Summary (English)
Recent progress in understanding the molecular mechanism of hepatobiliary disorders enabled the improvement of diagnostic accuracy and promoted the study of the regulation of gene expression and its potential modifying factors.
Current achievement in the field of genetically determined cholestatic disorders is well illustrated in this thesis, focused on low gamma-glutamyltransferase (γGT) cholestasis and hereditary jaundice. The study describes several distinct defects of hepatocyte transport system, characterises underlying mutations and their phenotypic consequences and, finally, extends these studies for detailed characterisation of *ATP8B1* gene regulatory regions.
Chapters related to low γGT cholestasis
- characterise rare type of mutation associated with benign course of PFIC type I (formerly BRIC1) and explain the putative mechanisms of mutation origin.
- provide extensive study of severe forms of *ABCB11* deficiency (PFIC2) including genotype-phenotype correlations in 109 affected families, evaluation of the specific *ABCB11* genotypes' impact on BSEP immunostaining and risk of hepatobiliary malignancy.
- identify and characterise yet unknown regulatory regions of *ATP8B1*, a gene mutated in Progressive Familial Intrahepatic Cholestasis type I. The studies demonstrate the complex structure of *ATP8B1* gene, identify novel untranslated exons and three independent promoter regions and provide a functional study of main *ATP8B1* promoter.
Chapters related to hereditary jaundice
- describe novel type of mixed, predominantly unconjugated hyperbilirubinemia that was proved on molecular level as digenic disorder caused by mutations in *ABCC2* and *UGT1A1* genes. The importance of the genetic analysis is illustrated in this case by misleading clinical presentation in the patient, who was at first reported as Dubin-Johnson syndrome, despite the lack of typical DJS liver pigmentation and predominantly unconjugated type of jaundice.
- hypothesise the role of *ABCC2*, the gene mutated in Dubin-Johnson syndrome, in another hereditary conjugated jaundice: Rotor syndrome. Present study demonstrates for the first time intact expression of ABCC2/MRP2 protein in hepatocytes of Rotor syndrome patients and on the genetic level excludes defects of *ABCC2* gene.