Any variants reaching P < 1 × 10-5 for SBP and DBP response to BBs were tested for replication in available ICAPS consortium data (N=1,328).

Results: Strong correlation between baseline BP and BP response shows patients with higher BP have greater BP reduction post-treatment.
No variants reached genome-wide significance in any of the GWAS analyses, and none replicated in ICAPS data.
Lookups of ~1,000 published BP-associated variants were performed, but none reached Bonferroni significance level. Ongoing analyses are testing BP genetic risk scores for association with treatment response.
Comparison of GWAS results shows correlation between SBP vs DBP response (r^2=0.48) and SBP vs PP response (r^2=0.76), but none between response to BBs vs CCBs.

Conclusions: Despite being the largest GWAS of antihypertensive response, we found no significant associations, showing that larger studies are still required to increase power for discoveries. Model comparisons show different genes are likely to influence response to different antihypertensive drugs, with different genetic architecture.

LOSS OF ADD1 METHYLATION ADDS ON BLOOD PRESSURE IN YOUNG ADULTS

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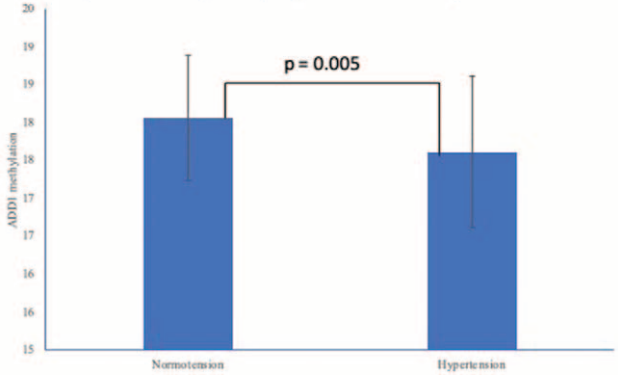
Objective: To investigate the association between alpha-Adducin (ADD1) methylation and blood pressure in young adults with essential hypertension.

Figure 1. ADD1 methylation in young adults of different blood pressure status



Design and method: A total of 160 subjects (80 normotensive and 80 incident hypertensive) aged between 18 to 45 years from Kuantan, Pahang were included in a cross-sectional study by purposive sampling. They were assessed for ADD1 methylation in peripheral blood using MethyLight assay. Anthropometric measurements and biochemical parameters were also examined.

Results: ADD1 methylation was inversely correlated with systolic (p = 0.006, r = –0.240), diastolic (p = 0.001, r= –0.281) and mean arterial pressures (p = 0.002, r = –0.270). Hypertensive subjects had significantly higher ADD1 methylation than normotensive control (p = 0.005). After adjusting for other relevant covariates (age, body mass index, HbA1c, high-sensitivity C-reactive protein and low density lipoprotein cholesterol), ADD1 methylation remained a significant predictor for hypertension in young adults (p = 0.020)

Conclusions: ADD1 methylation is a significant predictor of hypertension in young adults. ADD1 methylation could serve as a future preventive and therapeutic target for hypertension and related cardiovascular disease.

AQUAPORIN-3 AND CYBA GENETIC POLYMORPHISMS MAY PREDICT RISK OF DEVELOPING HYPERTENSION

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Objective: Preeclampsia, a placentation disorder, affects 7% of pregnancies in Europe. It influences future cardiovascular disease, such as hypertension. Preeclampsia and hypertension have been associated with oxidative stress, therefore, key proteins in redox signaling may be involved with the development of hypertensive disorders during/after pregnancy. This study aimed at determining associations between oxidative stress-related gene polymorphisms (AQP3-rs2231231 and CYBA-rs4673) with the development of preeclampsia and the risk for future hypertension.

Design and method: A cohort of 150pregnant Caucasian women, aged 35.24±5.47 years, 60(40%) normotensive and 90(60%) preeclamptic, was evaluated. Based on a prospective study(2-16 years later), these women were evaluated for the development of hypertension and classified as normotensive 98(67%) or hypertensive 48(33%). The influence of genetic polymorphisms on the susceptibility for cardiovascular disease was evaluated. In this cohort, anthropometric/haemodynamic parameters were studied. For statistical analysis chi-square and Student t-test were used.

