0.4531
HDL, mg/dl	49.85 (16.18)	46.92 (12.50)	0.1602
LDL, mg/dl	118.40 (44.63)	119.30 (41.43)	0.8877

SD – standard deviation; HDL – high-density lipoprotein; LDL – low-density lipoprotein
*Statistical significance set at $p < 0.05$ using Student's T-test

Poor responders were either on ARB monotherapy (32%) or antihypertensive polytherapy (68%). The majority of those on polytherapy were also taking dihydropyridine CCB (49%) and beta blockers (20%), while some used diuretics (4%), ACE inhibitors (3%), and non-dihydropyridine CCB (1%). By contrast, responders were all taking ARB monotherapy (Appendix Tables V and VI). Considering the co-existing medical conditions, study participants were also taking other medications such as statins, aspirin, and clopidogrel (Appendix Table VII).

Logistic regression analysis revealed significant variables nominally associated with poor ARB response. Five variants were noted to be nominally associated with poor response to ARBs after allelic and genotypic association analysis. On initial univariate analysis, 3 of these SNPs showed crude OR of > 2.5: rs10021303 of *BMPR1B*, rs2954033 in *AC091114.1*, and rs32790 in *U3* (Table 3). Further analysis using multiple regression investigated the contribution of significant clinical factors (Appendix Table VIII). Among the 5 variants, the T allele of the variant rs6596140 is nominally associated with poor response to ARBs, retaining its statistical significance after variable selection and adjustment for age and sex (dominant model; OR 2.36, $p = 0.009$) (Table 4).

DISCUSSION

ARBs are widely used in the management of hypertension among Filipinos. Recognizing that genetic influences may likely affect ARB response, this study investigated candidate gene variants that may affect ARB efficacy. Among the study participants, only the variant rs6596140 retained its statistical significance after adjusting for age and sex.

Description of rs6596140

The genetic variant rs6596140 is an intronic variant located between the first and second exons of the predicted mRNA transcript variant X1 (XM_011543283.1). This SNP, located in the long arm of chromosome 5, is a notable hotspot; many documented variants are distal to this SNP. The nearest gene, *FSTL4* (*follistatin-like 4* gene), is over 70kb away. Due to its proximity, this SNP may have a role in the regulation of the gene *FSTL4*. *FSTL4* codes for a protein with unknown function but most likely belongs to the follistatin family of transforming growth factor-beta (TGF-β) inhibitors (Guo *et al.* 2012; Tsuchida *et al*. 2000). Sequence analysis of *FSTL4* showed 1 Kazal domain, 1 EF-hand calcium-binding domain, and 2 Ig-like domains. The Kazal-1 type domain, in particular, is a canonical

Table 3. SNPs with significant association with poor ARB response after univariate analysis.

SNP	Chr	Nearest gene	Genotype	Model	Crude OR (95% CI)	*p*-value*
rs10021303	4	*BMPR1B*	TC *vs.* CC	Additive	2.37 (0.73, 7.73)	ns
			TT *vs.*CC		3.33 (1.05, 10.54)	0.040
rs1530440	10	*CABCOCO1*	TT/TC vs CC	Dominant	1.93 (1.06, 3.49)	0.031
rs2954033	8	*AC091114.1*	AG *vs.*GG	Additive	1.75 (0.93, 3.32)	ns
			AA *vs.*GG		2.83 (1.08, 7.40)	0.034
rs32790	5	*U3*	CC *vs.*TT/TC	Recessive	2.62 (1.20, 5.71)	0.016
rs6596140	5	*FSTL4*	TT / CT *vs.*CC	Dominant	2.13 (1.16, 3.92)	0.015

Chr – chromosome number; OR – odds ratio; CI – confidence interval; *BMPR1B* – bone morphogenetic protein receptor, type 1B; ns – not significant; *CABCOCO1* – ciliary associated calcium binding coiled-coil 1; *FSTL4* – follistatin-like 4
*Statistical significance set at $p < 0.05$ using simple logistic regression

Table 4. SNPs with significant association to ARB poor response after backward elimination.

Variable	Adjusted OR (95% CI)	*p*-value*
Age > 60 years old	2.12 (1.14, 3.98)	0.018
Female sex	2.59 (1.38, 4.86)	0.003
rs6596140 (TT and CT *vs.* CC)	2.36 (1.24, 4.49)	0.009

OR – odds ratio; CI – confidence interval
*Statistical significance set at $p < 0.05$

serine protease inhibitor that is conserved in metazoans and is essential in various physiological mechanisms (Swiss Institute of Bioinformatics 2011). The *FSTL4* protein is predominantly expressed in the brain, cardiac and smooth muscle cells, and intestinal epithelium (Guo *et al.* 2012; Tsuchida *et al*. 2000).

A study among Hong Kong Chinese participants showed that rs6596140 had the strongest association for hypertension out of more than 500,000 SNPs investigated (Guo *et al.* 2012). The C allele was associated with a 9.77 mmHg decrease in diastolic BP, 11.97 mmHg decrease in systolic BP, and a 9.24 mmHg decrease in mean arterial pressure.

FSTL4 and BDNF

FSTL4 has been reported to negatively regulate the maturation of brain-derived neurotrophic factor (BDNF) protein (Suzuki *et al.* 2014). The BDNF protein, known for its role in neural plasticity, is also expressed in endothelial cells and vascular smooth muscles, promoting the production of endothelial nitric oxide synthase which results in vasodilation (Bathina and Das 2015). Previous studies have linked low plasma levels of BDNF with increased diastolic pressure and increased mortality (Bathina and Das 2015), similar to the finding of Prigent-Tessier *et al*. (2013) that essential hypertension was associated with reduced endothelial BDNF expression as observed in mice.

Studies have shown that BDNF expression is induced by angiotensin II (Szekeres *et al.* 2010) and BDNF signaling affects angiotensin II-mediated suppression of voltage-gated potassium currents. Decreased voltage-gated potassium currents due to elevated BDNF (and angiotensin II) levels increase neuronal excitability in the sympathetic nervous system, contributing to hypertension (Becker *et al.* 2015). A loss-of-function variant in *FSTL4* may lead to unregulated maturation of BDNF. Increased angiotensin II and BDNF levels may lead to sympathoexcitation and unopposed vasoconstriction that may persist despite the use of ARBs, implying resistance.

Additionally, the use of candesartan resulted in an increase in BDNF in mice (Alhusban *et al.* 2016), while telmisartan was found to upregulate BDNF expression in the hypothalamus (Wincewicz *et al.* 2016). Further studies with BDNF may be done with regard to BP control with ARBs.

