Abstract

Autosomal recessive polycystic kidney disease (ARPKD) is a rare severe inherited disease manifested by cystic renal disease, congenital hepatic fibrosis and dilatatation of bile ducts. The spectrum of clinical manifestations is very wide and variable, depends on the age at which the disease was manifested. In severe forms of the disease, it is possible to detect the first symptoms prenatally around the 20th week of pregnancy due to increased echogenic kidneys and the presence of oligohydramnios. The causal gene of this disease is the*PKHD1* gene with protein product fibrocystin that is most likely contributing on maintaining the intracellular concentration of Ca^{2+} cations. The exact phatophysiology mechanism of ARPKD remains unknown. Phenotypic manifestations of this disease may overlap with mutations associated with other genes. One of the genes mimicking the ARPKD phenotype is the *HNF1B* gene. Mutations associated with HNF1B gene are the most common monogenic cause of developmental kidney abnormalities. HNF1B is a tissue-specific transcription factor that regulates the expression of *PKHD1*.

In experimental part I worked on genetic analysis of the *HNF1B* gene in 28 patients who have not been confirmed ARPKD diagnosis by detection of 2 *PKHD1* mutations. For the purposes of mutational screening, I used direct Sanger sequencing, NGS pyrosequencing techniques, and MLPA method to detect extensive deletions or duplications. In analysied patient cohort I identified five nonsense / missense mutations, one allelic deletion of the entire gene and one known polymorphism. I have identified three previously unpublished potentially pathogenic mutations.

The aim of this work was to introduce and optimize genetic analysis of *HNF1B*: Based on observations of genotypic-phenotypic correlation, *HNF1B* screening could be used for prenatal diagnosed hyperechogenic cystic kidneys.

Key words:
autosomal recessive polycystic kidney disease, *HNF1B, PKHD1*, transcriptional complexity in ARPKD, genotype-phenotype correlation, mutation screening, next generation sequencing, multiplex ligation-dependent probe amplification (MLPA)