PI-26

ASSOCIATION OF ANGIOTENSIN II TYPE I RECEPTOR (AGTR1) 1166A>C POLYMORPHISM WITH BLOOD PRESSURE RESPONSE TO ACE INHIBITOR IN A SUBGROUP OF PATIENTS OF THE INTERNATIONAL VERAPAMIL SR/TRANDOLAPRIL STUDY (INVEST). M. Brunner, MD, J. H. Karnes, Y. Gong, PhD, T. Y. Langaee, PhD, R. M. Cooper-DeHoff, PharmD, C. J. Pepine, MD, J. A. Johnson, PharmD, University of Florida, College of Pharmacy, Center for Pharmacogenomics, University of Florida, College of Medicine, Gainesville, FL.

BACKGROUND: The AGTR1 1166A>C gene polymorphism (SNP) has been associated with hypertension. We investigated whether this SNP affects blood pressure (BP) response to ACE inhibitor (ACEI) therapy in an ethnically diverse group of hypertensive coronary artery disease patients who had an ACEI (trandolapril) added to verapamil SR 240 mg monotherapy to achieve BP goals during INVEST.

METHODS: 575 patients met the criteria for analysis and were genotyped by pyrosequencing. ANCOVA was used to compare BP response to ACEI addition adjusting for genotype, age, gender, race, body mass index, ACEI dose, diabetes and interaction terms between genotype and other factors. For presentation, patients were divided into four 10 year age groups.

RESULTS: Mean duration from ACEI addition to BP assessment was 68 days. Systolic (SBP) and diastolic BP response did not differ between genotypes. Age was significantly associated with SBP response ($p=0.033$). Mean ($\pm$ SD) adjusted SBP and mean SBP reduction after ACEI addition are shown (table). BP response did not differ significantly between ethnic groups. In 87% of white and 88% of Hispanic patients, trandolapril 2 mg daily was added to verapamil, whereas in 93% of African Americans trandolapril 4 mg daily was added, consistent with study protocol recommendations.

CONCLUSIONS: Age was an important determinant of BP response to ACEI addition, while AGTR1 1166A>C genotype was not. African Americans achieved similar BP response as other ethnic groups, which might be due to higher ACEI dosing.

		SBP after ACEI addition to verapamil SR (mm HG)	SBP reduction after ACEI addition to verapamil SR (mm HG)
Genotype	A/A	142.2 ± 17.2	−8.2 ± 17.3
	A/C	140.3 ± 14.4	−10.1 ± 16.8
	C/C	143.2 ± 22.4	−8.5 ± 21.2
Age	50-59 years	138.5 ± 14.4	−10.1 ± 14.7
65.8 ± 9.8	60-69 years	142.2 ± 16.4	−9.3 ± 18.0
(mean ± SD)	70-79 years	142.7 ± 18.5	−8.4 ± 18.7
	80 years and older	144.3 ± 18.0	−8.3 ± 19.1
Ethnic groups	African American	140.9 ± 17.6	−7.0 ± 17.6
	Hispanic	142.4 ± 16.9	−9.6 ± 17.1
	White	142.4 ± 16.1	−8.9 ± 17.7

PI-27

A PHARMACOGENETIC AND FUNCTIONAL GENOMIC STUDY OF THE DRUG METABOLIZING UGT1A4 ENZYME. O. Bernard, M. Leblanc, M. H. Court, P. Caron, L. Villeneuve, Q. Hao, L. L. von Moltke, D. J. Greenblatt, C. Guillemette, Pharmacogenomics Laboratory of Canada, Tufts University School of Medicine, Sainte-Foy, PQ, Canada.

BACKGROUND: This study was designed to identify common UGT1A4 genetic variants and determine their contribution to interindividual differences in UGT1A4-mediated glucuronidation activity.

METHODS: Single nucleotide polymorphism (SNP) discovery was accomplished by resequencing the gene. Haplotypes were inferred and population frequencies estimated using PHASE version 2.1. HepG2 cells were used in transfection studies with UGT1A4/luciferase constructs. Glucuronidation activity and genotypes were assessed in a bank of human livers ($n=46$). Imipramine was selected as a probe substrate.

RESULTS: Sequence analysis revealed four UGT1A4 upstream SNPs and 2 common (27%) promoter region haplotypes were inferred. Promoter haplotype 2, in linkage disequilibrium with L48V, resulted in deletions and additions of putative binding sites for nuclear receptor 1 (HNF-1α) and octamer binding domain (OCT-1). Glucuronidation activities were not significantly different in livers with the haplotype 2 genotype compared to individuals homozygous for the reference promoter. The number of haplotype 2 carriers did not significantly differ in patients exhibiting the highest or lowest glucuronidation activities for imipramine. Haplotype 2 exhibited no significant change in luciferase activity with and without overexpression of HNF-1 and OCT-1.

CONCLUSION: Proximal promoter region polymorphisms of the UGT1A4 gene were not associated with a significantly altered hepatic imipramine glucuronidation profile.

PI-28

VARIATIONS IN THE α_{2A}-ADRENERGIC RECEPTOR GENE AND THEIR FUNCTIONAL EFFECTS. D. Kurnik, MD, M. Muszkat, MD, C. Li, PhD, G. G. Sofowora, MD, J. Solus, PhD, H. G. Xie, MD, PhD, P. A. Harris, PhD, L. Jiang, MSc, C. McMunn, BS, P. Ihrie, MS, E. P. Dawson, BS, S. M. Williams, PhD, A. J. Wood, MD, C. M. Stein, MD, Vanderbilt University, Bioventures Inc., Nashville, TN.

BACKGROUND: The α_{2A}-adrenergic receptor (ADRA2A) regulates systemic sympathetic activity and hence cardiovascular responses. The objectives of this study were to systematically search for variants in the *ADRA2A* gene, define its haplotype structure, and determine functional effects of genetic variants.

METHODS: We examined 5957 bp of contiguous sequence of *ADRA2A* (promoter, exonic, and 3'-flanking region) using bidirectional sequencing in 135 healthy subjects (85 Caucasian and 50 African-American). Haplotypes were inferred using an expectation-maximization algorithm. Plasma norepinephrine concentration, resting heart rate, and blood pressure were measured.

RESULTS: We identified 41 variants (24 novel); based on 9 selected markers, 11 haplotypes in 5 haplotype groups were inferred, representing 99% of the cohort. Two uncommon variants in complete linkage disequilibrium (G>C at -1903 and C>G at -1607, identified in 3 African-Americans) were associated with significantly increased plasma norepinephrine concentrations (376.7±6.1 vs. 218.4±95.0 pg/mL, $p=0.011$). There was no other significant association between genetic variants or haplotypes with phenotypes.

CONCLUSION: We describe novel variants and the haplotype structure of the *ADRA2A* gene. Common genetic *ADRA2A* variants do not contribute substantially to baseline cardiovascular measures (plasma norepinephrine, heart rate, and blood pressure) in healthy subjects.