Study of molecular markers of essential hypertension and associated cardiovascular events

PATIENT	
Name:	**N.A.**
Date of birth:	**N.A.**
Gender:	**N.A.**
Ethnicity:	**N.A.**
Consultancy referral number:	**N.A.**
Family history:	**N.A.**
Medical referral reason:	**N.A.**
Genetic laboratory referral reason:	**N.A.**
Purpose:	**Carrier**
Specimen type:	**DNA**

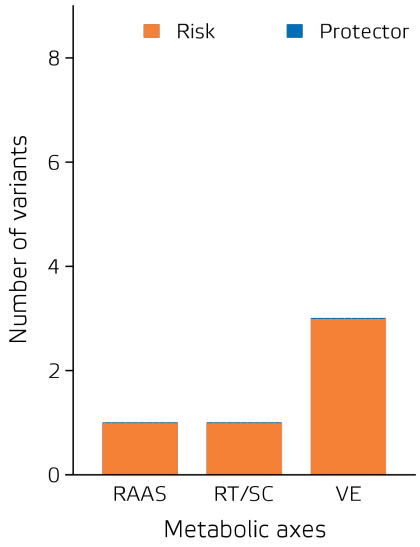
HEALTHCARE PROVIDER	
Referring physician:	**N.A.**
Medical reference:	**N.A.**
Harvesting facility:	**N.A.**
Referring facility:	**N.A.**
Requisition date:	**N.A.**
Fulfillment date:	**2017-12-11**

1. RESULTS

This genetic test identified 28 genetic variants (out of 57 analysed variants).

The bar chart displays the genetic variants that significantly contribute to risk:

- ADRA1A_CR065635
- NPPA_CM057551
- ACE_CG900332
- EDN1_CM993569
- DRD3_CM033372



ANS – Autonomous nervous system
RAAS – Renin-angiotensin-aldosterone system
RT/SC – Renal tubule and sodium channels
ST – Signal transduction
VE – Vascular endothelium

1.1. GENETIC RISK ANALYSIS

This patient presents a genetic profile that is similar to the one identified in patients with **low risk** for essential hypertension[1].

[1] Results obtained from HeartGenetics' clinical trial and scientific references presented in the appendix.

1.2. GUIDELINE RECOMMENDATIONS

General

For an integrated study of arterial hypertension, laboratory examination helps in stratifying patients who will need more extensive evaluation and aggressive therapy. The following routine tests are recommended - urianalysis, blood glucose, hematocrit, fasting plasma glucose, serum potassium and sodium, creatinine, or the corresponding estimated glomerular filtration rate, calcium, lipid profile and the measurement of urinary albumin excretion or albumin/creatinine ratio.

Antihypertensive drug therapy should be a function of blood pressure values (BP) and of each patient"s individual and total cardiovascular risk. Also non-pharmacologic interventions for effective BP control is an important component of reducing cardiovascular risk. Lifestyle modifications include limiting alcohol intake, increasing physical activity, and reducing sodium intake to <6 g of sodium chloride daily.

Arterial hypertension is a multifactorial disease with a genetic component that contribute to 35-50% for most cases. It

could be advised a carrier testing for this(ese) genetic variant(s) to direct members of the patient. The risks, benefits and limitations of testing should be discussed in the context of inheritance and cardiovascular risk and / or associated cardiovascular events.

Identifiable causes, other than genetics
Use clinical judgement for lyfestyle and pharmacologic treatment. Healthy lifestyle Changes: quit smoking, DASH/low sodium diet - maintain adequate dietary potassium, physical activity, healthy weight, limit alcohol.

1.3. PHARMACOGENETICS

Tables 1 and 2 describe the pharmacodynamics of antihypertensive therapy according to the patient genetic profile. This individual's data was compared with the data published in the scientific references presented in the appendix.