Other Significant Variants

BMPR1B encodes for a member of the bone morphogenetic protein (BMP) receptor family of serine/threonine kinases (USNLM). Although the association failed to hold after multiple logistic regression with age group and sex, such finding may imply linkage and physiological relevance. Moreover, the ligands are members of the TGF-β superfamily, similar to *FSTL4*. In the study by Guo *et al*. (2012), this SNP was among those with the strongest associations with dichotomous hypertensive/normotensive disease status.

Other variants significantly associated with univariate analyses were further described. The rs32790 variant is

found in a regulatory region of *U3* or *SNORD3A* (small nucleolar RNA, C/D box 3A) (NCBI 2018). *U3* is a small nucleolar RNA that functions primarily to guide modifications of pre-ribosomal RNA (Kent *et al.* 2002). In a patent submitted in 2009, the SNP was included as one of the markers with a strong association to hypertension in the individual marker analysis, where the C allele was associated with 0.30 times lower odds of hypertension (Salonen *et al.* 2009). The variant rs1530440 is an intronic SNP previously associated with diastolic and systolic hypertension, with its minor allele T conferring a decrease in BP of 0.39 mmHg/allele ($p = 1 \times 10^{-9}$) (Newton-Cheh *et al.* 2009). It is situated near genes that may modulate salt-sensitive hypertension [*RTKN2* (*rhotekin 2* gene) and *RHOBTB1* (*Rho related BTB domain containing 1* gene)] and smooth muscle differentiation in cardiovascular tissue (*ARID5B, AT-rich interaction domain 5B* gene). The variant rs2954033 is an intergenic locus 43kb downstream of *TRIB1* (*tribbles pseudokinase 1* gene), which encodes a protein involved in protein degradation, control of myeloid cell differentiation, and interaction with MAPK kinases as a secondary messenger (Kraja *et al.* 2011). Its A allele is associated with a 0.17 unit increase in the occurrence of triglyceride- BP trait in metabolic syndrome (Hwang *et al.* 2017).

Clinical Predictors of Response to ARBs

Age is one of the clinical factors found to be associated with poor response to ARBs. Treatment-resistant hypertension – which is more common among older individuals – is associated with arterial stiffening, increased sodium and fluid retention, and increased activation of RAAS (Hwang *et al*. 2017). Advanced age may cause increased arterial stiffening and central impairment of hemodynamic responses to elevated BP. Angiotensin II is a potent arterial vasoconstrictor contributing to increased vascular resistance, which ARBs counteract (Liu *et al.* 2002). Among older patients with inherently stiff arteries, this effect of ARBs may be diminished.

In addition, there are more females among non-responders to ARBs compared with responders. The reason may not be apparent, but some animal studies have shown synergistic actions of estrogen and RAS blockade to downregulate the AT1 receptor (Liu *et al.* 2002; Tsuda *et al.* 2005). Miller *et al*. (2006) found that healthy women had significantly decreased response to angiotensin II blockers. A meta-analysis also showed that among people with increased risk of cardiovascular events on ARBs, females have less SBP and DBP reductions compared with males (Turnball *et al*. 2008). This contrasts with the finding of Canzanello *et al.* (2008), where being female was associated with a higher response to ARB. Nonetheless, a sex predeliction cannot be discounted.

These clinical predictors, though useful, may not be too specific. As such, analyses of genes and how they may affect a disease phenotype or – as in this study, how they impact response to treatment – are of practical value.

Several limitations exist in this study. First, ascertainment bias is possible due to the observational nature of the study, where patient characteristics and medication records were obtained primarily from chart reviews and no further records on the duration of drug intake. Second, while most of the study's poor responders used the maximum dose of ARBs, some of them were also maintained on other antihypertensives, albeit on much lower doses. Third, this study – compared with similar foreign studies – had a much smaller sample size; thus, the effect of the different variables may have been either under- or overestimated. Lastly, there is a lack of information about the clear associations between variant rs6596140 and the links to hypertension in Filipinos.

CONCLUSION

Out of the five variants that showed initial nominal association on univariate analysis, only rs6596140 exhibited robust association with poor response to ARB therapy, as adjusted to age and female sex. Further studies are recommended for validation of the identified variant. The findings may offer the possibility of genetic application in the assessment of response to ARB therapy among Filipinos in the future.

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STATEMENT ON CONFLICT OF INTEREST

The authors declare no competing interests.

NOTES ON APPENDICES

The complete appendices section of the study is accessible at http://philjournsci.dost.gov.ph

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APPENDICES

Table I. Maximum doses of ARBs used in the Philippines

Medication	Starting dose	Maximum dose
Losartan	50 mg OD	100 mg OD or 50 mg BID
Telmisartan	40 mg OD	80 mg OD
Olmesartan	20 mg OD	40 mg OD
Irbesartan	150 mg OD	300 mg OD
Valsartan	60 mg OD	180 mg OD
Candesartan	8 mg OD	16 mg OD

Abbreviations: ARB – angiotensin receptor blockers; OD (*omne in die*) – once a day; BID (*bis in die*) – twice a day

Table II. Ninety-eight (98) variants were selected for their association with hypertension and ARB response.

