

## **Oxalate Homeostasis—Insights From Knockout Mice**

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SLC26A6 is an anion exchanger expressed on the apical membrane in many epithelial tissues, including kidney and intestine. Mouse Slc26a6 can function in multiple anion exchange modes, including Cl<sup>-</sup>-oxalate exchange. We found that mutant mice lacking Slc26a6 have a high incidence of calcium oxalate urolithiasis. Compared to wild-type mice, null mice have hyperoxaluria and hyperoxalemia, both of which are greatly attenuated by dietary oxalate restriction. *In vitro* flux studies indicated that null mice have a defect in intestinal oxalate secretion resulting in enhanced net absorption of oxalate. Taken together, these observations suggested that the anion exchanger SLC26A6 plays a major constitutive role in limiting net intestinal absorption of oxalate, thereby preventing hyperoxaluria and reducing the risk of calcium oxalate urolithiasis. These findings in Slc26a6 null mice raised the possibility that genetic variants of SLC26A6 may contribute to hyperoxaluria and increased risk of stones in humans. However, a key question concerning the inheritance of hyperoxaluria and propensity to stones on the basis of SLC26A6 mutations is whether a detectable phenotype can result from SLC26A6 haploinsufficiency or requires more severe loss of SLC26A6 function. To address this question, we compared Slc26a6 wild-type, heterozygote, and null mice with respect to urine and plasma oxalate levels, as well as the presence of bladder stones. We confirmed that complete loss of Slc26a6 expression in mice results in hyperoxaluria, hyperoxalemia, and urolithiasis. However, despite reduced transporter protein expression and function, we found that haploinsufficiency for Slc26a6 in mice does not result in a detectable increase in urine or plasma oxalate, or an increased incidence of urolithiasis. To the extent these findings can be extrapolated from mouse to man, they suggest that heterozygosity for a functionally defective SLC26A6 allele would not be sufficient to cause hyperoxaluria in humans. Only dominant negative or homozygous null alleles for SLC26A6 would be expected to cause hyperoxaluria and increased propensity to urolithiasis.

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