Table 1. Preferred combinations

DRUG A	DRUG B
ACE inhibitors (ACEI) options:	**CCB options:**
Perindopril	Verapamil, Nifedipine, Amlodipine, Unspecified calcium channel blocker, Diltiazem
ARB (if intolerant to ACEI):	**CCB options:**
Valsartan, Irbesartan	Verapamil, Nifedipine, Amlodipine, Unspecified calcium channel blocker, Diltiazem
ACE inhibitors (ACEI) options:	**Diuretics options:**
Perindopril	Thiazides, Unspecified diuretic, Hydrochlorothiazide
ARB (if intolerant to ACEI):	**Diuretics options:**
Valsartan, Irbesartan	Thiazides, Unspecified diuretic, Hydrochlorothiazide
ARB (if intolerant to ACEI):	**CCB options:**
Valsartan, Irbesartan	Verapamil, Nifedipine, Amlodipine, Unspecified calcium channel blocker, Diltiazem

Table 2. Acceptable combinations

DRUG A	DRUG B
Beta-blockers options:	**Diuretics options:**
Atenolol, Unspecified beta-blocker	Thiazides, Unspecified diuretic, Hydrochlorothiazide
CCB options:	**Diuretics options:**
Verapamil, Nifedipine, Amlodipine, Unspecified calcium channel blocker, Diltiazem	Thiazides, Unspecified diuretic, Hydrochlorothiazide
CCB options:	**Beta-blockers options:**
Verapamil, Nifedipine, Amlodipine, Unspecified calcium channel blocker, Diltiazem	Atenolol, Unspecified beta-blocker
Dual calcium channel blockade options:	

Unacceptable/ineffective combinations:

- ACE inhibitors (ACEI) + ARB
- Beta-blockers + ACE inhibitors
- Beta-blockers + ARB

Combination provides little additional BP lowering with more adverse effects than monotherapy and no cardiovascular outcomes benefit.

Evaluated drugs related to pharmacogenetics:

- **ACE (Angiotensin-converting enzyme) Inhibitors**: imidapril, captopril, perindopril, quinapril, benazepril;
- **ARB (Angiotensin II Receptor Blockers)**: valsartan, candesartan, losartan, Irbesartan;
- **CCB (Calcium Channel Blockers)**: amlodipine, diltiazem, nitrendipine, nifedipine, verapamil;
- **Diuretics**: thiazides, hydrochlorothiazide, spironolactone;
- **Beta-blockers**: metaprolol, atenolol.

2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults. Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014;311(5):507-520.

2. TECHNICAL INFORMATION

2.1. METHODOLOGY

1. DNA concentration and quality were evaluated with a spectrophotometer.
2. Genotyping was performed through molecular study of 57 genetic variants of 37 genes associated with arterial hypertension.
3. Genotyping was achieved using a high-throughput DNA Microchip platform, the iPLEX® MassARRAY® system (Agena Bioscience, Inc). This array platform allows an optimal genetic analysis by combining the benefits of accurate primer extension chemistry with MALDI-TOF mass spectrometry. The different masses of each generated PCR product are then converted into genotype information.
4. In accordance with Agena Bioscience's iPLEX® chemistry flyer, the MassARRAY® system performs SNP genotyping with a high level of accuracy and reproducibility (>99% accuracy on validated assays).

