PI-29

THE EFFECT OF TAMOXIFEN TREATMENT ON LDL SUBFRACTION PARTICLE SIZE IN BREAST CANCER PATIENTS. N. I. Ntukidem, MD, P. Blanche, PhD, L. Li, PhD, R. M. Krauss, MD, T. C. Skaar, PhD, Z. Desta, PhD, A. M. Storniolo, MD, V. Stearns, MD, D. F. Hayes, MD, D. A. Flockhart, MD, PhD, Indiana University, University of California, University of Michigan, Indianapolis, IN.

BACKGROUND: Small dense LDL particles are associated with increased atherogenicity. We examined the effect of tamoxifen treatment on LDL subfraction particle size.

METHODS: 49 breast cancer patients were prospectively followed on adjuvant tamoxifen treatment. LDL peak particle size measurements were performed on plasma using non-denaturing polyacrylamide gradient gel electrophoresis and standardized conditions at baseline and after 4 months of tamoxifen treatment. Genetic variants in the estrogen receptors α [rs#2234693 (PvuII) and rs#9340799 (XbaI)] and β [rs#1256049 (ESR2-01) and rs#4986938 (ESR-02)] were analyzed.

RESULTS: The mean LDL particle diameter were 268.09 and 266.82 Å at baseline and after 4 months of tamoxifen treatment respectively (p=0.088). 38 (77%) of the women had LDL Phenotype A at baseline compared to 35 (71%) after 4 months of tamoxifen treatment (P=0.9). The small dense LDL subfraction (phenotype B) was present in 9 (18%) of the women at baseline and 6 (12%) after 4 months of tamoxifen therapy. The baseline LDL major size was not significantly different in pre-and postmenopausal women (270.6 vs. 266.5, P=0.15). The effect of tamoxifen on lipid particle size was similar when analyzed by menopausal status (P=0.24). We found no association between estrogen receptor genotypes and LDL subfractions.

CONCLUSIONS: Tamoxifen treatment does not alter LDL subfraction particle size in breast cancer patients.

PI-30

FUNCTIONALLY SIGNIFICANT VARIANTS OF CYP2J2 AND EPHX2 ARE NOT ASSOCIATED WITH HYPERTENSION. D. L. Kroetz, PhD, Z. Yu, PhD, T. Y. Langaee, PhD, J. A. Johnson, PharmD, University of California San Francisco, University of Florida, San Francisco, CA.

BACKGROUND/AIMS: CYP2J2 catalyzes the formation of epoxyeicosatrienoic acids (EETs) with antihypertensive properties. The effects of the EETs are attenuated through hydrolysis by soluble epoxide hydrolase (sEH encoded by *EPHX2*). This study examined whether genetic variants of *CYP2J2* and *EPHX2* with decreased function/expression in vitro are associated with hypertension (HTN).

METHODS: Hypertensive (HT; n=199) and normotensive (NT; n=125) African Americans (AA) and HT (n=187) and NT (n=175) Caucasians (CA) between 35-65 years of age were studied. NT had BP < 140/90 mmHg and no primary family history of HTN. The following variants were genotyped by pyrosequencing: in AA the 372C>T (Arg103Cys) and 925G>A (Arg287Gln) variants of *EPHX2*, and in AA and CA the *CYP2J2**7 promoter allele. Minor allele frequencies (MAFs) were compared between NT and HT using a Chi-square test and differences in blood pressure between genotype groups was compared with a *t*-test.

RESULTS: The MAF (see Table) for the *EPHX2* and *CYP2J2* variants were similar in NT and HT. DBP and SBP were not associated with the *EPHX2* or *CYP2J2* genotypes or *EPHX2* diplotypes.

	***EPHX2* 372C>T**	***EPHX2* 925G>A**	***CYP2J2*7***
NT AA	11%	9.2%	12%
HT AA	9.6%	8.7%	12%
NT CA			8.6%
HT CA			8.8%

CONCLUSIONS: Functionally significant genetic variants of *CYP2J2* and *EPHX2* are not associated with HTN in AA and CA. The importance of these variants in the progression of cardiac endpoints associated with HTN is being investigated. Supported by NIH grants HL53994 and HL64691.

