SIGNIFICANCE STATEMENT

Branching morphogenesis of the ureteric bud is central to forming a normal kidney, and the most severe forms of congenital anomalies of the kidney and urinary tract (CAKUT) arise from mutations in genes involved in branching. The authors report that deletion in mice of *transcription factor 21* (*Tcf21*) results in a spectrum of renal developmental phenotypes that resemble human CAKUT. Germline deletion of *Tcf21* or *Tcf21* deleted specifically from the stromal mesenchyme resulted in branching defects and reduced expression of *Gdnf-Ret-Wnt11* (a key pathway required for branching morphogenesis), whereas *Tcf21* deletion specifically from the cap mesenchyme resulted in glomerular rather than branching defects and no downregulation of *Gdnf-Ret-Wnt11*. These findings suggest that Tcf21 has a central role in regulating the Gdnf axis and renal stromal factors crucial for branching.