rsID	Gene	Chr	Genetic effect	Clinical/ phenotypic effect	Reference
rs10021303	*BMPR1B*	4	Intron_variant	HTN susceptibility	PLoS One 2012; 7(2): e31489
rs1004467	*CYP17A1*	10	Intron_variant	systolic HTN susceptibility	Nat Genet 2009 Jun; 41(6): 677–687
rs10188442	*GPR39*	2	Intron_variant	HTN susceptibility	Hum Genet 2011 Dec; 130(6): 725–733
rs1024323	*GRK4*	4	Missense_variant	HTN susceptibility	Clin Chem 2002 Dec; 48(12): 2131–2140
rs10455872*	*LPA*	6	Intron_variant	ARB response	N Engl J Med 2013 Feb 07; 368(6): 503–512 Eur Heart J 2012 Feb; 33(3): 325–334 Eur Heart J 2012 Feb; 33(3): 325–334
rs10492602*	Intergenic	13	Unknown	HTN susceptibility	Br J Clin Pharmacol 2009 Sep; 68(3): 395–401
rs10503669	Intergenic	8	Unknown	HTN susceptibility	US20090155230
rs11014166	*CACNB2*	10	Intron_variant	HTN susceptibility	Blood 2008 Aug 15; 112(4): 1022–1027
rs11024074	*PLEKHA7*	11	Intron_variant	Diastolic HTN susceptibility	Science 2008 Dec 12; 322(5908): 1702–1705
rs1110183	Intergenic	9	Unknown	HTN susceptibility	Pharmacogenet Genomics 2011 Jun; 21(6): 333–340
rs11191548	*CNNM2/NT5C2*	10	Downstream_gene_variant	Systolic HTN susceptibility	Pharmacogenomics 2010 Mar; 11(3): 319–325
rs11646213	Intergenic	16	Unknown	HTN susceptibility	US20110269735
rs1173771	Intergenic	5	Unknown	Systolic HTN susceptibility	Am J Hum Genet 2013 Jun 6; 92(6): 904–916
rs11780975*	Intergenic	8	Unknown	HTN susceptibility	Nature 2011 Sep 11; 478(7367): 103–112
rs11823543	*ZNF259/BUD13*	11	Downstream_gene_variant	HTN susceptibility	J Hum Genet 2011 Jan; 56(1): 47–51
rs11825181*	*BUD13*	1	Intron_variant	HTN susceptibility	Eur J Hum Genet 2012 Mar; 20(3): 333–340
rs12046278	*CASZ1*	1	Intron_variant	Systolic HTN susceptibility	Hum Genet 2011 Dec; 130(6): 725–733
rs12522034	Intergenic	5	Unknown	HTN susceptibility	Pharmacogenomics J 2014 Feb; 14(1): 35–40
rs12653539	Intergenic	5	Unknown	HTN susceptibility	Hum Genet 2011 Dec; 130(6): 725–733
rs12946454	*PLCD3*	17	Intron_variant	Systolic HTN susceptibility	Nat Genet 2009 Jan; 41(1): 56–65
rs13052628	Intergenic	21	Unknown	HTN susceptibility	Lancet 2013 Aug 31; 382(9894): 790–796; JAMA 2009 Aug 26; 302(8): 849–857
rs13107325	*SLC39A8*	4	Missense_variant	Systolic / diastolic HTN susceptibility	Nat Genet 2009 Jun; 41(6): 666–676

rsID	Gene	Chr	Genetic effect	Clinical/ phenotypic effect	Reference
rs1327235	Intergenic	20	Unknown	Diastolic HTN susceptibility	Nature 2011 Sep 11; 478(7367): 103–112
rs13333226	*UMOD*	16	Upstream_gene_variant	HTN susceptibility	J Hum Genet 2013 Mar; 58(3): 120–126
rs13420028	*GPR39*	2	Intron_variant	HTN susceptibility	Hum Genet 2011 Dec; 130(6): 725–733
rs1367117	*APOB*	2	Missense_variant	ARB response	PLoS Genet 2010 Oct 28; 6(10): e1001177
rs1372662	*ZFAT*	8	Intron_variant	HTN susceptibility	Hum Genet 2011 Dec; 130(6): 725–733
rs1378942	*CSK*	15	Intron_variant	Systolic / diastolic HTN susceptibility	BMC Med Genet 2007 Sep 19; 8(Suppl 1): S4
rs1384394*	Intergenic	2	Unknown	HTN susceptibility	BMC Cardiovasc Disord 2004 Sep 28; 4(1): 16; Nature 2010 Aug 5; 466(7307): 707–713; PLoS Genet 2009 Nov; 5(11): e1000730
rs1458038	Intergenic	4	Unknown	Systolic / diastolic HTN susceptibility	US20090155230
rs1461656	*MYLK4*	6	Intron_variant	HTN susceptibility	BMC Med Genet 2007 Sep 19; 8(Suppl 1): S4
rs15285	*LPL*	8	3_prime_UTR_variant	HTN susceptibility	Circ Cardiovasc Genet 2012 Apr 1; 5(2): 257–264
rs1530440	*C10orf107*	10	Intron_variant	Diastolic HTN susceptibility	BMC Med Genet 2007 Sep 19; 8(Suppl 1): S4
rs1550576	Intergenic	15	Unknown	HTN susceptibility	Nat Genet 2009 Jun; 41(6): 666–676
rs16931920	Intergenic	9	Unknown	HTN susceptibility	Thromb Haemost 2006 Feb; 95(2): 253–259
rs16948048	*ZNF652*	17	Upstream_gene_variant	Diastolic HTN susceptibility	US20090155230
rs16982520	*ZNF831*	20	Upstream_gene_variant	HTN susceptibility	Nature 2010 Aug 5; 466(7307): 707–713
rs16998073	*FGF5*	4	Upstream_gene_variant	Diastolic HTN susceptibility	Biol Pharm Bull 2007 Mar; 30(3): 537–542
rs17367504	*MTHFR*	1	Missense_variant	Systolic HTN susceptibility	Arterioscler Thromb Vasc Biol 2010 Jul; 30(7): 1485–1492
rs17403547*	Intergenic	2	Unknown	HTN susceptibility	Am J Hum Genet 2013 Jun 6; 92(6): 904–916
rs17589290	Intergenic	4	Unknown	HTN susceptibility	Circ Cardiovasc Genet 2008 Oct; 1(1): 10–20
rs17608766*	*GOSR2*	17	3_prime_UTR_variant	Dystolic HTN susceptibility	Pharmacogenomics J 2014 Feb; 14(1): 35–40
rs1799945	*HFE*	6	Missense_variant	Systolic / diastolic HTN susceptibility	PLoS One 2010 Dec 13; 5(12): e15064
rs1801058	*GRK4*	4	Missense_variant	HTN susceptibility	Circulation 2004 May 18; 109(19): 2279–2284
rs1918974	*MECOM*	3	Intron_variant	Diastolic HTN susceptibility	J Hypertens 2004 Dec; 22(12): 2321–2328
rs2070762	*TH*	11	Intron_variant	HTN susceptibility	Pharmacogenomics 2009 Nov; 10(11): 1743–1751
rs2384550	Intergenic	12	Unknown	Diastolic HTN susceptibility	Arterioscler Thromb Vasc Biol 2010 Nov; 30(11): 2264–2277
rs2398162	*NR2F2-AS1*	15	Intron_variant	HTN susceptibility	Int J Mol Sci 2011; 12(9): 5815–5827; Pharmacogenet Genomics 2007 Aug; 17(8): 647–656
rs2469997	Intergenic	8	Unknown	HTN susceptibility	N Engl J Med 2008 Mar 6; 358(10): 999–1008
rs2521501	*FES*	15	Intron_variant	Systolic / diastolic HTN susceptibility	Nat Genet 2009 Jun; 41(6): 677–687
rs2681472*	*ATP2B1*	12	Intron_variant	HTN susceptibility	Nature 2011 Sep 11; 478(7367): 103–111
rs2681492	*ATP2B1*	12	Intron_variant	Systolic HTN susceptibility	Nat Genet 2009 Jan; 41(1): 35–46