2.2. GENETIC PANEL

ACE	**angiotensin I converting enzyme** | NM_000789
ADD1	**Adducin 1 (alpha)** | ENSG00000087274
ADRA1A	**Adrenoceptor Alpha 1A** | ENSG00000120907
ADRB1	**Adrenoceptor Beta 1** | ENSG00000043591
ADRB2	**adrenoceptor beta 2** | NM_000024
AGT	**angiotensinogen** | NM_000029
AGTR1	**Angiotensin II Receptor, Type 1** | NG_008468.1
AGTR2	**angiotensin II receptor type 2** | NM_000686
BDKRB2	**bradykinin receptor B2** | NM_000623
CACNA1C	**Calcium voltage-gated channel subunit alpha 1 C** | NM_000719
CACNB2	**Calcium voltage-gated channel auxiliary subunit beta 2** | ENSG00000165995
CALCA	**Calcitonin-Related Polypeptide Alpha** | ENSG00000110680
CLCNKA	**Chloride voltage-gated channel Ka** | ENSG00000186510
CLCNKB	**Chloride voltage-gated channel Kb** | ENSG00000184908
CORIN	**Corin, Serine Peptidase** | ENSG00000145244
CYBA	**Cytochrome B-245, Alpha Polypeptide** | ENSG00000051523
CYP17A1	**Cytochrome P450 family 17 subfamily A member 1** | ENSG00000148795
CYP4A11	**Cytochrome P450 family 4 subfamily A member 11** | ENSG00000187048
DRD3	**Dopamine Receptor D3** | ENSG00000151577
ECE1	**Endothelin Converting Enzyme 1** | ENSG00000117298
EDN1	**endothelin 1** | NM_001955
EDNRA	**Endothelin Receptor Type A** | ENSG00000151617
FGF5	**Fibroblast Growth Factor 5** | ENSG00000138675
GCH1	**GTP Cyclohydrolase 1** | NM_000161
GRK4	**G Protein-Coupled Receptor Kinase 4** | ENSG00000125388
KCNMB1	**Potassium calcium-activated channel subfamily M regulatory beta subunit 1** | ENSG00000145936
NOS2	**Nitric Oxide Synthase 2** | ENSG00000007171
NOS3	**nitric oxide synthase 3** | NM_000603
NPPA	**Natriuretic Peptide A** | ENSG00000175206
NPPC	**Natriuretic Peptide C** | ENSG00000163273
NR3C2	**Nuclear receptor subfamily 3 group C member 2** | ENSG00000151623
REN	**Renin** | ENSG00000143839
RETN	**Resistin** | ENSG00000104918
SCNN1A	**Sodium channel epithelial 1 alpha subunit** | ENSG00000111319
SLC12A3	**Solute carrier family 12 member 3** | ENSG00000070915
STK39	**Serine Threonine Kinase 39** | ENSG00000198648
WNK1	**WNK Lysine Deficient Protein Kinase 1** | ENSG00000060237

2.3. RISKS AND LIMITATIONS

HeartGenetics applies a rigorous quality control which may not exclude the possibility of error that might influence the test results. The reliability of the results is always guaranteed as HeartGenetics, Genetics and Biotechnology SA standard quality recommendations have been followed for the execution of this genetic test. The results presented in this report are limited to the available scientific knowledge at the time this test was developed. The company guarantees the accuracy of the scientific knowledge presented in the report. It has been assumed as truthful all the above declarations about patient and medical identity, the purpose of the study, index case and nature of analysed biological products.

2.4. QUALITY ASSURANCE

HeartGenetics, Genetics and Biotechnology SA is an ISO 9001 and ISO 13485 certified company for Quality Management System and applies an External Quality Assessment program from UK NEQAS. The laboratory that performs this genetic test undertakes to, at all times, comply with the all applicable certifications and Law in its territory.

2.5. TERMS AND CONDITIONS

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The results presented in Section 3.1, Genetic Information, are the responsability of the laboratory that performed the genetic test.

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3. APPENDIX

3.1. GENETIC INFORMATION

The results, described according to HGVS nomenclature (`http:www.hgvs.org`), are presented in the following table. The alleles that contribute to arterial hypertension are obtained from HeartGenetics´ clinical trial and scientific references.

No other genetic variants from HeartGenetics panel were identified, than those shown in the table.