Results: During pregnancy, no differences between the distribution of studied genetic polymorphisms in preeclampsia were found. However, based on the AQP3 dominant model of A, our data showed that AA+AC genotypes were more frequent (73.3%;p=0.014) in hypertensive individuals. Moreover, allele A, the allele of risk, was associated with a 3.405-fold higher risk (p=0.016,OR=3.405,95%CI[1.26-9.19]) to develop hypertension after pregnancy. In addition, a higher systolic(p=0.017) and diastolic(p=0.008) pressure were also observed in women carrying the AA+AC genotype. Furthermore, based on CYBA dominant model of C, TT genotype of polymorphism was also correlated with the development of hypertension(100.0%;p=0.007) after pregnancy. On the other hand, looking at the recessive model of C, CT+TT genotype was associated with the development of hypertension. Allele T, the allele of risk, was associated with 6.5-fold risk (p=0,024,OR=6.500,95%CI[1.28-33.03] to develop hypertension. Moreover, CT+TT genotypes of CYBA genetic polymorphism were more associated with increased weight (p=0.014), higher waist circumference(p=0.010), hip(p=0.008) and systolic(p<0.001) and diastolic blood pressure(p<0.001).

Conclusions: In this study, AQP3 genetic polymorphism was found associated with the hypertensive disorders after pregnancy for the first time. In addition, CYBA was also associated with the development of essential hypertension. These results open new perspectives in the development of new approaches for cardiovascular disease prevention.

RELATION BETWEEN APOLIPOPROTEIN E GENE POLYMORPHISM AND LIPID SPECTRUM IN HYPERTENSIVE PATIENTS

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Objective: To study the relationship between apolipoprotein E gene polymorphism and lipid spectrum modification in hypertensive patients.

Design and method: We examined 310 hypertensive patients (177 males and 133 females) ages 56,11±0,68 years and history duration 6,51±0,48 years, who were administrated with any antihypertensive components and no any specific lipid-lowering medications. According to office blood pressure measurement the average brachial value was 141,33±1,34/87,62±0,79 mmHg. The lipid spectrum components and apolipoprotein E gene polymorphism were assessed using automatic clinical biochemical analyzer «Cobas c311» and amplifier for single nucleotide polymorphism identification «Thermal Cycler CFX96TM Real-Time PCR Detection Systems» accordingly. Statistical data were presented like mean ± standard error and 95% confidence interval. Statistically significant difference was considered in case of P<0,05.

Results: The average values of total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL) and very low density lipoproteins (VLDL), triglycerides and indices of atherogenicity was 5,18±0,08 mmol/l [5,02-5,34], 1,32±0,03 mmol/l [1,27-1,37], 3,06±0,07 mmol/l [2,92-3,2], 0,79±0,02 mmol/l [0,75-0,83], 1,74±0,05 mmol/l [1,64-1,83] and 3,21±0,08 [3,05-3,38] respectively. Apolipoprotein E polymorphism was presented with alleles E2 (n=41, 13,26%), E3 (n=291, 93,87%) and E4 (n=95, 30,65%) as well. Based on single nucleotide polymorphism identification there were defined next variants of genotypes: E2/E2-rarest of all genotypes (n=2, 0,65%), E2/E3 (n=34, 10,97%), E2/E4 (n=5, 1,61%), E3/E3 (n=179, 57,74%), E3/E4 (n=78, 25,16%) and E4/E4 (n=12, 3,87%). This way, it was found the domination of homozygous variants (n=193, 62,26%). Besides that, overwhelming majority of them had both E3 allele and, as a result, E3/

E3 genotype (n=179, 92,75%). More over, this trend was independent of age and gender affiliation, but full spectrum of genotypes was inherent only for elderly patients (n=105, 33,87%).