rsID	Gene	Chr	Genetic effect	Clinical/ phenotypic effect	Reference
rs2820037*	Intergenic	1	Unknown	HTN susceptibility	Am J Nephrol 2010; 31(2): 95–103
rs2932538	*MOV10/CAPZA1*	1	Downstream_gene_variant	HTN susceptibility	J Med Genet 2006 Sep; 43(9): 740–744
rs2954033	Intergenic	8	Unknown	HTN susceptibility	Nat Genet 2008 Feb; 40(2): 189–197
rs2960306	*GRK4*	4	Missense_variant	HTN susceptibility	BMC Med Genet 2007 Sep 19; 8(Suppl 1): S4
rs2992257	*APBB1IP*	10	Intron_variant	ARB response	Nature 2011 Sep 11; 478(7367): 103–109
rs3184504	*SH2B3*	12	Missense_variant	Systolic / diastolic HTN susceptibility	Nat Genet 2009 Mar; 41(3): 283–285
rs32790	Intergenic	5	Unknown	HTN susceptibility	Thromb Res 2012 Apr; 129(4): 441–446
rs36217263	*KL*	13	Upstream_gene_variant	HTN susceptibility	PLoS One 2008 Sep 3; 3(9): e3117
rs3798440	*MYO6*	6	Intron_variant	HTN susceptibility	Nature 2010 Aug 5; 466(7307): 707–713; Circ J 2009 Jun; 73(6): 1119–1126; Nat Genet 2008 Feb; 40(2): 161–169
rs381815	*PLEKHA7*	11	Intron_variant	Systolic HTN susceptibility	Nat Genet 2011 Mar 6; 43(4): 333–338; US8216786
rs4290*	*ACE*	17	Upstream_gene_variant	HTN susceptibility	Pharmacogenetics 2004 Dec; 14(12): 823–829
rs448378	*MECOM*	3	Intron_variant	Systolic HTN susceptibility	Eur Heart J 2012 Jan; 33(2): 238–251; Arterioscler Thromb Vasc Biol 2010 Nov; 30(11): 2264–2276; Nature 2010 Aug 5; 466(7307): 707–713; Nat Genet 2009 Jan; 41(1): 56–65; Arterioscler Thromb Vasc Biol 2008 Nov; 28(11): 2078–2084; Nat Genet 2008 Feb; 40(2):189–197; Nat Genet 2008 Feb; 40(2): 161–169; Science 2007 Jun 1; 316(5829): 1331–1336
rs4686599	Intergenic	3	Unknown	HTN susceptibility	Twin Res Hum Genet 2012 Dec; 15(6): 691–699
rs4853136	Intergenic	2	Unknown	HTN susceptibility	US20090155230
rs5370	*EDN1*	6	Missense_variant	ARB response	US8216789
rs6015450*	Intergenic	20	Unknown	Systolic / diastolic HTN susceptibility	Thromb Res 2010 Jun; 125(6): e265–e268
rs632912	*Metazoa_SRP*	18	Upstream_gene_variant	HTN susceptibility	Thromb Res 2008; 123(2): 331–335
rs633185	*ARHGAP42*	11	Intron_variant	Systolic / diastolic HTN susceptibility	Clin Pharmacol Ther 2011 Mar; 89(3): 408–415
rs6433781	Intergenic	2	Unknown	HTN susceptibility	US20090155230
rs6495122	*CPLX3/ULK3/ LMAN1L*	15	Downstream_gene_variant	Diastolic HTN susceptibility	Genet Epidemiol 2013 Jul; 37(5): 512–521
rs6511720*	*LDLR*	19	Intron_variant	LDL level	US20090155230
rs653178*	*ATXN2*	12	Intron_variant	Diastolic HTN susceptibility	Nat Genet 2009 Jun; 41(6): 677–687
rs6596140	Intergenic	5	Unknown	HTN susceptibility	Nat Genet 2009 Jun; 41(6): 666–676
rs6711736	Intergenic	2	Unknown	HTN susceptibility in the young	US20090312410
rs6749447	*STK39*	2	Intron_variant	ARB response / HTN susceptibility	Hum Mol Genet 2012 Apr 1; 21(7): 1658–1664
rs6800226	*FGF12*	3	Downstream_gene_variant	HTN susceptibility	Stroke 2005 Jul; 36(7): 1394–1399
rs6896456	*LOC100996485*	5	Intron_variant	HTN susceptibility	US20090155230
rs6940007*	*SLC17A2*	6	Upstream_gene_variant	HTN susceptibility	US20090155230
rs7129220	*EF537580*	11	Upstream_gene_variant	Systolic / diastolic HTN susceptibility	Pharmacogenet Genomics 2013 Aug; 23(8): 442–444

rsID	Gene	Chr	Genetic effect	Clinical/ phenotypic effect	Reference
rs7328290	Intergenic	13	Unknown	HTN susceptibility	Pharmacogenomics 2012 Jun; 13(8): 869–881
rs7735940	Intergenic	5	Unknown	HTN susceptibility	Hum Genet 2011 Dec; 130(6): 725–733
rs7747120	*GSTA7P*	6	Downstream_gene_variant	HTN susceptibility	Arterioscler Thromb Vasc Biol 2008 Nov; 28(11): 2078–2084
rs7772131	*AK098012*	6	Intron_variant	ARB response	US20090155230
rs780093	*GCKR*	2	Intron_variant	HTN susceptibility	Pharmacogenetics 2004 Aug; 14(8): 523–525
rs7827545	*ZFAT*	8	Intron_variant	HTN susceptibility	Circ Cardiovasc Genet 2012 Apr 01; 5(2): 257–264
rs7984277	Intergenic	13	Unknown	HTN susceptibility	Hypertension 2012 Jun; 59(6): 1204–1211
rs805303	*BAG6*	6	Intron_variant	HTN susceptibility	Pharmacogenet Genomics 2011 Jan; 21(1): 10–17
rs901185*	*PIEZO2*	18	Intron_variant	HTN susceptibility	Nature 2007 Jun 7; 447(7145): 661–678
rs9308945	Intergenic	2	Unknown	HTN susceptibility in the young	Nat Genet 2010 Jul; 42(7): 608–613
rs932764	*PLCE1*	10	Intron_variant	HTN susceptibility	US20090155230
rs9350602	*MYO6*	6	Intron_variant	HTN susceptibility	Br J Clin Pharmacol 2010 Aug; 70(2): 213–221
rs9586037	Intergenic	13	Unknown	HTN susceptibility	Hum Genet 2011 Dec; 130(6): 725–733
rs9618567*	*HIRA*	22	Intron_variant	HTN susceptibility	Eur J Hum Genet 2012 Mar; 20(3): 333–340
rs9815354	*ULK4*	3	Intron_variant	Diastolic HTN susceptibility	Nature 2010 Aug 5; 466(7307): 707–713; Am J Hum Genet 2013 Jun 6; 92(6): 904–916
rs991316	Intergenic	4	Unknown	HTN susceptibility	Nat Genet 2009 Jun; 41(6): 677–687
rs9951631	*DSC1*	18	Intron_variant	HTN susceptibility	PLoS Genet 2009 Jul; 5(7): e1000564

