SIGNIFICANCE STATEMENT

The authors previously reported that mutations in *ANLN* can cause familial FSGS. Anillin is an F-actin binding protein that modulates cell motility and signaling through the phosphoinositide 3-kinase (PI3K) pathway. This study examines its signaling through the PI3K pathway in podocytes to understand its role in the pathobiology of FSGS. Mutant anillin induced hypermotility and apoptosis, enhanced cellular proliferation, and activated PI3K/AKT/mTOR/Rac1 signaling. Aberrant podocyte phenotypes induced by the mutation were ameliorated by inhibition of downstream effectors of PI3K and calcineurin phosphatase, and calcineurin inhibition ameliorates $ANLN_{R431C}$-induced podocyte apoptosis and downregulates endogenous mTOR and ANLN expression. Drugs targeting these pathways may be useful in the treatment of some forms of FSGS.