Supplementary Table 1. Genetic markers associated with antihypertensive agents and blood pressure response or cardiovascular outcomes

Gene	Gene function	rsID	Associated allele	Risk allele prevalence[a]	Population studied	Main finding
β-blocker						
β_1-adrenergic receptor (ADRB1)	Involved with renin release in the kidney, regulating heart rate and contractility.[64]	rs1801253	C	US Caucasian: 0.67 British Caucasian: 0.70 Asian: 0.79 African American: 0.63	40 hypertensive subjects from the US	An intervention study investigated blood pressure response to metoprolol. Results indicated CC carriers had significantly reduced 24-hour DBP compared to carriers of the A variant (-13.3%±8.4% versus -4.5%±8.2%, p=0 .0018; or -8.6 mmHg greater reduction [-3.5 to -13.6 mmHg], p=0.0014)[65]
β_1-adrenergic receptor (ADRB1)	Involved with renin release in the kidney, regulating heart rate and contractility.[64]	rs1801252, rs1801253	A-C (rs1801252-rs1801253) haplotype	N/A	40 hypertensive subjects from the US	An intervention study investigated blood pressure response to metoprolol. Results indicated individuals with the Ser49-Arg389/ Ser49-Arg389 diplotype had significant reduction in blood pressure in comparison to carriers of the Gly49-Arg389/Ser49-Gly389 diplotype (-14.7 mmHg vs -0.5 mmHg, p=0.006)[65]
β_1-adrenergic receptor (ADRB1)	Involved with renin release in the kidney, regulating heart rate and contractility.[64]	rs1801252, rs1801253	A-C (rs1801252-rs1801253) haplotype	N/A	Hypertensive patients randomly assigned to atenolol (n=2,973) or verapamil SR (n=2,922)	Randomized controlled trial investigated blood pressure response to atenolol vs verapamil SR. After an average follow-up period of 2.8 years, results indicated that carriers 1 or 2 of the A-C (rs1801252-rs1801253) haplotype had an increased risk of mortality if assigned to verapamil SR (HR: 8.58, [2.06-35.8], p=0.003).[64]
G Protein-Coupled Receptor Kinase 4 (GRK4)	Codes for an enzyme that deactivates activated G protein-coupled receptors via phosphorylation.	rs2960306, rs1024323	T-T (rs2960306-rs1024323) haplotype	N/A	768 hypertensive subjects from the US were randomized to receive monotherapy	Randomized controlled trial investigated blood pressure response to atenolol and hydrochlorothiazide. Results in Caucasians and African Americans indicated that increasing copies of the T-T

	GRK4 regulates the dopamine D_1 receptor. The D_1 receptor plays a role in regulating the renal tubule ion transport.[51]				with either atenolol (n=387) or hydrochlorothiazide (n=381)	haplotype were significantly associated with reduced DBP lowering when treated with atenolol (0 copies: −9.1±6.8; 1 copy: −6.8±7.1; 2 copies: −5.3±6.4 mmHg, p=0.0088).[66]
β-blockers or thiazide diuretics						
Neuronal precursor cell expressed developmentally down-regulated 4-like (NEDD4L)	Codes for an enzyme that helps regulate renal epithelial sodium channel (ENaC) and Na^+/Cl^- co-transporter (NCC)[67]	rs4149601	G	US Caucasian: 0.65 British Caucasian: 0.69 Asian: 0.79 African American: 0.65	Swedish and Norwegian hypertensive patients randomized to monotherapy β-blockers (n=1,337), diuretics (n=526) or to diltiazem (n=2,036)	A retrospective analysis of data from a randomized control trial conducted in hypertensive patients either receiving diltiazem, diuretics, or β-blocker was completed. Genetic analyses indicated G carriers (GG + GA vs AA) receiving β-blockers or diuretic monotherapy had significantly higher SBP (-19.5±16.8 vs. -15.0±19.3 mmHg, p <0.001) and DBP (-15.4±8.3 vs. -14.1±8.4 mmHg, p=0.02) reduction at 6-months.[67] Follow-up at 4.5 years in the same study indicated G carriers (GG + GA vs AA) randomized to β-blockers and/or diuretic monotherapy had lower cardiovascular events (MI and strokes) (RR =0.52, (0.36-0.74), p<0.001).[67]
Thiazide diuretic						
Neuronal precursor cell expressed developmentally down-regulated 4-like (NEDD4L)	Codes for an enzyme that helps regulate renal epithelial sodium channel (ENaC) and Na^+/Cl^- co-transporter (NCC)[67]	rs4149601	G	US Caucasian: 0.65 British Caucasian: 0.69 Asian: 0.79 African American: 0.65	1076 controls and 269 hypertensive cases from the US and Puerto Rico	A genetic sub-study indicated White AG carriers not treated with thiazide diuretic was significantly associated with increased risk of cardiovascular outcomes (all-cause death, nonfatal MI, nonfatal stroke) (OR: 10.65 [1.18-96.25], p=0.022).[68]

