SIGNIFICANCE STATEMENT

We previously identified that allograft *SHROOM3* expression, and a CKD-associated intronic *SHROOM3* locus with enhancer function, are associated with subsequent renal allograft fibrosis, whereas tubular Shroom3 knockdown reduced fibrosis. Although these data suggested potential to target SHROOM3 as therapy in kidneys carrying the A-allele (risk locus), they contrast with evidence of a protective role for SHROOM3 in glomerular development. We show here the interesting divergent associations of glomerular and non-glomerular *SHROOM3* expression with CKD, as well as the corresponding dichotomous associations of the enhancer A-allele with eGFR and albuminuria in allografts. In adult glomeruli, *Shroom3* knockdown caused albuminuria without podocyte loss in the short term. Shroom3 interacted with the Src-kinase FYN *via* SH3-binding site in podocytes, and regulated FYN-activation and downstream phosphorylation of Nephrin, and actin cytoskeletal organization. These current mechanistic data are essential before the design of a therapeutic intervention in humans targeting SHROOM3 to inhibit renal fibrosis.