SIGNIFICANCE STATEMENT

Mammals must concentrate their urine to adjust to limited water supplies. High concentrations of osmolytes in the interstitium of the renal medulla provide the driving force for transcellular water reabsorption in the collecting duct. This study delineates a novel role of the collecting duct epithelium in maintaining steep concentration gradients between the medullary interstitium and urine. Collecting duct cells produce a transcription factor, GRHL2, which enforces expression of components of a tight paracellular barrier. The collecting ducts from mice lacking renal GRHL2 are leaky, and the mice lose osmolytes from the renal medulla and produce large amounts of dilute urine, similar to patients with diabetes insipidus. The study thus identifies a novel role of the GRHL2-mediated collecting duct epithelial barrier in renal osmoregulation.