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Interindividual variability of hepatic membrane transporters and its impact on precision medicine

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Precision medicine aims to identify factors that contribute to the interindividual variability in drug response. Drug effects essentially depend on the processes of absorption, distribution, metabolism and excretion of therapeutic compounds. It has been well established that hepatic membrane transporters are important determinants of the biliary elimination of endogenous compounds and various drugs. Examples of endogenous compounds are bile salts and bilirubin glucuronides whereas examples of drugs include the cholesterol-lowering statins and the anti-diabetic agent metformin. Several membrane transporters have been identified that mediate the sinusoidal uptake of these and other compounds into the hepatocytes (e.g. SLC10A1, SLCO1B1, SLCO1B3, SLCO2B1, SLC22A1, SLC22A7, SLC22A9) and the elimination of these or their metabolites across the canalicular membrane into bile (e.g. ABCB1, ABCC2, ABCG2). Functional genetic variants e.g. in SLCO1B1 have been identified to be associated with simvastatin-induced myopathy.

Interindividual variability in expression of hepatic membrane transporters may affect response to drugs or predispose to the development of hepatic disorders such as acquired forms of intrahepatic cholestasis. We therefore investigated genetic variants and expression of hepatic transporters in a large normal liver tissue bank by next-generation sequencing, comprehensive transcriptome analysis and proteomics analysis. We demonstrated a considerable interindividual variety of protein expression for each transport protein in normal human liver. Moreover, absolute protein levels were much higher for the sinusoidal uptake transporters compared with the canalicular transporters. Several genetic variants were identified that affected protein expression of some transporters. In conclusion, variable membrane transporter expression may impair the hepatic elimination and response to a variety of drugs that depend on transporter-mediated biliary elimination.

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