

## Human *SLC26A6* Variation in Oxalate Homeostasis

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**Introduction:** Recently, two independently generated lines of null *Slc26a6* (-/-) mice demonstrated a phenotype of hyperoxaluria, with additional observations of hyperoxalemia and calcium oxalate urolithiasis in one of these lines. In humans, *SLC26A6* is widely expressed in renal and gastrointestinal epithelium, leading us to postulate that genetic variation in *SLC26A6* may modify or cause hyperoxaluria.

**Methods:** To test the hypothesis that functional sequence variation in *SLC26A6* might account for unexplained forms of hyperoxaluria (“non-PH1/PH2 primary hyperoxaluria”) or modify the expression of types 1 (PH1) or 2 (PH2) primary hyperoxaluria, we performed *SLC26A6* screening in primary hyperoxaluria probands (PH1 = 80, PH2 = 6, non-PH1/PH2 = 8) from the International Primary Hyperoxaluria Registry and in controls (n = 96).

**Results:** A rare frequency variant (c. 487 C > T, P163S) was detected solely in a “non-PH1/PH2” pedigree but it failed to segregate with the hyperoxaluria, and functional expression studies in *Xenopus* oocytes showed oxalate transport comparable to wildtype. Notably, we detected a common (11%) frequency variant (c.616 G > A, V206M) in cases and controls, with a 30 percent reduction in oxalate transport when expressed in *Xenopus* oocytes. In PH1 patients with GFR > 60, heterozygosity for this variant appeared to correlate with lower plasma concentrations of oxalate, an effect that was not attributable to differences in renal oxalate handling or response to pyridoxine treatment. A similar effect at lower levels of GFR could not be systematically evaluated due to unavailability of a sufficient number of patients.

**Conclusions:** These are the first human studies to identify and characterize *SLC26A6* variants in hyperoxaluria. We excluded *SLC26A6* as the monogenic basis of “non-PH1/PH2” primary hyperoxaluria in our cohort of patients and identified a functional common frequency (11%) variant (V206M). In contrast to mice, preliminary studies in human patients suggest that the presence of this variant may impart a favorable effect on plasma oxalate, perhaps by upregulation of the gene in tissue epithelia. Studies in a larger cohort of V206M heterozygous and homozygous patients are needed to confirm this association.

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