Adducin 1 (ADD1)	Codes for a protein found in the renal tubule that helps regulate ion transport.[69]	rs4961	T	US Caucasian: 0.22 British Caucasian: 0.26 Asian: 0.54 African American: 0.06	477 hypertensive individuals and 322 normotensive individuals in Milan and France	An intervention study investigated blood pressure response to hydrochlorothiazide. Results indicated heterozygous carriers of the T allele had a significant response to hydrochlorothiazide when compared to carriers of the AA genotype at two-months (mean: -14.7 (SE 2.2) vs -6.8 (SE 1.4) mmHg, p=0.002).[69]
Number of antihypertensive agents						
G Protein-Coupled Receptor Kinase 4 (GRK4)	Codes for an enzyme that deactivates activated G protein-coupled receptors via phosphorylation. GRK4 regulates the dopamine D_1 receptor. The D_1 receptor plays a role in regulating the renal tubule ion transport.[51]	rs296036, rs1024323	A-T (rs296036-rs1024323) haplotype	N/A	100 patients with hypertension in Zurich	GRK4 variants were investigated and associated with the number of antihypertensive agents required for blood pressure control. Results indicated individuals homozygous for the A-T haplotype (vs 1 or 0 copies) required significantly more antihypertensive agents for blood pressure control (2.59 vs 1.95, p=0.043).[70]

Adapted from a published review[63]

[a]Based on 1000 Genomes Project Samples.[53]

Ethnic groups defined by specific 1000 Genomes Project populations: *US Caucasian:* Utah residents with northern and western European ancestry (CEU); *British Caucasian:* British in England and Scotland (GBR); *Asian:* Han Chinese in Beijing, China (CHB); *African American:* Americans of African Ancestry in SW USA (ASW)

Abbreviations:

SR= sustained release, HR = hazard ratio, SBP= systolic blood pressure, DBP= diastolic blood pressure, MI=myocardial infarction, RR=relative risk, OR=odds ratio, SE = standard error

Supplementary Table 2. A summary of genetic markers associated with resistant hypertension and treatment efficacy