Note: variants with * were excluded after quality control.

**Public patent databases Patentscope (WIPO, https//patentscope.wipo.int) and ESpacenet (European Patent Office) were searched for patents on SNPs associated with hypertension.

Abbreviations: *BMPR1B* – bone morphogenetic protein receptor type 1B; *CYP17A1* – cytochrome P450 family 17 subfamily A member 1; *GPR39* – G protein-coupled receptor 39; *GRK4* – G protein-coupled receptor kinase 4; *LPA* – lipoprotein a; *CACNB2* – calcium voltage-gated channel auxiliary subunit beta 2; *PLEKHA7* – pleckstrin homology domain containing A7; *CNNM2* – cyclin and CBS domain divalent metal cation transport mediator 2; *NT5C2* – 5'-nucleotidase, cytosolic II; *ZNF259* – or *ZPR1*, zinc finger; *BUD13* – BUD13 homolog; *CASZ1* – castor zinc finger 1; *PLCD3* – phospholipase C delta 3; *SLC39A8* – solute carrier family 39 member 8; *UMOD* – uromodulin; *APOB* – apolipoprotein b; *ZFAT* – zinc finger and AT-hook domain containing; *CSK* – C-terminal Src kinase; *MYLK4* – myosin light chain kinase family member 4; *LPL* – lipoprotein lipase; *C10orf107* – or *CABCOCO*, ciliary associated calcium binding coiled-coil 1; *ZNF652* – zinc finger protein 652; *ZNF831* – zinc finger protein 831; *FGF5* – fibroblast growth factor 5; *MTHFR* – methylenetetrahydrofolate reductase; *GOSR2* – golgi SNAP receptor complex member 2; *HFE* – homeostatic iron regulator; *MECOM* – MDS1 and EVI1 complex locus; *TH* – tyrosine hydroxylase; *NR2F2-AS1* – nuclear receptor subfamily 2 group F member 2 (NR2F2) antisense RNA 1; *FES* – FES proto-oncogene, tyrosine kinase; *ATP2B1* – ATPase plasma membrane Ca2+ transporting 1; *MOV10* – Mov10 RISC complex RNA helicase; *CAPZA1* – capping actin protein of muscle Z-line subunit alpha 1; *APBB1IP* – amyloid beta precursor protein binding family B member 1 interacting protein; *SH2B3* – SH2B adaptor protein 3; *KL* – klotho; *MYO6* – myosin VI; *ACE* – angiotensin I converting enzyme; *EDN1* – endothelin 1; Metazoa_SRP or *ATG10* – autophagy related 10; *ARHGAP42* – rho GTPase activating protein 42; *CPLX3* – complexin 3; *ULK3* – unc-51 like kinase 3; *LMAN1L* – lectin, mannose binding 1 like; *LDLR* – low density lipoprotein receptor; *ATXN2* – ataxin 2; *STK39* – serine/threonine kinase 39; *FGF12* – fibroblast growth factor 12; *LOC100996485* or *C5orf66* – chromosome 5 open reading frame 66; *SLC17A2* – solute carrier family 17 member 2; *EF537580* – CAND 1.11, uncharacterized LOC100130460; *GSTA7P* – glutathione S-transferase alpha 7, pseudogene; *GCKR* – glucokinase regulator; *BAG6* – BCL2 associated athanogene 6; *PIEZO2* – piezo type mechanosensitive ion channel component 2; *PLCE1* – phospholipase C epsilon 1; *HIRA* – histone cell cycle regulator; *ULK4* – unc-51 like kinase 4; *DSC1* – desmocollin 1

Table III. List of 82 variants after genotypic association tests.

CHR	SNP	A1	A2	TEST	AFF	UNAFF	*P*
4	rs10021303	A	B	ALLELIC	33/105	88/164	0.02946
4	rs10021303	A	B	REC	4/65	19/107	0.06442
4	rs10021303	A	B	DOM	29/40	69/57	0.1007
10	rs1004467	B	A	REC	1/68	11/115	0.05925
10	rs1004467	B	A	ALLELIC	29/109	64/188	0.3848
10	rs1004467	B	A	DOM	28/41	53/73	0.88
2	rs10188442	A	B	ALLELIC	7/131	10/242	0.6119
2	rs10188442	A	B	DOM	6/63	9/117	0.7805
2	rs10188442	A	B	REC	1/68	1/125	1
4	rs1024323	A	B	DOM	13/56	30/96	0.4738
4	rs1024323	A	B	ALLELIC	16/122	36/216	0.5342
4	rs1024323	A	B	REC	3/66	6/120	1
8	rs10503669	A	B	ALLELIC	11/127	27/225	0.4759
8	rs10503669	A	B	DOM	9/60	22/104	0.5398
8	rs10503669	A	B	REC	2/67	5/121	1
10	rs11014166	A	B	ALLELIC	12/126	36/216	0.1461
10	rs11014166	A	B	DOM	12/57	34/92	0.1592
10	rs11014166	A	B	REC	0/69	2/124	0.5404
11	rs11024074	B	A	ALLELIC	25/113	45/207	1
11	rs11024074	B	A	DOM	21/48	38/88	1
11	rs11024074	B	A	REC	4/65	7/119	1
9	rs1110183	B	A	REC	18/51	25/101	0.3672
9	rs1110183	B	A	DOM	43/26	86/40	0.4312
9	rs1110183	B	A	ALLELIC	61/77	111/141	1
10	rs11191548	B	A	REC	1/68	9/117	0.1012
10	rs11191548	B	A	ALLELIC	28/110	56/196	0.7005
10	rs11191548	B	A	DOM	27/42	47/79	0.8776
16	rs11646213	B	A	ALLELIC	60/78	106/146	0.8306
16	rs11646213	B	A	REC	16/53	28/98	0.8601
16	rs11646213	B	A	DOM	44/25	78/48	0.8774
5	rs1173771	A	B	DOM	44/25	62/64	0.07084
5	rs1173771	A	B	ALLELIC	50/88	75/177	0.2124
5	rs1173771	A	B	REC	6/63	13/113	0.8049
11	rs11823543	A	B	DOM	3/66	3/123	0.6677
11	rs11823543	A	B	ALLELIC	3/135	3/249	0.6702
11	rs11823543	A	B	REC	0/69	0/126	1
1	rs12046278	A	B	DOM	50/19	79/47	0.2059
1	rs12046278	A	B	ALLELIC	58/80	90/162	0.2313
1	rs12046278	A	B	REC	8/61	11/115	0.6148
5	rs12522034	B	A	DOM	51/18	83/43	0.263
5	rs12522034	B	A	ALLELIC	64/74	110/142	0.6702
5	rs12522034	B	A	REC	13/56	27/99	0.7144
5	rs12653539	B	A	REC	3/66	2/124	0.3482

