STATEMENT OF SIGNIFICANCE

Ureteropelvic junction obstruction (UPJO) is a major cause of congenital dilation of the renal pelvis. The pathogenesis of UPJO is undefined, no biomarkers are identified to predict its natural history, and surgical correction is the only treatment. This study demonstrates that increased Hedgehog signaling activity, caused by *Ptch1* deficiency within a narrow time window during mouse development, results in ectopic localization of cortical stromal cells to the ureteropelvic junction, causing blockage of urinary outflow and dilation of the renal pelvis. Expression of genes characteristic of cortical stromal cells and Hedgehog signaling activity was increased in obstructive ureteric tissue resected from affected children. These results provide a basis for genetic studies in human UPJO and therapeutic strategies targeting the Hedgehog signaling pathway.