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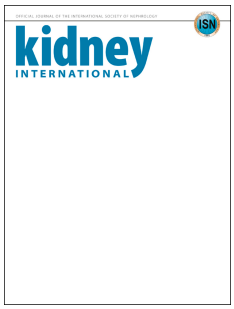
DOI: https://doi.org/10.1016/j.kint.2020.05.055

Originally published at:
Gillion, Valentine; Devuyst, Olivier (2020). Genetic variation in claudin-2, hypercalciuria and kidney stones. Kidney International, 98(5):1076-1078.
DOI: https://doi.org/10.1016/j.kint.2020.05.055



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PII: S0085-2538(20)30802-4

DOI: https://doi.org/10.1016/j.kint.2020.05.055

Reference: KINT 2192

To appear in: *Kidney International*

Received Date: 15 May 2020

Accepted Date: 27 May 2020

Please cite this article as: Gillion V, Devuyst O, Genetic variation in claudin-2, hypercalciuria and kidney stones, *Kidney International* (2020), doi: https://doi.org/10.1016/j.kint.2020.05.055.

Genetic variation in claudin-2, hypercalciuria and kidney stones

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Refers to: Curry JN, Saurette M, Askari M, Pei L, Filla MB, Beggs MR, Rowe PS, Fields T, Sommer AJ, Tanikawa C, Kamatani Y, Evan AP, Totonchi M, Alexander RT, Matsuda K, Yu ASL. Claudin-2 deficiency associates with hypercalciuria in mice and human kidney stone disease. J Clin Invest. 2020 Mar 9:127750

Keywords: cell polarity, hypercalciuria, proximal tubule, calcium

Idiopathic hypercalciuria is a major risk factor for kidney stones, which affect 5 to 10% of the population and are increasing on a global scale. Potential causes for idiopathic hypercalciuria include increased intestinal absorption, abnormal bone resorption, and reduced reabsorption of calcium by the kidney (1). In steady state, the kidney tubules reabsorb approximately 98% of the filtrated Ca^{2+}, via transcellular and paracellular pathways. The transcellular pathway is mediated by transporters expressed in the apical and basolateral membrane domains of cells, whereas the paracellular pathway depends on transepithelial electrochemical gradients and involves specialized proteins, the claudins (2).

The claudins belong to a family of membrane proteins encoded by 27 genes. Their structure includes 4 transmembrane domains and 2 extracellular loops, with the COOH- and NH2-terminal domains located in the cytosol (Figure 1). The claudins form homo- and heteropolymers in the tight junction complexes, primarily acting as pores or barrier structures, defining permeability and selectivity of the paracellular space (3). Through specific expression profiles and interactions, the claudins play a major role in paracellular transport along the kidney tubule. For instance, the leaky epithelium lining the proximal tubule is involved in the paracellular reabsorption of water and many different solutes, largely determined by the expression of claudin-2 and claudin-10a (4). Isolated proximal tubules from claudin-2 knockout (*Cldn2*$^{Y/-}$) mice show increased paracellular shunt resistance, indicating that they are "tighter" compared to those isolated from control, *Cldn2*$^{Y/+}$ mice. Furthermore, the *Cldn2*$^{Y/-}$mice are hypercalciuric, suggesting that claudin-2 plays a role in the paracellular reabsorption of Ca^{2+} in the proximal tubule (5).

The role of claudin-2 in the tubular handling of Ca^{2+} and in idiopathic hypercalciuria and kidney stones is supported by a recent study, based on the *Cldn2* mouse model and on genetic evidence obtained in population-based and rare family studies (6).

In this elegant work, Curry et al. first confirmed that *Cldn2*$^{Y/-}$ mice show hypercalciuria without changes in glomerular filtration rate or serum calcium levels, even after a calcium-deficient diet, and without compensatory changes in distal tubular Ca^{2+} transporters. These data support the existence of a defective paracellular transport of Ca^{2+} in the proximal tubule of *Cldn2*$^{Y/-}$ mice. Levels of parathyroid hormone (PTH) and 1,25 diOH vitamin D3, and bone mineral density were unchanged in *Cldn2*$^{Y/-}$ mice, suggesting that increased enteral absorption of calcium may contribute to the observed hypercalciuria. This hypothesis was confirmed by the marked attenuation of hypercalciuria when the *Cldn2*$^{Y/-}$ mice were exposed to a calcium-deficient diet. The *Cldn2*$^{Y/-}$ mice showed a reduction in paracellular Ca^{2+} permeability in the colon, hence a reduced passive secretion of Ca^{2+}, explaining the net increased intestinal

absorption. Importantly, aged *Cldn2*$^{Y/-}$ mice exhibited papillary nephrocalcinosis, made up of hydroxyapatite (calcium phosphate) with a small amount of calcium carbonate. The majority of deposits are not localized in a specific part of the tubules, suggesting that they were formed in the interstitium or by tubules that subsequently degenerated.

