PII-19

KCNMB1 GENOTYPE ASSOCIATED WITH CARDIOVASCULAR OUTCOMES IN THE INTERNATIONAL VERAPAMIL SR/TRANDOLAPRIL STUDY (INVEST). A. L. Beitelshees, PharmD, MPH, Y. Gong, PhD, R. M. Cooper-DeHoff, PharmD, L. Burt, L. A. Stauffer, BS, C. J. Pepine, MD, J. A. Johnson, PharmD, University of Florida, Gainesville, FL.

BACKGROUND: Glu65Lys in *KCNMB1* has been found to have functional and clinical significance. We tested whether Glu65Lys or Val110Leu were associated with cardiovascular (CV) outcomes (death, nonfatal myocardial infarction (MI) or nonfatal stroke) in a substudy of INVEST.

METHODS: INVEST studied patients with HTN and CAD randomized to verapamil SR- or atenolol-based treatment strategies. Codons 65 and 110 were genotyped in 271 cases and 813 age, sex, and race-matched controls from the genetic cohort. Age, sex, BMI, baseline BP, race, ACE inhibitor use, diuretic use, previous MI or stroke, history of heart failure (HF) or diabetes (DM), genotype (Lys 65 or Leu 110 carrier status), treatment strategy, and interaction between strategy and genotype were included in logistic regression analysis.

RESULTS: Odds ratios for all significant parameters are shown in the table. Lower BMI, history of DM or HF, and higher SBP at baseline were all associated with an increased risk of CV outcome. ACE inhibitor and diuretic use were associated with a decreased risk. Individuals with the Val110Val genotype had an increased risk of CV outcome compared to Leu110 carriers. The interaction between treatment and genotype was not significant.

Variable	Odds Ratio	95% Confidence Interval
Val110Val	1.585	1.021-2.461
ACE use	0.537	0.38-0.756
Diuretic use	0.573	0.416-0.810
SBP (per 1 mm Hg)	1.014	1.006-1.021
BMI (per 1 kg/m^2)	0.936	0.907-0.965
DM	2.03	1.46-2.80
HF	2.57	1.46-4.55

CONCLUSIONS: These data suggest that in addition to traditional risk factors, the Val110Val genotype may be associated with an increased risk of death, nonfatal MI or stroke. This genetic effect was not influenced by treatment strategy, and Glu65Leu did not influence outcomes.

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PII-20

IRINOTECAN (CPT-11) RELATED DIARRHEA: FUNCTIONAL SIGNIFICANCE OF THE POLYMORPHIC ABCC2 TRANSPORTER PROTEIN. F. A. de Jong, T. Scott-Horton, D. L. Kroetz, H. L. McLeod, L. E. Friberg, R. H. Mathijssen, J. Verweij, A. Sparreboom, S. Marsh, Erasmus MC - Daniel den Hoed Cancer Center, Washington University School of Medicine, University of California, Uppsala University, National Cancer Institute, Rotterdam, The Netherlands.

BACKGROUND: PK variability of the anticancer agent CPT-11 is high. Life-threatening grade 3-4 diarrhea is seen in up to 25% of patients and has been related with CPT-11 PK and UGT1A1-status. Aim of this study was to evaluate the association of *ABCC2* polymorphisms and haplotypes with CPT-11 disposition and diarrhea.

METHODS: 105 European Caucasian cancer patients who were previously assessed for CPT-11 PK (90-min infusion; three-weekly), toxicity and *UGT1A1*∗*28*, were genotyped for *ABCC2* using Pyrosequencing (table 1).

RESULTS: Frequencies of wild type alleles and haplotypes (13 identified in 85 patients) are given in table 1. *ABCC2*∗*1* was associated with slower CPT-11 clearance (28.4 *vs* 33.9 L/h; P=.005). In 67 patients who received the recommended single agent dose (350 mg/m^2 or 600 mg), *ABCC2*∗*1* was negatively correlated with grade 3-4 diarrhea (P=.040). A 3-fold reduced risk (30% *vs* 10%) was unrelated to *UGT1A1*∗*28* since severe diarrhea manifested itself in particular in patients homozygous for the *UGT1A1*∗*1* allele (P=.011).

CONCLUSIONS: This study suggests that the *ABCC2*∗*1* haplotype is associated with CPT-11 related diarrhea, maybe as a consequence of altered CPT-11 excretion via the bile into the gut, and hence less local activation into the active metabolite, SN-38. As its protective effect on diarrhea is seen predominantly in patients not at risk for diarrhea due to *UGT1A1*∗*28*, additional studies of the relationships of *ABCC2* genotypes to CPT-11 PK and toxicity are warranted.

Frequencies wild type alleles (p) of 6 ABCC2 polymorphisms, and constructed haplotypes (%; N=85).

polymorphism	p	haplotype	%
−1549G>A	0.60	**GGCGTC (*ABCC2∗1*)**	35
−1019A>G	0.45	**GGCATC**	19
−24C>T	0.84	**AATGTT**	15
1249G>A	0.79	**AACGTT**	12
IVS26 −34T>C	0.96	**AACGTC**	8
3972C>T	0.67	**AACGCC**	5