Hepatic Expression of the Na+-Taurocholate Cotransporting Polypeptide Is Independent from Genetic Variation

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Abstract

The hepatic Na+-taurocholate cotransporting polypeptide NTCP/SLC10A1 is important for the uptake of bile salts and selected drugs. Its inhibition results in increased systemic bile salt concentrations. NTCP is also the entry receptor for the hepatitis B/D virus. We investigated interindividual hepatic SLC10A1/NTCP expression using various omics technologies. SLC10A1/NTCP mRNA expression/protein abundance was quantified in well-characterized 143 human livers by real-time PCR and LC-MS/MS-based targeted proteomics. Genome-wide SNP arrays and SLC10A1 next-generation sequencing were used for genomic analyses. SLC10A1 DNA methylation was assessed through MALDI-TOF MS. Transcriptomics and untargeted metabolomics (UHPLC-Q-TOF-MS) were correlated to identify NTCP-related metabolic pathways. SLC10A1 mRNA and NTCP protein levels varied 44-fold and 10.4-fold, respectively. Non-genetic factors (e.g., smoking, alcohol consumption) influenced significantly NTCP expression. Genetic variants in SLC10A1 or other genes do not explain expression variability which was validated in livers (n = 50) from The Cancer Genome Atlas. The identified two missense SLC10A1 variants did not impair transport function in transfectants. Specific CpG sites in SLC10A1 as well as single metabolic alterations and pathways (e.g., peroxisomal and bile acid synthesis) were significantly associated with expression. Inter-individual variability of NTCP expression is multifactorial with the contribution of clinical factors, DNA methylation, transcriptional regulation as well as hepatic metabolism, but not genetic variation.