

Polycystic kidney disease (PKD), comprising autosomal dominant polycystic kidney disease (ADPKD) and autosomal recessive polycystic kidney disease (ARPKD), is characterized by incessant cyst formation in the kidney and liver. ADPKD and ARPKD represent the leading genetic causes of renal disease in adults and children, respectively. ADPKD is caused by mutations in PKD1 encoding polycystin1 (PC1) and PKD2 encoding polycystin 2 (PC2). PC1/2 are multi-pass transmembrane proteins that form a complex localized in the primary cilium. Predominant ARPKD cases are caused by mutations in polycystic kidney and hepatic disease 1 (PKHD1) gene that encodes the Fibrocystin/Polyductin (FPC) protein, whereas a small subset of cases are caused by mutations in DAZ interacting zinc finger protein 1 like (DZIP1L) gene. FPC is a type I transmembrane protein, localizing to the cilium and basal body, in addition to other compartments, and DZIP1L encodes a transition zone/basal body protein. Apparently, PC1/2 and FPC are signaling molecules, while the mechanism that cilia employ to govern renal tubule morphology and prevent cyst formation is unclear. Nonetheless, recent genetic and biochemical studies offer a glimpse of putative physiological malfunctions and the pathomechanisms underlying both disease entities. In this review, I summarize the results of genetic studies that deduced the function of PC1/2 on cilia and of cilia themselves in cyst formation in ADPKD, and I discuss studies regarding regulation of polycystin biogenesis and cilia trafficking. I also summarize the synergistic genetic interactions between Pkd1 and Pkhd1, and the unique tissue patterning event controlled by FPC, but not PC1. Interestingly, while DZIP1L mutations generate compromised PC1/2 cilia expression, FPC deficiency does not affect PC1/2 biogenesis and ciliary localization, indicating that divergent mechanisms could lead to cyst formation in ARPKD. I conclude by outlining promising areas for future PKD research and highlight rationales for potential therapeutic interventions for PKD treatment.