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POLYCYSTIC KIDNEY DISEASE

FPC in ARPKD

Although mutations in *PKHD1* are known to cause autosomal recessive polycystic kidney disease (ARPKD), very little is known about the function of its gene product, fibrocystin/polyductin (FPC). Recent research using a novel mouse model to enable tracking of full-length FPC and its cleaved C-terminus has provided new insights into the processing of FPC and raised questions about its function. "We confirmed that cleavage products are present in kidney tissue, providing the first evidence that Notch-like processing occurs *in vivo*," say researchers Gregory Germino and Terry Watnick. "We were, however, not able to co-precipitate polycystin-2 (PC2) with FPC and surprisingly found that deletion of the PC2-binding domain had no obvious pathologic effect in mice."

> Deletion of the PC2-binding domain had no obvious pathologic effect

In vitro studies had suggested that FPC undergoes proteolytic cleavage. However, a lack of validated antibodies precluded verification of these findings *in vivo*. To assess the processing and function of the FPC C-terminus *in vivo*, Watnick and Germino introduced a haemagglutinin (HA)-epitope tag into the C-terminus of FPC as well as LoxP sites flanking exon 67 to enable cre-recombinase-mediated deletion of most of the C-terminus of FPC, which contains a PC2-binding domain and a nuclear localization signal. Examination of HA-tagged products revealed the presence of FPC cleavage products in kidneys, urine and urinary exosome-like vesicles. However, the researchers could not identify interaction between FPC and PC2, and mice lacking exon 67 were normal. "These observations suggest that an FPC–PC2 interaction, if it occurs *in vivo*, is not essential for the function of either gene," note the researchers. "Remarkably, this is the first rodent model where manipulation of *Pkhd1* has not resulted in liver disease."

The FPC PC2-binding domain and nuclear localization signal are evolutionarily conserved, suggesting they may be functionally important under certain conditions. "*Pkhd1* may have redundant but important functional properties that might be unmasked by environmental or genetic stresses," says Watnick. "What if any factors can elicit a phenotype in our knockout mouse remain to be determined."

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ORIGINAL ARTICLE Outeda, P. *et al.* A novel model of autosomal recessive polycystic kidney questions the role of the fibrocystin C-terminus in disease mechanism. *Kidney Int.* http://dx.doi.org/10.1016/j.kint.2017.04.027 (2017)