# OLYMORPHISMS OF THE ABCB1 GENE PREDICT DRUG RESISTANCE IN EPILEPTIC PATIENTS

Lastella Marianna*, Danesi Romano*, Cascio Elisa*, Jensen Stella[§] , Iudice Alfonso[§], Murri Luigi[§] , Del Tacca Mario*, Di Paolo Antonello*

*Division of Pharmacology and Chemotherapy, Department of Internal Medicine;
[§]Division of Neurology, Department of Neurosciences - University of Pisa

**Background.** ABCB1, coded by the Mdr1 gene, is a member of the ABC (ATP-binding cassette) transporter superfamily. It reduces cytoplasmic drug accumulation as a result of transmembrane drug transport (1). Preliminary reports documented that high or low expression of Mdr1 gene is associated with the C or T allele at position 3435 of exon 26, respectively (2). Two additional single nucleotide polymorphisms (SNPs) (G2677 T/A in exon 21 and C1236T in exon 12) are in linkage disequilibrium with C3435T. **Aim.** To evaluate the correlation among C3435T, G2677T and C1236T SNPs and the efficacy of antiepileptic drugs (AEDs) in patients affected by partial epilepsy. **Patients and Methods.** Genomic DNA, obtained from blood samples of 70 patients, was analysed for C3435T and G2677T polymorphisms by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay, and for C1236T SNP by the TaqMan probe-based 5' nuclease assay. Plasma levels of all AEDs were determined by high performance liquid chromatography. **Results.** Frequencies of CC, CT and TT genotype for C3435T in exon 26 and C1236T in exon 12 were 25.5%, 62.7% and 11.8%, and 37.2%, 51% and 11.8%, respectively. In the case of G2677T SNP, GG, GT and TT genotypes displayed a frequency of 43.1%, 41.2% and 15.7%, respectively. The analysis of ABCB1 haplotypes based on exons 12 and 26 revealed that the AED resistant phenotype was related to the CC3435 and to the CC or CT1236 genotypes, whereas all other haplotypes were associated with drug responsiveness. Moreover, in all patients, plasma levels of AEDs were within the therapeutic range, suggesting that ABCB1 genotype influences drug distribution from plasma to central nervous system, rather than intestinal absorption or kidney excretion. **Conclusions.** ABCB1 haplotypes are associated with clinical response to AEDs in patients affected by partial epilepsy. Genotyping for ABCB1 SNPs may support the identification of individuals at risk for drug resistance and it should become a reliable assay in clinical settings.

1. Shinkel A.H. (1999) Advanced Drug Deliv. Rev. 36: 179-194.
2. Sisodiya S.M., Lin W.R., Harding B.N., Squier M.V. and Thom M. (2002) Brain. 125: 22-31.