PII-45

ANGIOTENSIN SYSTEM POLYMORPHISMS AND TRADITIONAL RISK FACTORS AS PREDICTORS OF HEART FAILURE PROGNOSIS. A. A. Hudson, I. Zineh, PharmD, H. N. Yarandi, PhD, T. Y. Langaee, PhD, D. F. Pauly, MD, PhD, J. A. Johnson, PharmD, University of Florida, Gainesville, FL.

BACKGROUND: Traditional risk factors affect heart failure (HF) severity and outcomes. We investigated whether angiotensin system gene polymorphisms would offer additional prognostic information when considered with traditional risk factors.

METHODS: Patients with chronic HF were enrolled and followed for first event (all-cause mortality, heart transplant, or HF hospitalization). Logistic regression was used to examine the effects of covariates on outcome. Variables included risk factors previously shown to affect prognosis in our population as well as polymorphisms in the ACE (ACE I/D), angiotensinogen (AGT 235T/C), and angiotensin type 1 receptor (AGTR1 1166A/C) genes determined by pyrosequencing or dHPLC. β-blocker, ACE inhibitor, and diuretic use was near unity at baseline and end of follow-up and not included in the model. Significance for inclusion in the model was set at 0.1.

RESULTS: Patients (n=237) were followed for a median of 18 months (6 months min, 36 months max). Significant markers of HF prognosis are presented (Table).

Variable	Odds Ratio	90% CI	P-value
Serum sodium	0.86	0.78–0.93	0.003
NYHA class	1.84	1.31–2.60	0.003
Previous CABG	1.85	1.03–3.30	0.08

Polymorphisms in three genes of the angiotensin system were not associated with outcomes, nor were age, race, sex, diabetes, dyslipidemia, or serum creatinine.

CONCLUSION: Angiotensin system genes were not associated with HF prognosis in this population. The high use of ACE inhibitors and β-blockers in this population may have ameliorated genetic influence on prognosis.

PII-46

IDENTIFICATION OF GERMLINE GENETIC VARIATIONS IN THE 5' REGION OF THE ESTROGEN RECEPTOR BETA GENE. S. Philips, BS, A. Bermes, BS, A. T. Nguyen, BS, R. Luzcando, BS, P. B. Narayanan, PhD, D. A. Flockhart, MD, PhD, T. C. Skaar, PhD, Indiana University, Indianapolis, IN.

BACKGROUND: Tamoxifen therapy causes variable phenotypic effects on target tissues. Currently, there is no way to predict which patients will have beneficial or harmful side effects from it. Germline genetic polymorphisms in the estrogen receptors (ERs) are associated with altered responses to estrogenic therapies and baseline parameters (e.g. bone mineral density and serum lipids). Little information is available on the germline genetic variations in the estrogen receptor beta (ERβ) gene. We hypothesize that genetic variations in the ERs may account for part of the variability in the tamoxifen induced side effects. The *aim* of this study was to identify genetic polymorphisms in the promoter of the ERβ gene.

METHODS: Using a bioinformatic approach, we compared the promoter sequences of the human, chimpanzee, rat and mouse ERβ genes. We found a region of strong homology immediately upstream of the exon 0N. This region has also been shown to be a site of *in vivo* methylation. Therefore, we resequenced approximately 1.6 kb of the ERβ promoter, exon 0N and intron 1 in 50 African-American (AA) and 50 Caucasian (Cau) subjects.

RESULTS: In AA samples, we found 5 single nucleotide polymorphisms (SNPs) in the promoter, one of which altered the predicted TATA box in the promoter. We also found a SNP in intron 1 that was observed in both Cau and AA. There were no SNPs detected in the exon 0N.

CONCLUSION: The promoter of the ERβ gene contains at least one SNP that may alter its transcriptional activity and tamoxifen responses.

PII-47

IDENTIFICATION OF GENETIC POLYMORPHISMS IN 40 CHEMOTHERAPY PATHWAY GENES. R. R. Freimuth, PhD, S. Marsh, PhD, M. Xiao, PhD, P. Kwok, MD, PhD, H. L. McLeod, PharmD, Washington University, University of California, San Francisco, St. Louis, MO.

BACKGROUND: We set out to identify functionally significant common polymorphisms in 40 genes involved in the pharmacokinetic or pharmacodynamic pathways of anticancer drugs.

METHODS: We used a pooled approach to resequence 120 DNA samples from African-Americans, Asians, and Caucasians (40 samples each).

RESULTS: Approximately 338 kb of sequence was analyzed from each sample. 193 of the 711 variant loci that were identified were located in exons. The PolyMAPr program was used to mine the dbSNP, JSNP, and CGAP databases. 243 of the 711 variants were novel, and 78% of the remaining 468 were listed as unvalidated in the databases. Based on estimated allele frequencies, 274 variants were population-specific and 284 were common to all 3 groups. Of the 115 ORF SNPs, 61 were population-specific and 31 were in all 3 groups. Resequencing and database mining identified 523 variants in the ORF. The PolyPhen program was used to predict functional significance of 275 nonsynonymous biallelic SNPs: 174, 43, and 48 were predicted to be benign, possibly damaging, and probably damaging, respectively. Estimated allele frequency and BLOSUM62 score decreased with increasing predicted severity of the amino acid change.

CONCLUSIONS: These results will aid future pharmacogenetic studies of anticancer drugs.

PII-48

TAMOXIFEN THERAPY REDUCED PLATELET COUNTS WITHOUT CHANGE IN PLATELET FUNCTION. Y. Jin, MD, B. Ward, A. Storniolo, MD, Z. Desta, PhD, A. Nguyen, D. Hayes, MD, V. Stearns, MD, D. A. Flockhart, MD, PhD, Indiana University, University of Michigan, Indianapolis, IN.

BACKGROUND/AIMS: Tamoxifen therapy can cause a 4% decrease in platelet count, yet increases risk of thrombosis. We hypothesized that this decrease was influenced by concentrations of tamoxifen or its metabolites that may lead to changes in platelet function.

METHODS: Candidates for tamoxifen therapy (n=88) participated in a prospective, observational trial. Before and 4 months after tamoxifen treatment, we measured platelet counts (N=88), platelet aggregation (N=17), and plasma concentrations of tamoxifen and its metabolites (N=41).

RESULTS: Tamoxifen therapy led to a 4% decrease in platelet counts (P= 0.039) in our cohort. This decrease was negatively correlated with plasma concentrations of endoxifen (R^2= 0.27, P=0.0006) and 4-hydroxy tamoxifen (R^2= 0.22, P=0.003), but not with tamoxifen and N-desmethyl tamoxifen.. There were no significant changes in either ADP (13.33±12.3 Ω *vs* 11.6±11.5 Ω, P = 0.12) or arachadonic acid (9.6±46.1 *vs* 7.0±37.6 Ω, P=0.19) induced platelet aggregation.

CONCLUSION: Decrease in platelet counts after tamoxifen was negatively correlated with endoxifen and 4-hydroxy tamoxifen concentrations, and did not lead to changes in platelet function.