Study results challenge current thinking about autosomal dominant polycystic kidney disease

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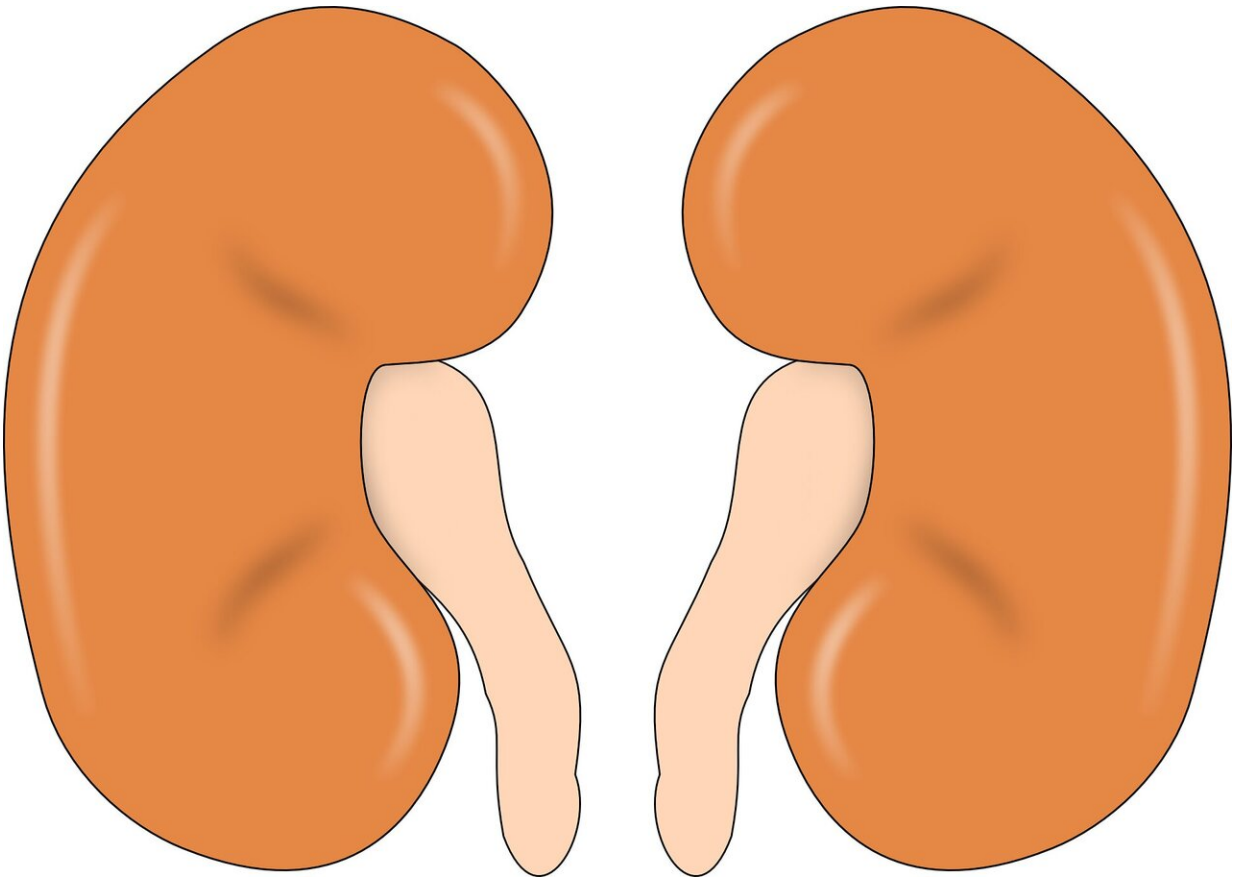

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Autosomal dominant polycystic kidney disease (ADPKD) is a common

genetic condition that can lead to kidney failure and that has no cure. Recent research published in *JASN* uncovers an over-looked mechanism that likely contributes to this condition. The findings provide a better understanding of ADPKD and may lead to new strategies to treat it.

Mutations in the *PKD1* gene, which codes for polycystin-1 (PC1), or the *PKD2* gene, which codes for polycystin-2 (PC2), cause most cases of ADPKD. The PC1 and PC2 proteins function as receptor-channel complexes for calcium and other ions, and they're found in cell structures called primary cilia. Primary cilia are tiny, fingerlike projections that line the small tubes where urine is formed.

Loss of PC1 and PC2 in cilia is believed central to the pathogenesis of cyst formation that's a hallmark of ADPKD. PC1 and PC2 can be expressed in other locations, however, and it's unclear if these forms of the proteins are also important for preventing ADPKD.

To investigate, Chou-Long Huang, MD, Ph.D. (University of Iowa Carver College of Medicine) and his colleagues examined the role of PC2 in the endoplasmic reticulum (ER), a structure within cells that's involved in protein and lipid synthesis. The team found that PC2 in the ER is important for maintaining kidney health and that its loss can lead to cyst formation.

ER-localized PC2 blocks cysts presumably by functioning as a potassium channel to facilitate the exchange of potassium and calcium. When the researchers bred mice to lack PC2, the animals developed cysts, but this could be reversed by breeding the PC2-lacking mice to express a different potassium channel called TricB in the ER.

"Current dogma of ADPKD is that it is a disease in which defects primarily originate in the cilia. We demonstrate that defects in the ER perhaps play a more important role," said Dr. Huang. "Furthermore, the

function of PC2 in the ER is to regulate potassium movement to affect calcium balance indirectly." In addition to providing these insights, the research suggests that activating TricB may be a promising treatment strategy for ADPKD.

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More information: Channel Function of Polycystin-2 in Endoplasmic Reticulum Protects Against Polycystic Kidney Disease, *Journal of the American Society of Nephrology* (2022). DOI: 10.1681/ASN.2022010053

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