SIGNIFICANCE STATEMENT

Early in kidney development, the Wolffian duct (WD) inserts into the cloaca and gives rise to a ureteric bud. These steps establish the connection between ureters and bladder, and initiate kidney development. Defects in these processes result in congenital anomalies of the kidneys and urinary tract (CAKUT). Using innovative mutant mice, whole three-dimensional confocal immunofluorescence and three-dimensional x-Ray nano-computed tomography imaging in conjunction with whole urinary tract cultures, this study delineates that RET-Y1062-ERK–mediated cell survival regulates ureteric budding and distal WD growth. RET-Y1015 and YAP signaling through spatiotemporally regulated apoptosis between the WD and cloaca are required for WD-cloaca fusion. The findings provide novel insights into the crosstalk between the WD tip and cloaca, fundamental to explaining the mechanisms of many CAKUT.