SIGNIFICANCE STATEMENT

Autosomal dominant polycystic kidney disease (ADPKD) is a ciliopathy caused by mutations in *PKD1* and *PKD2*, characterized by renal epithelial cell proliferation and progressive CKD. Among the genetic mechanisms proposed for cystogenesis are inactivating constitutional and somatic mutations in *PKD1/2* genes, and *PKD1/2* gene dosage effects. This article describes the identification, by genomic sequencing methods, of the high prevalence of inactivating somatic mutations in *PKD1/2* and non-*PKD1/2* genes in epithelial cells obtained from kidney cysts in patients with ADPKD. The findings support a primary cellular recessive mechanism for cyst formation in ADPKD caused by mutations in these genes in the renal epithelium. Potential interactions of *PKD1/2* genes with other ciliopathy- and cancer-related genes that might influence ADPKD severity is proposed.