Conclusions: The course of arterial hypertension reflects the mild degree of activity (isolated systolic hypertension) of the disease. Arterial hypertension associated with mixed-dyslipidemia (type 2b). Apolipoprotein E gene polymorphism is characterized by a wide range of alleles and genotypes among the hypertensive population. In hypertensive subjects the most common allele is E3 as well as genotype – is E3/E3 (opposite to E3/E4 in case of heterozygous variant).

ASSOCIATION OF AGT GENE M235T AND ACE GENE I/D POLYMORPHISMS WITH HYPERTENSION IN MONGOLIAN POPULATION

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Objective: In Mongolia, hypertension is major public health problem due to its high prevalence of stroke and mortality rate. The objective of this study was to analyse the relationship between AGT M235T gene variant and ACE I/D gene variant with hypertension in a sample of the Mongolian population of the Ulaanbaatar city.

Design and method: Design and Method: A case-control study has been performed in 146 subjects including 96 hypertensives and 50 normo-tensive subjects, aged 18-60 years. Hypertension was defined as systolic BP =>130 mm Hg and/or diastolic BP=>80 mm Hg). After isolation DNA from peripheral blood, the following specific primers were used for polymerize chain reaction (PCR). PCR purification kit and QIAquick Gel extraction kit were used to establish nucleic acid sequence.

Name	Sequence (5'-3')	Length	Tm (℃)	Lenth of the
hAGT-F/DNA	CTATCTGGGAGCCTTGGACCACACAGC	27	65	504 bp
hAGT-R/DNA	CATCTCCAAGGCCTGACTGGCTGATCTC	28	65	
hACE-F/DNA	CTGTAAGCCACTGCTGGAGAGCCACT	26	71	354 bp
hACE-R/DNA	GGCGCACGTAGGCATGCAGGTTGAG	25	72.4	

Results: The mean age of the participants was 39.6 years and 54.7% were men. The M235T variant of AGT gene was identified in 97.9% of all participants (96.8% of hypertensive patients and 100% of normotensive subjects). According to the genotype results, the frequencies of the AGT TT, MT and MM genotypes were 57.3%, 39.6%, and 3.1% in cases and 64.0%, 36.0% and 0.0% in controls respectively.
The genotypic distribution of the M235T variant of the AGT gene did not differ in hypertensives and normotensives group (p >0.328). In this study, we did not observe any significant differences in blood pressure levels with regard to ACE gene I/D polymorphism in both hypertensive and normotensive groups (40% vs 38%, p>0.543).

Conclusions: Conclusion: This is the first report on the frequency of AGT and ACE gene polymorphisms among Mongolian population. About 97.9% of Mongolians carry the M235T variant of the AGT gene that makes them more prone to hypertension when they eat too much sodium.

IN SILICO DRUG REPOSITIONING OF TOPIRAMATE AS AN ANTIHYPERTENSIVE BY CONVERGING KIDNEY TRANSCRIPTOMIC, EPIGENOMIC AND GENOMIC DATA

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Objective: No new antihypertensive medication has been introduced to clinical practice since 2007. Mendel's second law states that genotype is allocated randomly at conception therefore, short nucleotide variants acting in cis can be utilised to deduce the pharmacological action on the same protein as in an RCT. Here, we investigate new therapeutic opportunities for hypertension through exploiting the druggable genome.

Design and method: We conducted expression(e), splicing(s) and methylation(m) quantitative trait loci (QTL) analysis on 430 human kidneys from 5 studies [TRANScriptome of renaL humAn TissuE (TRANSLATE) study, Tissue Cancer Genome Atlas (TCGA), moleculAr analysis of human kiDney-Manchester renal tIssue pRojEct (ADMIRE) study, Molecular analysis of mechanisms regulating gene expression in post-ischemic injury to renal allograft (REPAIR) and Renal gEne expreSsion and PredispOsition to cardiovascular and kidNey Disease (RESPOND)]. Through their intersection with blood pressure variants from all previous genome wide association studies (GWAS) we identified genetic variants partnering with protein-coding kidney e-Genes, s-Genes and m-Genes. We then mapped the proteins encoded by these genes onto a set of licensed drugs or compounds with bioactivities against these targets in-silico.