To test the human relevance of these findings, the authors examined 12 single-nucleotide polymorphisms (SNPs) in the *CLDN2* locus in a population of more than 10,000 kidney stone cases and nearly 200,000 controls (6). They found 9 SNPs (all in the non-coding region of *CLDN2*) that were significantly associated ($P < 0.05$) with the risk of kidney stones in this cohort. For 6 of these SNPs, the risk allele was strongly associated with decreased expression of claudin-2 in pancreatic tissue (taken as index tissue in the absence of sufficient kidney samples) in the Genotype-Tissue-Expression (GTEx) project. Finally, the authors detected a rare missense variant in *CLDN2* (p.Gly161Arg) in 5 male subjects from a family of Iranian origin presenting with obstructive azoospermia and a history of kidney stones with marked hypercalciuria, compared to 2 unaffected siblings. A female carrier in the family exhibited mild hypercalciuria.

Overall, the findings of Curry et al. provide multi-level evidence suggesting a role for claudin-2 in idiopathic hypercalciuria and kidney stones (6). Although these findings should be confirmed by more direct evidence such as micropuncture studies, these results substantiate the role of claudin-2 in the paracellular pathway for Ca^{2+} operating in the kidney proximal tubule and the colon. The *Cldn2*$^{Y/-}$ mice show a combination of reduced kidney calcium reabsorption and increased gut absorption of calcium (due to reduced passive backleak in the colon), similar to many subjects with idopathic hypercalciuria (1). In turn, the hypercalciuria leads to papillary nephrocalcinosis in *Cldn2*$^{Y/-}$ mice, also resembling the intratubular plugs and interstitial plaques observed in patients with kidney stones (Figure 1). The increased risk of kidney stones observed in carriers of *CLDN2* variants that reduce the expression or function of claudin-2 adds to the existing genetic evidence supporting the role of the paracellular pathway in Ca^{2+} handling and the risk of kidney stones. Recently, common variants in *CLDN14* were associated with the risk of kidney stones and the specific handling of divalent cations (Ca^{2+} and Mg^{2+}) in the thick ascending limb (7).

Future studies should provide additional information about the effects of the *CLDN2* variants on the structure of the tight junctions, the handling of Ca^{2+} and other solutes by kidneys and the gut, and the influence of diet, genetic dosage, and gender. These insights should also substantiate the potential therapeutic value of modulating the paracellular route of Ca^{2+} movement in patients with idiopathic hypercalciuria.

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Acknowledgements: Work in our laboratory is supported by the European Reference Network for Rare Kidney Diseases (ERKNet) – project ID N° 739532; the Cystinosis Research Foundation (USA); the NCCR Kidney.CH program (Swiss National Science Foundation); and the Swiss National Science Foundation 310030-189044.

Disclosure: The authors declare no potential conflict of interest relevant to this article.

Figure 1. Role of claudin-2 in the paracellular pathway for calcium and the propensity for kidney stones.

The epithelial cells lining the kidney proximal tubule and the colon are connected by tight junction (TJ) complexes delineating the apical and basolateral domains and forming a paracellular barrier. The claudins are cell-cell adhesion molecules that are an essential component of the tight junctions. The claudins typically contain 4 transmembrane domains and 2 extracellular loops, with the N-terminal and C-terminal region in the cytosol. The claudins polymerize to form tight junction strands through *cis* (intracellular) and *trans* (intercellular) interactions. These interactions can involve different claudin isoforms. Claudin-2, which is represented here, interacts with the TJ protein ZO-1 through a PDZ-binding motif at the C-terminus (indicated by the red box). ZO-1 binds to actin and to the transcription factor ZONAB, which is involved in epithelial differentiation (8,9).
Using a combination of mouse and genetic studies, Curry et al. demonstrate that claudin-2 plays a role in the paracellular pathway for Ca^{2+} operating in the kidney proximal tubule and the colon. The *Cldn2*$^{Y/-}$ mice show a combination of reduced kidney calcium reabsorption and increased gut absorption of calcium, leading to hypercalciuria, papillary nephrocalcinosis and kidney stones. Carriers of *CLDN2* variants reducing the expression or function of claudin-2 also show increased risk of kidney stones.
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Portions	part of 1A
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