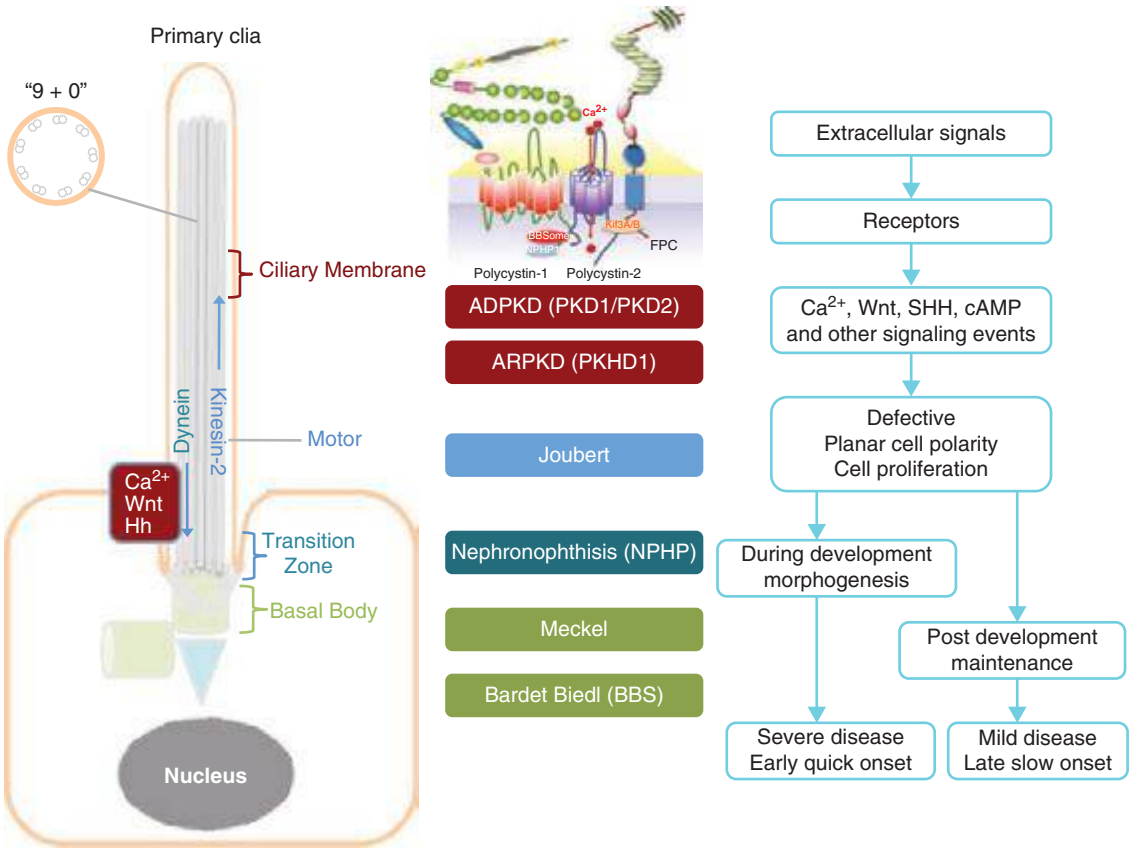

FIGURE 339-1 **Scheme of the primary cilium and cystic kidney disease proteins.** ***Left.*** A scheme of the primary cilium. Primary cilia share a "9+0" organization of microtubule doublets. Proteins are transported into the cilium by motor protein kinesin 2 and transported out of the cilium by dynein. The cilium is connected to the basal body through the transition zone. ***Middle.*** Topology of autosomal dominant polycystic kidney disease (ADPKD) and autosomal recessive polycystic kidney disease (ARPKD) proteins polycystin-1, polycystin-2, and fibrocystin/polyductin (FPC) are shown. PC1 also interacts with other proteins such as components of the BBSome and NPHP1. PC2 and FPC both interact with kinesin 2 (KIF 3A/B). Localization of disease proteins in the cilium, the transition zone, and the basal body is color coded. ***Right.*** Potential disease mechanisms due to cilium-mediated signaling events.

