Birt-Hogg-Dubé (BHD) syndrome is an inherited familial cancer syndrome characterized by the development of cutaneous lesions, pulmonary cysts, renal tumors and cysts and caused by loss-of-function pathogenic variants in the gene encoding the tumor-suppressor protein folliculin (FLCN). FLCN acts as a negative regulator of TFEB and TFE3 transcription factors, master controllers of lysosomal biogenesis and autophagy, by enabling their phosphorylation by the mechanistic Target Of Rapamycin Complex 1 (mTORC1). We have previously shown that deletion of Tfeb rescued the renal cystic phenotype of kidney-specific Flcn KO mice. Using Flcn/Tfeb/Tfe3 double and triple KO mice, we now show that both Tfeb and Tfe3 contribute, in a differential and cooperative manner, to kidney cystogenesis. Remarkably, the analysis of BHD patient-derived tumor samples revealed increased activation of TFEB/TFE3-mediated transcriptional program and silencing either of the two genes rescued tumorigenesis in human BHD renal tumor cell line-derived xenografts (CDXs). Our findings demonstrate in disease-relevant models that both TFEB and TFE3 are key drivers of renal tumorigenesis and suggest novel therapeutic strategies based on the inhibition of these transcription factors.