Exploring the relationship between genotypes and liver protein expression of *CYP2C9, CYP2C19, CYP2D6,* and *CYP3A5* using postmortem tissue

Jornil J.R.[1*], Pedersen K.W.[2], Hansen J.[2] & Hasselstrøm J.B.[2]

1 jjor@forens.au.dk, Institute of Forensic Medicine, Aarhus University, Denmark

2 Institute of Forensic Medicine, Aarhus University, Denmark

Abstract

The cytochrome P450 (CYP) enzymes are important for the elimination of a large range of drugs. Many of these CYP enzymes are polymorphic; however, due to limited access to hepatic tissue the correlation between genotype and CYP protein expression is poorly understood for less frequent *CYP* genotypes.

In this study, we determined the *CYP2C9, CYP2C19, CYP2D6,* and *CYP3A5* genotypes of 250 Danish individuals included in a postmortem study. For 116 of the individuals the hepatic CYP protein levels were investigated by a proteomics approach.

For the less investigated genotypes we found 1) statistically significantly lower levels of hepatic CYP2C9 in individuals carrying the *CYP2C9**3 variant compared to individuals with two wild types (wt) alleles, 2) comparable levels of CYP2C19 in *CYP2C19*2/*17* and *CYP2C19*1/*2* individuals, and 3) significantly lower levels of CYP3A5 protein in *CYP3A5**3 homozygous individuals compared to individuals with one or two wt alleles.

Individuals with two active CYP2D6 alleles had on average the double amount of hepatic CYP2D6 compared to individuals with one active allele, confirming the idea that the number of active alleles is a major determinant of hepatic CYP2D6 levels. However, there was a 20-fold variation in CYP2D6-levels within a certain genotype group, and a large overlap in CYP2D6 levels between genotype groups. Therefore, conclusions about genotype and activity of a certain genotype must be taken with caution.

In conclusion, we found the genotyping / postmortem proteomics data to agree with those of other studies performed on fresh hepatic tissue. The use of postmortem material significantly increases the access to human specimens for research purposes, and postmortem proteomics can be used to investigate the link between *CYP* genotypes and hepatic protein expression. It is a novel approach to use a large postmortem cohort to investigate genetic / protein expression correlations.