CHR	SNP	A1	A2	TEST	AFF	UNAFF	*P*
5	rs12653539	B	A	DOM	8/61	21/105	0.4041
5	rs12653539	B	A	ALLELIC	11/127	23/229	0.8514
17	rs12946454	B	A	DOM	21/48	50/76	0.2164
17	rs12946454	B	A	REC	7/62	7/119	0.2556
17	rs12946454	B	A	ALLELIC	28/110	57/195	0.611
21	rs13052628	A	B	DOM	3/66	4/122	0.6997
21	rs13052628	A	B	ALLELIC	3/135	4/248	0.7018
21	rs13052628	A	B	REC	0/69	0/126	1
4	rs13107325	A	B	DOM	2/67	2/124	0.6155
4	rs13107325	A	B	ALLELIC	2/136	3/249	1
4	rs13107325	A	B	REC	0/69	1/125	1
20	rs1327235	A	B	REC	3/65	17/109	0.05082
20	rs1327235	A	B	ALLELIC	41/95	91/161	0.2622
20	rs1327235	A	B	DOM	38/30	74/52	0.7613
16	rs13333226	B	A	DOM	6/63	13/113	0.8049
16	rs13333226	B	A	ALLELIC	7/131	15/237	0.8211
16	rs13333226	B	A	REC	1/68	2/124	1
2	rs13420028	B	A	ALLELIC	12/126	13/239	0.1966
2	rs13420028	B	A	DOM	9/60	11/115	0.3373
2	rs13420028	B	A	REC	3/66	2/124	0.3482
2	rs1367117	A	B	DOM	15/54	32/94	0.6039
2	rs1367117	A	B	REC	4/65	5/121	0.723
2	rs1367117	A	B	ALLELIC	19/119	37/215	0.8805
8	rs1372662	A	B	REC	3/66	12/114	0.2651
8	rs1372662	A	B	ALLELIC	37/101	78/174	0.4179
8	rs1372662	A	B	DOM	34/35	66/60	0.7647
15	rs1378942	A	B	REC	5/64	8/118	0.7737
15	rs1378942	A	B	ALLELIC	32/106	56/196	0.8993
15	rs1378942	A	B	DOM	27/42	48/78	1
4	rs1458038	A	B	REC	14/55	23/103	0.8487
4	rs1458038	A	B	ALLELIC	66/72	118/134	0.9156
4	rs1458038	A	B	DOM	52/17	95/31	1
6	rs1461656	A	B	ALLELIC	13/125	25/227	1
6	rs1461656	A	B	DOM	11/58	21/105	1
6	rs1461656	A	B	REC	2/67	4/122	1
8	rs15285	A	B	DOM	8/60	22/103	0.3083
8	rs15285	A	B	ALLELIC	9/127	23/227	0.4433
8	rs15285	A	B	REC	1/67	1/124	1
10	rs1530440	A	B	DOM	38/31	49/77	0.03527
10	rs1530440	A	B	ALLELIC	45/93	61/191	0.09532
10	rs1530440	A	B	REC	7/62	12/114	1
15	rs1550576	A	B	DOM	16/53	38/88	0.3204
15	rs1550576	A	B	ALLELIC	16/122	38/214	0.3625
15	rs1550576	A	B	REC	0/69	0/126	1

CHR	SNP	A1	A2	TEST	AFF	UNAFF	*P*
9	rs16931920	B	A	ALLELIC	7/131	7/245	0.2637
9	rs16931920	B	A	REC	1/68	0/126	0.3538
9	rs16931920	B	A	DOM	6/63	7/119	0.5493
17	rs16948048	B	A	REC	7/62	10/116	0.6044
17	rs16948048	B	A	DOM	33/36	64/62	0.765
17	rs16948048	B	A	ALLELIC	40/98	74/178	1
20	rs16982520	B	A	REC	1/68	0/126	0.3538
20	rs16982520	B	A	DOM	3/66	9/117	0.5446
20	rs16982520	B	A	ALLELIC	4/134	9/243	1
4	rs16998073	A	B	REC	14/55	17/109	0.2251
4	rs16998073	A	B	ALLELIC	66/72	106/146	0.2876
4	rs16998073	A	B	DOM	52/17	89/37	0.5082
1	rs17367504	B	A	DOM	45/23	79/47	0.7542
1	rs17367504	B	A	REC	6/62	13/113	0.8058
1	rs17367504	B	A	ALLELIC	51/85	92/160	0.9122
4	rs17589290	A	B	DOM	22/47	48/78	0.4368
4	rs17589290	A	B	REC	3/66	3/123	0.6677
4	rs17589290	A	B	ALLELIC	25/113	51/201	0.6889
6	rs1799945	B	A	DOM	2/67	7/119	0.4963
6	rs1799945	B	A	ALLELIC	2/136	8/244	0.5047
6	rs1799945	B	A	REC	0/69	1/125	1
4	rs1801058	A	B	DOM	42/27	89/37	0.2021
4	rs1801058	A	B	ALLELIC	61/77	127/125	0.2461
4	rs1801058	A	B	REC	19/50	38/88	0.7442
3	rs1918974	B	A	DOM	21/48	28/98	0.229
3	rs1918974	B	A	ALLELIC	24/114	33/219	0.2941
3	rs1918974	B	A	REC	3/66	5/121	1
11	rs2070762	B	A	REC	14/55	24/102	0.8516
11	rs2070762	B	A	ALLELIC	60/78	109/143	1
11	rs2070762	B	A	DOM	46/23	85/41	1
12	rs2384550	A	B	ALLELIC	25/113	46/206	1
12	rs2384550	A	B	DOM	22/47	41/85	1
12	rs2384550	A	B	REC	3/66	5/121	1
15	rs2398162	A	B	REC	8/61	10/116	0.4424
15	rs2398162	A	B	ALLELIC	44/94	72/180	0.49
15	rs2398162	A	B	DOM	36/33	62/64	0.765
8	rs2469997	A	B	DOM	1/68	4/122	0.6578
8	rs2469997	A	B	ALLELIC	1/137	4/248	0.66
8	rs2469997	A	B	REC	0/69	0/126	1
15	rs2521501	A	B	DOM	12/57	28/98	0.4637
15	rs2521501	A	B	ALLELIC	13/125	31/221	0.5034
15	rs2521501	A	B	REC	1/68	3/123	1
12	rs2681492	B	A	DOM	23/46	55/71	0.172
12	rs2681492	B	A	ALLELIC	28/110	61/191	0.4492