Gene	Genetic variant references		Nucleotidic change [1]	Aminoacidic change	Observation [2]
	HGMD	Ensembl			
ACE	CG900332	rs4646994	-/(289BP ALU) intr16	–	htz
ADRA1A	CM064954	rs1048101	c.1039C>T	p.Arg347Cys	hmz
ADRA1A	CR065635	rs17333700	c.1269+4397G>C	–	wt
ADRB1	CM994344	rs1801253	c.1165G>C	p.Gly389Arg	htz
AGTR1	–	rs5182	c.573C>T	p.Leu191Leu	wt
CYBA	CR033688	rs9932581	c.*-932A>G	–	hmz
CYBA	CR073543	rs72811418	c.*-675A>T	–	hmz
CYP17A1	–	rs11191548	c.*3251C>T	–	htz
CYP4A11	CR086218	rs9332978	c.*-845A>G	–	wt
DRD3	CM033372	rs6280	c.25A>G	p.Ser9Gly	htz
ECE1	–	rs212526	c.762+245A>G	–	hmz
EDN1	CM993569	rs5370	c.594G>T	p.Lys198Asn	htz
FGF5	–	rs1458038	g.81164723G>A	–	htz
KCNMB1	CM078442	rs2301149	c.328G>C	p.Val110Leu	hmz
NOS3	CM981388	rs1799983	c.894T>G	p.Asp298Glu	hmz
NPPA	CM040788	rs5065	c.454T>C	p.Term152Arg	wt
NPPA	–	rs5068	c.*92C>T	–	hmz
NPPA	CM057551	rs5063	c.94A>G	p.Met32Val	htz
NPPC	CR024227	rs5268	c.*82G>A	–	hmz
NR3C2	CR030126	rs2070951	c.*-2C>G	–	htz
REN	CR023838	rs12750834	c.*-5319C>T	–	htz
REN	CS080736	rs5707	c.492+17T>G	–	htz
REN	–	rs11240688	c.98+802T>C	–	htz
RETN	CR032443	rs3745368	c.*62A>G	–	hmz
SCNN1A	CM994637	rs2228576	c.1987A>G	p.Thr663Ala	htz
SCNN1A	CR024763	rs3759324	c.*-756A>G	–	wt
SLC12A3	–	rs13306673	c.283-54T>C	–	hmz
WNK1	CR054937	rs1468326	c.*-5231A>C	–	hmz

[1] The numeric identification associated with each variant is indexed to a reference sequence obtained from Ensembl database (`http://www.ensembl.org/index.html`).
[2] hmz – Homozygosity; htz – Heterozygosity; wt – Wild type

3.2. PHARMACOGENETICS DETAILED INFORMATION

Drug class	Drug [1]	Metabolic axis	Variant	Observation	Antihypertensive effect
ACE inhibitors	Perindopril	RAAS	AGTR1, – / rs5182	Wild type	Effective. Reduced risk for cardiac events
Angiotensin II receptor antagonist	Irbesartan	VE	EDN1, CM993569 / rs5370	Heterozygous	Effective
Angiotensin II receptor antagonist	Valsartan	RAAS	REN, CR023838 / rs12750834	Heterozygous	Moderate efficacy

Beta-blockers	Atenolol	VE	ADRB1, CM994344 / rs1801253	Heterozygous	Efective in the presence of haplotype C(CM994344)/A(CM004689) (Arg389-Ser49)
Beta-blockers	Unspecified beta-blocker	VE	ADRB1, CM994344 / rs1801253	Heterozygous	Efective in the presence of haplotype C(CM994344)/A(CM004689) (Arg389-Ser49)
Beta-blockers	Unspecified beta-blocker	RAAS	CYP17A1, – / rs11191548	Heterozygous	Moderate efficacy in reducing diastolic blood pressure
Beta-blockers	Atenolol	VE	EDN1, CM993569 / rs5370	Heterozygous	Effective
Calcium channel blockers	Nifedipine	VE	ADRA1A, CM064954 / rs1048101	Homozygous	Effective in decreasing blood pressure
Calcium channel blockers	Unspecified calcium channel blocker	RT/SC	NPPA, CM040788 / rs5065	Wild type	Individuals with TT genotype benefit from treatment with calcium channel blockers
Calcium channel blockers	Verapamil	VE	KCNMB1, CM078442 / rs2301149	Homozygous	Decreased risk for adverse cardiovascular outcomes in hypertensive CAD patients
Calcium channel blockers	Diltiazem	RAAS	CYP17A1, – / rs11191548	Heterozygous	No association with therapeutic response
Calcium channel blockers	Amlodipine	VE	NOS3, CM981388 / rs1799983	Homozygous	Effective in reducing the risk of cardiovascular events
Diuretics	Unspecified diuretic	RAAS	CYP17A1, – / rs11191548	Heterozygous	Moderate efficacy in reducing diastolic blood pressure
Diuretics	Hydrochloroth-iazide	VE	NOS3, CM981388 / rs1799983	Homozygous	Effective in reducing diastolic blood pressure
Diuretics	Thiazides	RT/SC	SLC12A3, – / rs13306673	Homozygous	Effective

