

## **SIGNIFICANCE STATEMENT**

The primary hyperoxalurias (PH) are a group of rare, inherited disorders characterized by kidney stone formation and severe kidney damage resulting from excessive endogenous oxalate synthesis. Limited treatment options are available for PH. Hydroxyproline metabolism, known to contribute to oxalate synthesis, is a potential target for oxalate reduction therapy. Using a stable isotope of hydroxyproline, the contribution to urinary oxalate excretion was measured in healthy and PH subjects. Our results show that hydroxyproline accounts for up to half of the endogenous oxalate synthesis in PH2 and PH3, more than twice that of healthy subjects. In PH1, surprisingly, the bulk of the oxalate synthesized in PH1 was not derived from hydroxyproline and its source remains to be determined.