CHR	SNP	A1	A2	TEST	AFF	UNAFF	*P*
12	rs2681492	B	A	REC	5/64	6/120	0.5237
1	rs2932538	A	B	ALLELIC	38/100	51/201	0.1031
1	rs2932538	A	B	DOM	31/38	45/81	0.2222
1	rs2932538	A	B	REC	7/62	6/120	0.2278
8	rs2954033	A	B	ALLELIC	52/86	64/188	0.01478
8	rs2954033	A	B	DOM	41/28	54/72	0.0357
8	rs2954033	A	B	REC	11/58	10/116	0.09519
4	rs2960306	A	B	DOM	5/64	17/109	0.2397
4	rs2960306	A	B	ALLELIC	5/133	17/235	0.2543
4	rs2960306	A	B	REC	0/69	0/126	1
10	rs2992257	A	B	REC	19/50	30/96	0.6063
10	rs2992257	A	B	DOM	49/20	94/32	0.614
10	rs2992257	A	B	ALLELIC	68/70	124/128	1
12	rs3184504	A	B	ALLELIC	2/136	5/247	1
12	rs3184504	A	B	DOM	2/67	5/121	1
12	rs3184504	A	B	REC	0/69	0/126	1
5	rs32790	B	A	REC	17/52	14/112	0.02291
5	rs32790	B	A	ALLELIC	62/76	86/166	0.03861
5	rs32790	B	A	DOM	45/24	72/54	0.2885
13	rs36217263	B	A	REC	10/59	13/113	0.4866
13	rs36217263	B	A	DOM	41/28	80/46	0.6439
13	rs36217263	B	A	ALLELIC	51/87	93/159	1
6	rs3798440	A	B	ALLELIC	2/136	4/248	1
6	rs3798440	A	B	DOM	2/67	4/122	1
6	rs3798440	A	B	REC	0/69	0/126	1
11	rs381815	A	B	ALLELIC	17/121	28/222	0.7429
11	rs381815	A	B	DOM	15/54	25/100	0.8533
11	rs381815	A	B	REC	2/67	3/122	1
3	rs448378	B	A	REC	5/64	2/124	0.09913
3	rs448378	B	A	ALLELIC	30/108	43/209	0.2786
3	rs448378	B	A	DOM	25/44	41/85	0.6368
3	rs4686599	B	A	DOM	36/33	73/53	0.4545
3	rs4686599	B	A	ALLELIC	43/95	87/165	0.5745
3	rs4686599	B	A	REC	7/62	14/112	1
2	rs4853136	A	B	REC	2/67	0/126	0.124
2	rs4853136	A	B	ALLELIC	5/133	4/248	0.2892
2	rs4853136	A	B	DOM	3/66	4/122	0.6997
6	rs5370	A	B	DOM	31/38	73/53	0.09898
6	rs5370	A	B	ALLELIC	35/103	85/167	0.108
6	rs5370	A	B	REC	4/65	12/114	0.4262
18	rs632912	A	B	REC	4/65	3/123	0.2466
18	rs632912	A	B	DOM	17/52	39/87	0.4094
18	rs632912	A	B	ALLELIC	21/117	42/210	0.7745

CHR	SNP	A1	A2	TEST	AFF	UNAFF	*P*
11	rs633185	B	A	DOM	47/22	74/52	0.2193
11	rs633185	B	A	ALLELIC	60/78	95/157	0.2804
11	rs633185	B	A	REC	13/56	21/105	0.6977
2	rs6433781	B	A	DOM	20/49	28/98	0.3023
2	rs6433781	B	A	ALLELIC	21/117	29/223	0.3422
2	rs6433781	B	A	REC	1/68	1/125	1
15	rs6495122	B	A	DOM	27/42	45/81	0.6449
15	rs6495122	B	A	ALLELIC	30/108	51/201	0.7942
15	rs6495122	B	A	REC	3/66	6/120	1
5	rs6596140	A	B	DOM	46/23	61/65	0.01633
5	rs6596140	A	B	ALLELIC	57/81	74/178	0.0188
5	rs6596140	A	B	REC	11/58	13/113	0.2626
2	rs6711736	A	B	ALLELIC	56/82	103/149	1
2	rs6711736	A	B	DOM	44/25	81/45	1
2	rs6711736	A	B	REC	12/57	22/104	1
2	rs6749447	A	B	ALLELIC	35/103	72/180	0.5535
2	rs6749447	A	B	DOM	30/39	60/66	0.6528
2	rs6749447	A	B	REC	5/64	12/114	0.7916
3	rs6800226	B	A	DOM	37/32	75/51	0.4516
3	rs6800226	B	A	ALLELIC	45/93	89/163	0.6558
3	rs6800226	B	A	REC	8/61	14/112	1
5	rs6896456	A	B	DOM	17/52	40/86	0.3268
5	rs6896456	A	B	ALLELIC	19/119	43/209	0.4695
5	rs6896456	A	B	REC	2/67	3/123	1
11	rs7129220	A	B	ALLELIC	3/135	1/251	0.129
11	rs7129220	A	B	DOM	2/67	1/125	0.286
11	rs7129220	A	B	REC	1/68	0/126	0.3538
13	rs7328290	A	B	DOM	39/30	67/59	0.7638
13	rs7328290	A	B	ALLELIC	44/94	77/175	0.8193
13	rs7328290	A	B	REC	5/64	10/116	1
5	rs7735940	B	A	DOM	49/20	85/41	0.6321
5	rs7735940	B	A	REC	14/55	29/97	0.7205
5	rs7735940	B	A	ALLELIC	63/75	114/138	1
6	rs7747120	A	B	ALLELIC	12/126	16/236	0.4157
6	rs7747120	A	B	DOM	11/58	15/111	0.5095
6	rs7747120	A	B	REC	1/68	1/125	1
6	rs7772131	B	A	ALLELIC	1/137	3/249	1
6	rs7772131	B	A	DOM	1/68	3/123	1
6	rs7772131	B	A	REC	0/69	0/126	1
2	rs780093	A	B	DOM	41/28	86/40	0.2713
2	rs780093	A	B	ALLELIC	55/83	115/137	0.287
2	rs780093	A	B	REC	14/55	29/97	0.7205
8	rs7827545	B	A	REC	3/66	11/115	0.3858
8	rs7827545	B	A	ALLELIC	36/102	77/175	0.414