[1] **ACE Inhibitors:** imidapril, captopril, perindopril, quinapril, benazepril;
ARB (Angiotensin II Receptor Blockers): valsartan, candesartan, losartan, Irbesartan;
CCB (Calcium Chanel Blockers): amlodipine, diltiazem, nitrendipine, nifedipine, verapamil;
Diuretics: thiazides, hydrochlorothiazide, spironolactone;
Beta-blockers: metaprolol, atenolol.

3.3. EVIDENCES FOR MOLECULAR MARKERS AND FOR PHARMACOGENETICS

The appendix includes a detailed interpretation concerning the genetic risk that predispose to arterial hypertension and the level of evidence regarding pharmacogenetics. All evidences are supported by PubMed scientific papers (`http://www.ncbi.nlm.nih.gov/pubmed`) and HGMD Professional database release 2015.4 (`http://www.hgmd.org`), accessed on March 2016.

ACE, CG900332 / rs4646994

The angiotensin-converting-enzyme (ACE) plays a critical role in sodium homeostasis promoting angiotensin II synthesis and bradykinin inactivation, resulting in increased vasoconstriction and higher blood pressure. In HyperGen study the effect of the *ACE* I/D variant also depended upon the genotype at the *AGT* gene pointing out to the importance of an integrated genetic analysis [1, 2]. The Rotterdam Study population-based cohort showed that, among type 2 diabetic patients, the systolic blood pressure and the genetic risk for hypertension increased with the number of risk genotypes, namely for the RAS genetic variants ACE_CG900332 and AGT_CM920010 and for the salt sensitivity gene variant ADD1_CM021240 [3].

ADRA1A, CM064954 / rs1048101

ADRA1A protein plays a role in arterial blood pressure homeostasis, modulation of peripheral vasoconstriction and cardiovascular response to stress. Polymorphisms in *ADRA1A* gene that alter the α-1-adrenoceptor activity might contribute to arterial hypertension in normotensive subjects at risk for the disease and to worsen the clinical condition of hypertensive patients [4, 5]. Despite several studies have shown association between *ADRA1A* gene variants and blood pressure alterations, the results differ among populations. According to HeartGenetics' clinical trial, the evaluation of 600 caucasians showed a predisposition to arterial hypertension related to TT genotype.

Therapeutics
Hypertensive patients homozygous for the T allele:
- nifedipine is more effective reducing the arterial blood pressure [6].

ADRA1A, CR065635 / rs17333700

ADRA1A protein plays a role in arterial blood pressure homeostasis, modulation of peripheral vasoconstriction and cardiovascular response to stress. Polymorphisms in *ADRA1A* gene that alter the α-1-adrenoceptor activity might contribute to arterial hypertension in normotensive subjects at risk for the disease and to worsen the clinical condition of hypertensive patients [4, 5]. Despite several studies have shown association between *ADRA1A* gene variants and blood pressure alterations, the results differ among populations. According to HeartGenetics' clinical trial, the evaluation of 600 caucasians showed a predisposition to arterial hypertension related to GG genotype.

