

Birt-Hogg-Dubé (BHD) syndrome is an inherited familial cancer syndrome characterized by the development of cutaneous lesions, pulmonary cysts, and renal tumors and cysts. The syndrome is caused by loss-of-function pathogenic variants in the gene encoding the tumor-suppressor protein folliculin (FLCN). FLCN, acting as a negative regulator of the TFEB and TFE3 transcription factors, serves as a master controller of lysosomal biogenesis and autophagy. Its function involves enabling the phosphorylation of TFEB and TFE3 by the mechanistic Target Of Rapamycin Complex 1 (mTORC1). Previous studies demonstrated that the deletion of Tfeb rescued the renal cystic phenotype in kidney-specific Flcn knockout (KO) mice. Building upon this, the current research, utilizing Flcn/Tfeb/Tfe3 double and triple KO mice, reveals that both Tfeb and Tfe3 contribute differentially and cooperatively to kidney cystogenesis. Analysis of tumor samples derived from BHD patients further indicates increased activation of the TFEB/TFE3-mediated transcriptional program. Notably, silencing either of the two genes rescued tumorigenesis in human BHD renal tumor cell line-derived xenografts (CDXs). These findings, established in disease-relevant models, underscore the key roles of both TFEB and TFE3 as drivers of renal tumorigenesis. The study suggests novel therapeutic strategies that involve the inhibition of these transcription factors, providing potential avenues for the development of targeted treatments for BHD syndrome and related conditions.