New Insights into ARPKD

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Autosomal recessive polycystic kidney disease is a significant cause of pediatric morbidity and mortality with an estimated incidence of 1 in 20,000 live births. The clinical spectrum is widely variable: approximately 30% of affected neonates die shortly after birth, whereas others survive into adulthood. In affected neonates, the kidneys are symmetrically enlarged and cysts appear as fusiform dilations of collecting ducts extending radially from the renal pelvis to the cortex. Congenital hepatic fibrosis, characterized by increased numbers of interlobular bile ducts and varying degrees of portal fibrosis, is an invariant finding.

Mutations of a single gene on chromosome 6, *PKHD1*, cause all typical forms of the disease in humans. The gene is ~470 kb in length and undergoes a complicated pattern of splicing to produce a complex set of transcripts. A >12 kb mRNA that is comprised of 67 exons encodes the longest open reading frame. The gene is most abundantly expressed in the kidney, though it is expressed in numerous other tissues at a low level. Almost 300 unique mutations have been described, and they have been identified in most of the 67 exons. Genotype-phenotype analyses suggest that the nature of the germline mutations plays an important role in determining clinical outcome. Missense substitutions are more commonly associated with non-lethal presentations whereas chain-terminating mutations are more commonly associated with neonatal death. Individuals with two truncating changes universally do not survive beyond the neonatal period.

The expected gene product is a novel 4074 aa single-membrane spanning protein (fibrocystin/polyductin, referred to as PD1) that has a lengthy extracellular N-terminal domain made up of multiple TIG/IPT and PbH1 repeats and a short cytoplasmic C-terminus. It is predicted to function either as a receptor, a ligand or possibly both, though there is no direct evidence for either. Multiple studies have recently shown that PD1 localizes to the primary cilium. Recent studies by our group have shown that the protein undergoes a complicated pattern of post-translational Notch-like processing that includes shedding of the extracellular domain from the primary cilium and translocation of the intracellular C-terminus to the nucleus upon cellular activation. This is the first known example of this process involving a protein of the primary cilium and suggests a novel mechanism whereby proteins that localize to this structure may function as bi-directional signaling molecules. Regulated release from the primary cilium into the lumen also may be a mechanism to distribute signal to down-stream targets using flow.

To study the pathobiology of this disease, we generated a mouse line with a floxed allele of *Pkhd1*. Cre-mediated excision of exons 3-4 results in a probable hypomorphic allele. $Pkhd1^{del3-4/del3-4}$ developed a range of phenotypes that recapitulate key features of the human disease. Like in humans, abnormalities of the biliary tract were an invariant finding. Most mice 6 months or older also developed renal cysts. Subsets of animals presented with either perinatal respiratory failure or exhibited growth retardation that was not due to the renal disease. We then tested for genetic interaction between *Pkhd1* and *Pkd1*, the mouse orthologue of the gene most commonly linked to human autosomal dominant polycystic kidney disease. $Pkd1^{+/-;Pkhd1del3-4/del3-4}$ mice had markedly more severe disease than $Pkd1^{+/+;Pkhd1del3-4/del3-4}$ littermates. These studies are the first to show genetic interaction between the major loci responsible for human renal cystic disease in a common polycystic kidney disease pathway.