ADRB1, CM994344 / rs1801253

The β1-adrenergic receptor (ADRB1) is a transmembrane receptor with high affinity for epinephrine and norepinephrine, playing a role in arterial blood pressure homeostasis, cardiac stimulation and coronary vasodilation.

Therapeutics
Patients harbouring ADRB1 C(CM994344)/A(CM004689) haplotype (also described as Arg389-Ser49 haplotype):
- treatment with atenolol is more effective than with verapamil [7, 8, 9, 10].
- several evidences indicate that therapy with β-blockers promote an increase in ejection fraction and survival level related to heart failure [7, 8, 11].

AGTR1, – / rs5182

Angiotensin II type 1 receptors (AGRT1) play an important role in vasoconstriction and retention of salt and water [12].

Therapeutics
Hypertensive patients with coronary artery disease harbouring the TT genotype:
- perindopril is more effective and the risk for cardiac events is lower [13].

CYBA, CR033688 / rs9932581

CYBA gene encodes the light α subunit of the cytochrome b-245, a protein that plays a role in phagocytosis and in the generation of superoxide anion, which is implicated in the etiology of arterial hypertension. The G allele is associated with arterial hypertension [14].

CYBA, CR073543 / rs72811418

CYBA gene encodes the light α subunit of the cytochrome b-245, a protein that plays a role in the generation of superoxide anion and in phagocytosis. This polymorphism is related to an increased NADPH oxidase-mediated oxidative stress, which is implicated in the etiology of arterial hypertension, stroke and asymptomatic atherosclerosis [15]. The prevalence of the TT genotype is higher in hypertensive caucasian patients comparing to normotensive subjects (153 normotensive subjects, TT 81.7%, vs. 199 hypertensive, TT 90.9%, P = 0.018). Hypertensives harbouring the TT genotype also show higher systolic blood pressure [16]. According to HeartGenetics' clinical trial, the evaluation of 600 caucasians showed a predisposition to arterial hypertension related to TT genotype.

CYP17A1, – / rs11191548

The *CYP17A1* gene encodes a member enzyme of the cytochrome P450 superfamily that is involved in the production of progestins, mineralocorticoids, glucocorticoids, androgens, and estrogens. Several studies identified an association between the T allele and higher arterial blood pressure [17, 18, 19].

Therapeutics
Hypertensive patients harbouring the T allele:
- lower decrease of diastolic blood pressure when treated with β-blockers or diuretics (P = 0.018).
- no association with therapeutic response to diltiazem [20].

CYP4A11, CR086218 / rs9332978

CYP4A11 enzyme catalyses the conversion of arachidonic acid into 20-hydroxyeicosatetraenoic acid, a metabolite that plays a role in the regulation of arterial blood pressure. According to HeartGenetics' clinical trial, the evaluation of 600 caucasians showed a predisposition to arterial hypertension related to AA genotype.

DRD3, CM033372 / rs6280

The *DRD3* gene, encoded by the D3 type dopamine receptor, participates in sodium balance regulation as dopamine inhibits both proximal and distal renal tubule NaCl reabsorption. Several studies *in vitro* and in animal models show an association with impaired renal dopaminergic system and the etiology of salt-dependent hypertension [21, 22]. According to HeartGenetics' clinical trial, the evaluation of 600 caucasians showed a predisposition to arterial hypertension related to G allele.

ECE1, – / rs212526

Endothelin 1 converting enzyme participates in the proteolytic conversion of endothelin precursors into their active forms. Endothelin 1 is a potent vasoconstrictor and its production is related to angiotensin II levels and arterial blood pressure. The G allele is associated with increased diastolic blood pressure in both genders and with increased systolic blood pressure in female subjects [23].

EDN1, CM993569 / rs5370

Endothelin 1 is a vasoconstrictor peptide produced by vascular endothelial cells that plays a key role in vascular homeostasis. High levels of circulating endothelin 1 are associated with increased arterial blood pressure [24, 25, 26]. In caucasians, genetic variants in the *EDN1* gene are associated with blood pressure phenotypes, being the genotype effect modulated by physical activity or cardiorespiratory fitness level [27]. According to HeartGenetics' clinical trial, the evaluation of 600 caucasians showed a predisposition to arterial hypertension related to GT genotype.

