Mechanisms in the kidney that control magnesium and calcium levels discovered

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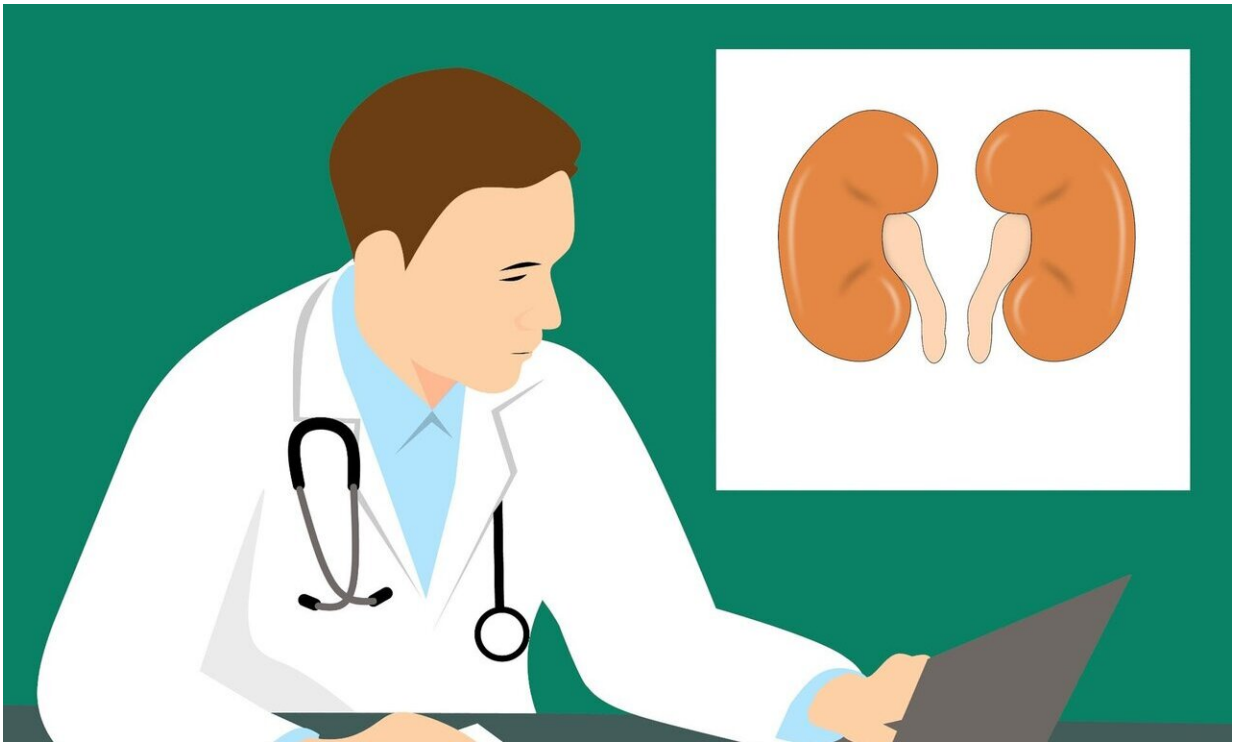

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While investigating the underlying causes of a rare skin disorder, a researcher at Massachusetts General Hospital (MGH) discovered a previously unknown mechanism in the kidneys that is important for regulating levels of magnesium and calcium in the blood.

The discovery, described in the journal *Cell Reports*, highlights the role of a previously little-studied gene called KCTD1. The gene directs production of a protein that regulates the kidney's ability to reabsorb magnesium and calcium from urine and return it to the bloodstream.

A genetic mutation causing the loss of KCTD1 results in defects in nephrons, the basic filtration units of the kidney, reports Alexander G. Marneros, MD, Ph.D., an investigator at the Cutaneous Biology Research Center at MGH and an associate professor of Dermatology at Harvard Medical School. KCTD1 is particularly important in the segments of the nephron involved in the regulation of reabsorption of salt, magnesium and calcium from filtered urine into the bloodstream.

Defects in nephrons resulting from KCTD1 loss in turn cause abnormally low levels of magnesium (hypomagnesemia) and calcium (hypocalcemia) in the bloodstream. The abnormally low blood levels of calcium trigger the parathyroid hormone-producing parathyroid glands in the neck to go into overdrive, a condition known as secondary hyperparathyroidism. The resulting high levels of parathyroid hormone lead to a release of calcium from bones in an attempt to counter the low calcium blood levels, eventually causing a loss of bone mass.

Marneros described the initial identification of kidney abnormalities that occur as a consequence of KCTD1 deficiency in a study published in 2020 in the journal *Developmental Cell*, which demonstrated that lack of KCTD1 in mutant mice leads to progressive kidney abnormalities, in part resembling the findings in patients with chronic kidney disease. Indeed, he observed that patients with KCTD1 mutations also developed chronic kidney disease with renal fibrosis (scarring of kidney tissue). These findings suggested that KCTD1 plays an important function in the kidney.

In the current study, Marneros reports that KCTD1 acts in a part of the

nephron known as the distal nephron to regulate the reabsorption of electrolytes from urine into the bloodstream and maintain balanced levels (homeostasis) of these electrolytes.

"The distal nephron is important not just for salt reabsorption, but also for reabsorption of magnesium and calcium, and this study shows that KCTD1 is critical for the ability of the distal nephron to reabsorb these electrolytes from urine," he says.

The paper provides a detailed description of changes in proteins that shuttle electrolytes across membranes in the distal nephron when KCTD1 is missing. Collectively, the findings reveal that KCTD1 is a key regulator of the ability of distal nephrons not only to reabsorb salt but also magnesium and calcium from urine, thereby maintaining a healthy balance.

More information: Alexander G. Marneros et al, Magnesium and Calcium Homeostasis Depend on KCTD1 Function in the Distal Nephron, *Cell Reports* DOI:doi.org/10.1016/j.celrep.2020.108616

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