PI-31

GENOTYPE FREQUENCIES FOR TEN POLYMORPHISMS OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM BETWEEN HEALTHY FRENCH-CANADIANS AND OTHER ETHNIC GROUPS. M. Zakrzewski-Jakubiak, MSc, S. de Denus, MSc, M. Dubé, PhD, F. Bélanger, MSc, M. White, MD, J. Turgeon, PhD, University of Montreal, Institut de Cardiologie de Montreal, Montreal, PQ, Canada.

BACKGROUND/AIMS: Differences exist in frequencies of certain genotypes within different populations. We analysed the polymorphism frequency of ten polymorphisms of the RAAS in our population and compared them to other ethnic groups.

METHODS: This is an observational study performed on 18 to 25 years old 200 healthy males of French-Canadian origin. The Gen Elute Blood Genomic DNA kit (Sigma PC# NA2020) was used to extract DNA. The studied polymorphisms were: ACE I/D, ATR1 A1166C, AGT M235T, AGT T174M, CYP11B2 T-344C, α-adducin G460W, beta-2 adrenergic receptor Q27E, bradykinin β2R +9/-9, eNOS T-786C and eNOS E298D. They were analysed by the standard PCR/enzymatic digestion/electrophoresis method.

RESULTS: All polymorphisms tested were in Hardy-Weinberg equilibrium. When compared to other ethnic groups, our population's genotype frequencies differed from the Asian and the African-American populations with respect to every polymorphism, except for the bradykinin β2R gene (data was unavailable) and differed from the African population with respect to the polymorphism of ACE, AGT235, AGT174 and CYP11B2. When compared with other Caucasian populations, we obtained different genotype frequencies for the ATR1, AGT235, beta-2 adrenergic receptor, eNOS-786 and eNOS298 genes.

CONCLUSION: Our study depicts the genetic profile of ten polymorphisms of the RAAS in French-Canadian healthy man. We noted differences in that profile when compared to Africans, African-Americans, Asians and other Caucasians.

PI-32

THE EFFECTS OF FOLATE SUPPLEMENTATION ON HUMAN CYP2C9 TRANSACTIVATION. H. G. Xie, MD, PhD, M. Muszkat, MD, C. M. Stein, MD, R. B. Kim, MD, Vanderbilt University School of Medicine, Hadassah University Hospital, Nashville, TN.

BACKGROUND/AIMS: Folic acid (FA) supplementation can increase the metabolism of phenytoin and warfarin, both of which are CYP2C9 substrates, but the mechanisms underlying this are unknown. This study examined the hypothesis that FA affects transactivation of a defined core promoter in human *CYP2C9* gene, in which CAR, PXR, HNF1α, and HNF4α binding sites exist.

METHODS: *CYP2C9*-luciferase reporter constructs (-3kb) were transfected into HepG2 cells, and human CAR, PXR, HNF1α, and HNF4α were co-transfected either alone or in combination. The transfected cells were treated with or without FA (100μM), and the cells co-transfected with PXR were simultaneously treated with rifampin (Rif, 10μM), followed by dual luciferase assays. Data were expressed as fold activation versus vector control.

RESULTS: Compared with each of the vehicle controls, FA treatment did not significantly affect luciferase activities (FA vs DMSO: 1.9 ± 0.6 vs 1.8 ± 0.6 for CAR; 12.9 ± 4.2 vs 12.5 ± 3.8 for CAR + HNF1α; 14.9 ± 7.8 vs 15.4 ± 9.3 for CAR + HNF4α; 1.3 ± 0.3 vs 1.3 ± 0.4 for PXR/Rif; 9.4 ± 2.8 vs 8.9 ± 2.6 for PXR/Rif + HNF1α; 3.1 ± 1.5 vs 3.1 ± 1.8 for PXR/Rif + HNF4α; all $P > 0.05$, $n = 6$ each).

CONCLUSIONS: In transfected HepG2 cells, acute administration of folic acid has no effect on *CYP2C9* transcriptional activity, regardless of co-transfection with CAR, PXR, HNF1α, and HNF4α, alone or in combination. The effect of folic acid on the metabolism of CYP2C9 substrates is not mediated by alteration of transcription by key nuclear receptors.