FGF5, – / rs1458038

The fibroblast growth factor FGF5 is involved in a variety of biological processes such as cell growth, embryonic development, tissue repair and tumor growth. This polymorphism is associated with a higher susceptibility for arterial hypertension [28, 29].

KCNMB1, CM078442 / rs2301149

Subunit β 1 of calcium-activated potassium channel regulates the transport of potassium ions, being involved in diastolic blood pressure (DBP) control [30]. Combined functional and population-based genetic epidemiological studies showed a direct involvement of the BK channel in the control of DBP [30]. According to HeartGenetics' clinical trial, the evaluation of 600 caucasians showed a predisposition to arterial hypertension related to C allele.

Therapeutics
Hypertensive CAD patients harbouring CC genotype:
- verapamil reduces the risk of adverse cardiovascular outcomes [31].

NOS3, CM981388 / rs1799983

The nitric oxide synthase 3 (NOS3) is a cardiovascular mediator that promotes relaxation of vascular smooth muscle. Subjects harbouring the GG genotype show a greater risk for arterial hypertension (OR = 2.79; 95%CI = [1.32;5.89];P = 0.007) [32, 33]. This risk is even higher in combination with the GG genotype (CM950016) of *ADRB2* gene (OR = 7.64, 95%CI = [2.88;20.29], P = 0.00005) [34].

Therapeutics
Hypertensive patients harbouring GG genotype:
- hydrochlorothiazide is effective reducing diastolic blood pressure [35].

Hypertensive patients harbouring G allele:
- lower risk of cardiovascular events, namely MI, ischemic cardiomyopathy and stroke, when treated with amlodipine by comparison to lisinopril [35].

NPPA, – / rs5068

The natriuretic peptide precursor A (NPPA) regulates the vascular tone and the sodium homeostasis. The T allele is associated with higher concentration of natriuretic peptide precursors A and B [36, 37]. Subjects harbouring the T allele have lower arterial blood pressure, both systolic (0.9-1.5 mmHg) and diastolic (0.3-0.8 mmHg) [37] and lower risk for arterial hypertension (OR = 0.85, P = 4×10^{-5}) [37].

NPPA, CM040788 / rs5065

The natriuretic peptide precursor A (NPPA) regulates the vascular tone and the sodium homeostasis [38].

Therapeutics
Hypertensive patients harbouring TT genotype:
- calcium channel blockers originate more favorable cardiovascular disease outcomes [39].

NPPA, CM057551 / rs5063

The natriuretic peptide precursor A (NPPA), encoded by the *NPPA* gene, plays an important role in cardiovascular homeostasis by regulating natriuresis, diuresis and vasodilation. Evidence exists that polymorphisms in *NPPA* gene affect circulating levels of atrial natriuretic peptide (ANP) and several studies have shown association between *NPPA* gene variants and blood pressure alterations, although the results differ among populations [40]. According to HeartGenetics' clinical trial, the evaluation of 600 caucasians showed a predisposition to arterial hypertension related to AG genotype.

NPPC, CR024227 / rs5268

The natriuretic peptide precursor C (NPC), encoded by the *NPPC* gene, plays a vasoactive and natriuretic role. Atrial natriuretic peptide concentrations are increased by raised filling pressure due to vasodilatation, natriuresis and suppression of the renin-angiotensin system (RAS) in patients with arterial hypertension [41]. The A allele is associated with a greater risk for arterial hypertension, especially in subjects less than 65 years of age [42]. According to HeartGenetics' clinical trial, the evaluation of 600 caucasians showed a predisposition to arterial hypertension related to AA genotype.

NR3C2, CR030126 / rs2070951

The NR3C2 is an aldosterone receptor that regulates electrolyte balance and arterial blood pressure. When present in heterozygosity, this variant is not associated with the pathology [43].