Results: Altogether, 479 informative genetic variants mapping onto 918 protein coding genes were identified. Of these, 201 (21.9%) genes were druggable. We found 209 unique associations with 44 (21.9%) protein coding genes. Of these, 23 associations acting on 7 drug targets were precisely concordant (captopril associated with ACE gene) and 16 associations (4 targets) had the indication association within the same disease area [for example, ambrisentan (an endothelin receptor antagonist) acting on a BP GWAS gene EDNRA]. 3 (1.3%) drugs were identified as repurposing opportunities for hypertension based on clinical evidence and directionality of effect on gene activity. Of those, topiramate [target for the alpha-subunit of Gamma-Aminobutyric Acid Type A receipt Alpha2 Subunit (GABRA2) gene], was deemed as clinically strongest drug repurposing opportunity for hypertension. The alpha subunit of this receptor is coded by GABRA2 gene, which is a hypertension risk gene identified in our study.

Conclusions: Integration of pharmacological databases with -omic data of tissue of key relevance to hypertension may uncover novel drug repurposing opportunities.

THE ROLE OF GUT METABOLITE-SENSING RECEPTORS GPR41 AND GPR43 IN CARDIOVASCULAR DISEASE

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Objective: Fibre intake is associated with lower incidence of hypertension and cardiovascular mortality. Prebiotic fibre, such as resistant starches and soluble fibre, are fermented by commensal gut microbiota to short-chain fatty acids (SCFAs), which have a protective role in cardiovascular disease. We, and now others, have shown that supplementation of SCFA such as acetate, propionate and butyrate can reduce blood pressure (BP) and their complications. The main receptors for SCFAs, the G-coupled protein receptors GPR41 and GPR43, have redundant functions, but their contribution to cardiovascular health and disease is uncertain. Therefore, we aimed to characterize their contribution to the cardiovascular phenotype using a unique mouse model where both receptors are absent, the GPR41/43 knockout (KO)

Design and method: We studied female (n=12) and male (n=15) double GPPR41/43 KO mice compared to wild-type (WT) C57BL/6 mice (n=4-8) at 10 weeks of age. We performed BP measurements using tail cuff, sodium and water loading, real-time PCR, flow-cytometry of immune cells, and histology of the heart, kidney and gut

Results: GPR41/43 KO male and female mice did not have significant difference in BP compared to WT mice (P=0.387–0.676), but female GPR41/43 KO had significantly smaller kidneys (adjusted to tibia length) compared to WT female (P=0.006). Upon saline challenge, both male and female GPR41/43 KO mice excreted more urine (P=0.01 male, P=0.116 female), but not sodium (P=0.461 male, P=0.141 female), compared to WT mice over a 5 hour period. GPR41/43 KO had lower levels of pro-renin receptor (Atp6ap2) mRNA (P= 0.012 male, P=0.057 female) but higher levels of renal collagen genes mRNA (Col3a1 P=0.055 male, Col1a1 P=0.023 female), indicative of fibrosis.

Conclusions: GPR41/43 KO mice expressed lower pro-renin receptor mRNA but higher levels of fibrosis markers. GPR41/43 KO mice excreted more urine than WT mice and did not have higher BP. Moreover, female GPR41/43 KO mice had significantly smaller kidneys, proposing a role for these receptors in renal development. Together, these findings suggest that the gut metabolite-sensing receptors GPR41/43 are likely to contribute to cardiovascular regulation via a role in water absorption and excretion, as well as in fibrosis

FUNCTIONAL IN SILICO ANALYSIS OF GENETIC VARIANTS FROM GENOME-WIDE ASSOCIATION STUDIES OF BLOOD PRESSURE AND HYPERTENSION

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