SIGNIFICANCE STATEMENT

A number of single gene mutations have been identified as causes of nephrotic syndrome (NS). This paper describes the discovery of two new monogenic genes with mutations associated with NS, *GAPVD1*, with definite evidence for causality, and *ANKFY*1, as probably causal. The genes are the first endosomal regulators and known RAB5 interactors implicated in NS. Both proteins interact and affect podocyte migration rate. GAPVD1 also interacts with the slit diaphragm protein nephrin. The mutations of *GAPVD1* observed in patients affect binding to nephrin and RAB5. Silencing the ortholog of *GAPVD1* in the podocyte-like *Drosophila* nephrocytes results in mistrafficking of fly nephrin. These findings implicate RAB5 regulation as a novel pathogenetic pathway of NS, potentially critical for nephrin trafficking.