REN, – / rs11240688

Renin is an enzyme encoded by *REN* gene that catalyses the first reaction of the angiotensin II activation cascade, that leads to aldosterone secretion, vasoconstriction and increase of arterial blood pressure [44]. When present in heterozygosity, this variant is not associated with the pathology [45].

REN, CR023838 / rs12750834

Renin is an enzyme encoded by *REN* gene that catalyses the first reaction of the angiotensin II activation cascade, that leads to aldosterone secretion, vasoconstriction and increase of arterial blood pressure. The T allele was found to be associated to an increased expression of REN, and thus to an increased diastolic arterial blood pressure and higher susceptibility to arterial hypertension (population I: mean = 1.5 mmHg and 95%CI = [0.3;2.8] and population II: mean = 1.1 mmHg and 95%CI = [0.1;2.1]) [46].

Therapeutics
Hypertensive patients harbouring carrying the T allele:
- valsartan associated with a lower reduction of the arterial blood pressure [47].

REN, CS080736 / rs5707

Renin is an enzyme encoded by *REN* gene that catalyses the first reaction of the angiotensin II activation cascade, that leads to aldosterone secretion, vasoconstriction and increase of arterial blood pressure. When present in heterozygosity, this variant is not associated with the pathology [44].

RETN, CR032443 / rs3745368

Resistin is a cytokine encoded by the *RETN* gene that promotes insulin resistance in adipocytes, linking obesity to diabetes. Diabetic patients with GG genotype exhibit higher values of both systolic and diastolic arterial blood pressure (GG:GA/AA; 144 $\pm$ 21 mmHg:139 $\pm$ 21 mmHg, P = 0.004; 87 $\pm$ 13 mmHg:84 $\pm$ 14 mmHg, P = 0.002). The GG genotype is also more frequent among hypertensive diabetic subjects (GG:GA/AA = 40.0%:29.4%; OR = 1.464; 95%CI = [1.180;1.817]; P<0.001). The presence of the GG genotype might hence be related to an increased risk for the development of insulin-resistant related hypertension [48].

SCNN1A, CM994637 / rs2228576

The α subunit of the amiloride-sensitive sodium channel mediates sodium electrodiffusion across the membrane of epithelial cells, osmotic water diffusion and renal reabsorption of sodium [49]. When present in heterozygosity, this variant is not associated with the pathology [50].

SCNN1A, CR024763 / rs3759324

The α subunit of the amiloride-sensitive sodium channel mediates sodium electrodiffusion across the membrane of epithelial cells, osmotic water diffusion and renal reabsorption of sodium. Lower expression levels of this subunit in subjects with the AA genotype might lead to decreased renal reabsorption of sodium and thus act as a protective factor against arterial hypertension [51].

SLC12A3, – / rs13306673

The *SLC12A3* gene encodes a Na:K cotransporter of distal tubular cells. This channel is sensitive to thiazides, which promote a decreased reabsorption of salt and water and an increased excretion of sodium, potassium and magnesium ions. It was demonstrated an association between this polymorphism and arterial hypertension but further studies are necessary to provide diretct clinical evidence [52]. However, this polymorphism have significance to therapeutics.

Therapeutics
Hypertensive patients harbouring the CC genotype:
- thiazides are effective [53].

WNK1, CR054937 / rs1468326

WNK1 gene encodes a serine/threonine-protein kinase that plays an important role in the regulation of electrolyte homeostasis. The WNK1 protein is expressed in the distal nephron and is considered a key regulator of the arterial blood pressure by controlling sodium and chloride transport across the epithelial cells of the renal tubule. The analysis of 100 families with European ancestry (MRC British Genetics of Hypertension study resource) showed a significant association between the C allele, arterial hypertension and high systolic (Z = +2.241, P = 0.025) and diastolic (Z = +1.992, P = 0.046) arterial blood pressure [54].

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