Cystic kidney diseases and syndromic ciliopathies

Cystic kidney diseases encompass a clinically and genetically heterogeneous group of diseases characterized by progressive cyst development associated with decline of kidney function. Autosomal dominant polycystic kidney disease (ADPKD) occurs with a prevalence of 1:1,000 and is therefore considered as one of the most common inherited diseases. In about 80% of patients a mutation of the *PKD1* gene on chromosome 16p13 can be detected. About 20% of affected harbor a mutation of the *PKD2* gene on chromosome 4q21. Clinical manifestation is usually in adulthood but up to 2-5% of patients have medically actionable signs already in childhood. In rare cases severe prenatal manifestations with bilaterally enlarged polycystic kidneys and oligohydramnios with high perinatal mortality can occur. For early onset ADPKD patients autosomal recessive polycystic kidney disease (ARPKD) has to be considered as the most important differential diagnosis. ARPKD is caused by mutations in the large *PKHD1* gene (66 exons) on chromosome 6p12. Our research group focusses on the genetics of ARPKD and early manifestations of ADPKD. We established a locus specific PKHD1 mutation database (www.humgen.rwth-aachen.de) in order to catalogue and validate changes of the *PKHD1* gene and to provide this information to the scientific community, clinicians and patients. In this context we arranged a collaboration with the international ARPKD patient register ARegPKD (https://www.aregpkd.org/).

Almost all cystoproteins including the gene products of *PKHD1*, *PKD1* and *PKD2* colocalize at the primary cilium or associated structures as the basal body. Primary – non motile – cilia are found on almost all cell types. Several functions of these organelles have been described to date e.g. a mechano-, osmo-, and chemo-sensory function. Furthermore they are involved in many signalling pathways as the sonic hedgehog or Wnt pathway and are therefore crucial e.g. for organ development and tissue homeostasis. Diseases impairing ciliary function are consequently denoted as primary ciliopathies.

Based on the knowledge of the great genetic, phenotypic and pathogenetic overlap between the ciliopathies we extended our scientific and diagnostic focus towards the genetics of the syndromic ciliopathies Meckel syndrome (MKS), Joubert syndrome and related disorders (JS/JSRD), Bardet-Biedl syndrome (BBS) and nephronophthisis (NPHP). Besides renal cysts, biliary dysgenesis with congenital liver fibrosis, retinal dystrophy, neural tube defects and other CNS anomalies, skeletal anomalies, and cognitive impairment are shared findings among the ciliopathies. The syndromic ciliopathies are genetically highly heterogeneous with more than 50 genes known and many more to be identified. Better knowledge of the underlying pathomechanisms contributes to our understanding of cyst development in different organs. Further research is directed towards the complex genetic mechanisms of syndromic ciliopathies which are characterized by frequent multiple allelism, oligogenic inheritance and mutational load.

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