

SIGNIFICANCE STATEMENT

Although nephrin plays crucial roles in formation of the podocyte slit diaphragm and in dynamic regulation of signaling pathways in the slit diaphragm, the mechanisms at molecular level are poorly understood. In addition, several mutations in *NPHS1* (the gene encoding nephrin) that affect nephrin's atypical PDZ-binding motif (PBM) have been associated with glomerular diseases. Using a variety of approaches, the authors demonstrate that nephrin's PBM specifically interacts with the PDZ3 domain of MAGI1, a member of the membrane-associated guanylate kinase family. The findings provide a molecular basis of nephrin/MAGI1 interaction in slit diaphragm assembly and signaling, as well as possible insights at the molecular level for diseases caused by alterations in *NPHS1*.