CHR	SNP	A1	A2	TEST	AFF	UNAFF	*P*
8	rs7827545	B	A	DOM	33/36	66/60	0.5531
13	rs7984277	B	A	DOM	16/53	32/94	0.8622
13	rs7984277	B	A	ALLELIC	20/118	39/213	0.8829
13	rs7984277	B	A	REC	4/65	7/119	1
6	rs805303	A	B	DOM	48/21	82/44	0.6339
6	rs805303	A	B	ALLELIC	63/75	111/141	0.8314
6	rs805303	A	B	REC	15/54	29/97	1
2	rs9308945	B	A	REC	13/56	26/100	0.8525
2	rs9308945	B	A	ALLELIC	60/78	111/141	1
2	rs9308945	B	A	DOM	47/22	85/41	1
10	rs932764	B	A	DOM	54/15	95/31	0.726
10	rs932764	B	A	ALLELIC	71/67	124/128	0.7508
10	rs932764	B	A	REC	17/52	29/97	0.8605
6	rs9350602	A	B	REC	2/67	0/126	0.124
6	rs9350602	A	B	ALLELIC	6/132	7/245	0.3956
6	rs9350602	A	B	DOM	4/65	7/119	1
13	rs9586037	A	B	DOM	3/66	3/123	0.6677
13	rs9586037	A	B	ALLELIC	3/135	3/249	0.6702
13	rs9586037	A	B	REC	0/69	0/126	1
3	rs9815354	A	B	REC	10/59	8/118	0.07249
3	rs9815354	A	B	ALLELIC	34/104	45/207	0.1158
3	rs9815354	A	B	DOM	24/45	37/89	0.5185
4	rs991316	B	A	DOM	8/61	18/108	0.6649
4	rs991316	B	A	ALLELIC	8/130	18/234	0.6765
4	rs991316	B	A	REC	0/69	0/126	1
18	rs9951631	A	B	REC	0/69	5/121	0.1633
18	rs9951631	A	B	DOM	14/55	23/103	0.8487
18	rs9951631	A	B	ALLELIC	14/124	28/224	0.865

*Models labelled with "ALLELIC" are assumed to be additive, *i.e.* the more copies of the risk allele present, the higher the odds of being poorly responsive to beta-blockers.
**Significance set at $p < 0.00061$ (adjusted α; Fisher exact test). No variant was associated after adjusting for multiple testing. Five SNPs are nominally associated at $p < 0.05$.
Abbreviations: *Chr* – chromosome; *SNP* – single nucleotide polymorphism; *A1* – minor allele; *A2* – major allele; *Aff* – frequency of affected with the alleles A1 and A2 (A1/A2); *Unaff* – frequency of unaffected with the alleles A1 and A2 (A1/A2); *P* – *p*-value

Table IV. Distribution of cases and controls on different ARBs. Data are given as percentage.

ARB	Poor responders (n = 69)	Responders (n = 126)	Total (n = 195)
Losartan	76.81	64.29	68.72
Telmisartan	18.84	21.43	20.51
Irbesartan	2.90	13.49	9.74
Olmesartan	1.45	0.79	1.03
Total	100	100	100

Table V. Distribution of cases and controls on polytherapy with ARBs and other antihypertensive medications, and on monotherapy with ARBs. Data are given as percentage.

	Poor responders (n = 69)	Responders (n = 126)
On polytherapy with ARBs and other antihypertensives	68	0
On monotherapy with ARBs	32	100
Total	100	100

Abbreviations: *ARB* – angiotensin receptor blocker; *CCB* – calcium channel blockers

Table VI. Number of poor responders on polytherapy with ARBs and other antihypertensives.

	Poor responders on polytherapy with ARB and mentioned drug* (n = 46)
ACE inhibitors	2
Beta-blockers	14
Dihydropyridine CCB	34
Non-dihydropyridine CCB	1
Diuretics	3

Abbreviations: *ARB* – angiotensin receptor blocker; *ACE* – angiotensin-converting enzyme; *CCB* – calcium channel blockers
*Eight of the 46 poor responders on polytherapy had more than one other antihypertensive medicine aside from ARB.

Table VII. Other medications taken by study participants (n = 195). Data are given as percentage.

	Poor responders (n = 69)	Responders (n = 126)
Statins	55	33
Aspirin	39	26
Clopidogrel	10	6
Other medications	67	53

Table VIII. Full model table by multiple logistic regression analysis.

Variable	Adjusted ORs (95% CI)	*p*-value*
Age ≥ 60 yr	2.21 (1.10, 4.41)	0.025
Female sex	2.86 (1.42, 5.76)	0.003
Abnormal BMI ≥ 25 kg/m^2	0.84 (0.42, 1.67)	0.610
rs10021303		
TC *vs.* CC	2.16 (0.60, 7.78)	0.239
TT *vs.*CC	2.21 (0.63, 7.74)	0.214
rs1530440 (TT and TC vs CC)	1.99 (1.01, 3.90)	0.047
rs2954033		
AG *vs.*GG	1.82 (0.88, 3.75)	0.106
AA *vs.*GG	2.73 (0.83, 8.96)	0.097
rs32790 (CC *vs.*TT and TC)	1.75 (0.67, 4.59)	0.256
rs6596140 (TT and TC *vs.*CC)	2.46 (1.22, 4.95)	0.012

*Statistical significance set at $p < 0.05$