that loss of ciliary function of PC1 and PC2 leads to reduced calcium signaling and a subsequent increase of adenylyl cyclase activity and decrease of phosphodiesterase activity, which, in turn, causes increased cellular cyclic AMP (cAMP). Increased cAMP promotes protein kinase A activity, among other effectors, and, in turn, leads to cyst growth by promoting proliferation and fluid secretion of cyst-lining cells through chloride and aquaporin channels in ADPKD kidneys.

Genetic Considerations ADPKD is inherited as an autosomal dominant trait with complete penetrance but variable expressivity. The disease affects all ethnic groups worldwide with an estimated prevalence of 1:1000 to 1:400. Only half of the patients with ADPKD are clinically diagnosed during their lifetime. ADPKD is genetically heterogeneous. The first disease gene (*PKD1*) was localized to the region of the α-globin gene on chromosome 16p13 in 1985, and a second disease gene (*PKD2*) locus was mapped to chromosome 4q21-q23 in 1993. Mutations of *PKD1* and *PKD2* are responsible for ~85% and ~15% of ADPKD cases, respectively. However, patients with *PKD2* mutations may be higher than 15% because they tend to have milder clinical disease and, as a result, may be underdiagnosed. Embryonic lethality of *Pkd1* and *Pkd2* knockout mice suggests that human homozygotes may be lethal and thus not clinically recognized.

PKD1 is comprised of 46 exons occupying ~52 kb of genomic DNA. It produces an ~14-kb transcript that encodes PC1, a protein of ~4300 amino acids. A feature of the *PKD1* gene is that the 5′ three-quarters of *PKD1* have been duplicated at six other sites on chromosome 16p, and many of them produce mRNA transcripts, which provides a major challenge for genetic analysis of the duplicated region. *PKD2* is a single-copy gene with 15 exons producing an ~5.3-kb mRNA transcript that encodes PC2, a protein of 968 amino acids. The presence of additional genes for ADPKD was suggested based on several families linked to neither *PKD1* nor *PKD2* genes. However, careful analyses have excluded the existence of a third ADPKD gene.

In ADPKD patients, every cell carries a germline mutant allele of either *PKD1* or *PKD2*. However, cysts develop in only a small fraction of the nephrons. Cysts are thought to originate from clonal growth of single cells that have received a somatic "second hit" mutation in the "normal" allele of the *PKD1* or *PKD2* gene. Accumulating evidence in mouse models now shows that partial loss of function of the second allele of *Pkd1* in a proliferative environment is sufficient for cystogenesis, suggesting that a critical amount of *PKD1* is needed in a cell. Somatic inactivation of the second allele of *Pkd1* in adult mice results in very slow onset of cyst development in the kidney, but a "third hit," such as an additional genetic or epigenetic event, the inactivation of a growth-suppressor gene, the activation of a growth-promoting gene(s), or an event like renal injury that activates the developmental program, may promote rapid cyst formation.

Clinical Manifestations ADPKD is characterized by the progressive bilateral formation of renal cysts. Focal renal cysts are typically detected in affected subjects before 30 years of age. Hundreds to thousands of cysts are usually present in the kidneys of most patients in the fifth decade (Fig. 339-2). Enlarged kidneys can each reach a fourfold increase in length and weigh up to 20 times the normal weight. The clinical presentations of ADPKD are highly variable. Although many patients are asymptomatic until the fourth to fifth decade of life and are diagnosed by incidental discoveries of hypertension or abdominal masses, back or flank pain is a frequent symptom in ~60% of patients with ADPKD. The pain may result from renal cyst infection, hemorrhage, or nephrolithiasis. Gross hematuria resulting from cyst rupture occurs in ~40% of patients during the course of their disease, and many of them will have recurrent episodes. Flank pain and hematuria