

## SIGNIFICANCE STATEMENT

The mechanism by which mutations in cullin 3 (*CUL3*) cause familial hyperkalemic hypertension (FHHt) is controversial. Previous work showed that the *CUL3*Δ9 mutant does not bind normally to the COP9 signalosome (CSN). Here, genetic deletion of the CSN catalytic subunit *Csn5/Jab1* in mouse kidney upregulated the WNK-SPAK pathway, probably resulting from the decreased abundance of KLHL3, which links WNKs with *CUL3* for ubiquitination and degradation. NCC expression decreased despite the upregulation of WNK signaling, and the mice developed polyuria, salt wasting, hypokalemia, and kidney tubule damage. The findings present a mixed phenotype that resembles the kidney-specific *Cul3*<sup>-/-</sup> phenotype but also suggests that the inability of the *CUL3*Δ9 mutant to interact with the CSN contributes to FHHt by enhancing KLHL3 degradation.