Gene	Gene function	rsID	Associated risk allele	Risk allele prevalence[a]	Population studied	Main finding
Resistant hypertension						
Inducible nitric oxide synthase (iNOS)	Induced when inflammation or cardiac damage is present and can cause vascular dysfunction when nitric oxide reacts with oxygen species to produce peroxynitrite.[72]	rs2297518	A	US Caucasian: 0.18 British Caucasian: 0.24 Asian: 0.16 African American: 0.15	113 normotensive, 115 with controlled hypertension, and 82 individuals with resistant hypertension in Brazil	In a retrospective analysis, GA and AA carriers were more commonly found among hypertensive and resistant hypertensive individuals when compared to normotensive individuals (OR = 2.05, p=0.016).[73]
Angiotensinogen (AGT)	Codes for a protein that is part of the first step of the renin-angiotensin system, which causes eventual blood vessels to constrict and increases blood pressure.[74]	rs699	T	US Caucasian: 0.59 British Caucasian: 0.63 Asian: 0.21 African American: 0.23	70 normotensive, 80 with controlled hypertensive, and 70 with resistant hypertension in Brazil	In a prospective study, a multifactor dimensionality reduction model was developed, which indicated that T allele carriers were at an increased risk for hypertension (controlled and resistant), especially for subjects over the age of 50 years.[73]
Angiotensinogen (AGT)	Codes for a protein that is part of the first step of the renin-angiotensin system, which causes eventual blood vessels to constrict and increases blood pressure.[74]	rs699, rs5051	T (rs699), G (rs5051)	rs699 US Caucasian: 0.59 British Caucasian: 0.63 Asian: 0.21 African American: 0.23 rs5051 US Caucasian: 0.61 British Caucasian: 0.63 Asian: 0.22 African American: 0.77	2,354 treatment responsive controls, 2,203 treatment resistant cases from a multicenter study	In a case-control retrospective analysis, variants that were significantly associated with resistant hypertension included the rs699 T allele (OR: 1.27 (1.12-1.44), p=0.0001), and rs5051 G allele (OR: 1.36 (1.20-1.53), p<0.0001). This relationship was found in Caucasians but not African Americans.[75]
ATPase Plasma Membrane Ca2+ Transporting 1 (ATP2B1)	Codes for a protein that is involved with intracellular calcium homeostasis and smooth cell contraction.[76]	rs12817819	A	US Caucasian: 0.13 British Caucasian: 0.12 Asian: 0.06 African American: 0.02	1,225 with controlled hypertension and 526 with resistant hypertension individuals from the US and Puerto Rico	In a genetic sub-study of a larger randomized controlled trial, the A allele was associated with resistant hypertension in European Americans (OR: 1.57 (1.17–

						2.01), p=2.44×10^{-3}) and Hispanics (OR:1.76 (1.27–2.44), p=7.69×10^{-4}). Each additional copy of the A allele increased risk of resistant hypertension (57% to 76%).[76]
Treatment efficacy						
Epithelial sodium channel (ENaC)	Major regulator of the reabsorption of salt across several epithelial tissues, including the colon, sweat glands, salivary ducts, and nephron.[77]	rs80311498	T	N/A	22 Black Africans and mixed-ancestry individuals with resistant hypertension in South Africa	An intervention study involving the addition of amiloride to antihypertensive regimen was conducted. Average reduction of 36/17 mmHg was observed (from an average of 172/99 mmHg).[78] Carriers of at least one T allele may benefit from treatment with amiloride.[72]
Cytochrome P45011B2 (CYP11B2)	Aldosterone synthase is the rate-limiting step in the synthesis of aldosterone.[72]	rs1799998	T	US Caucasian: 0.58 British Caucasian: 0.49 Asian: 0.74 African American: 0.84	62 resistant hypertension individuals in Brazil	A cross-sectional analysis investigating the impact of rs1799998 in patients with resistant hypertension using a multiple linear regression model, and the TT genotype was a significant factor for plasma aldosterone concentration levels.[79] Results indicated that spironolactone treatment may not be preferred for TT carriers.[72 79]
Cytochrome P450 4A11 (CYP4A11)	Causes vasoconstriction and natriuresis through the oxidation of arachidonic acid.[80]	rs3890011	C	US Caucasian: 0.78 British Caucasian: 0.77 Asian: 0.51 African American: 0.39	83 African Americans with resistant hypertension	A randomized controlled pilot study investigated the genetic impact of rs3890011 on blood pressure controlled with placebo, spironolactone, amiloride, and

						spironolactone plus amiloride. CC carriers had a higher response in blood pressure to amiloride (SBP: −6.3±7.3/DBP: −3.2±4.0 mmHg) than spironolactone (SBP: +6.8±7.9/DBP: +4.8±8.6, p<0.01/<0.05).[67] Results indicated spironolactone treatment may not be effective for CC carriers.[72 80]

Adapted from a published review[72]

[a]Based on 1000 Genomes Project Samples.[53]
Ethnic groups defined by specific 1000 Genomes Project populations: *US Caucasian:* Utah residents with northern and western European ancestry (CEU); *British Caucasian:* British in England and Scotland (GBR); *Asian:* Han Chinese in Beijing, China (CHB); *African American:* Americans of African Ancestry in SW USA (ASW)

Abbreviations:
OR=odds ratio, SBP=systolic blood pressure, DBP=diastolic blood pressure