SIGNIFICANCE STATEMENT

Pierson and Alport syndromes are genetic diseases that affect the laminin and type IV collagen components, respectively, of the glomerular basement membrane. Understanding the pathogenic mechanisms of mutations found in patients may provide guidance for choosing therapeutic approaches. Engineering a human LAMB2 mutation that causes a delayed nephrotic syndrome and impairs laminin polymerization into the mouse resulted in no detectable defect in glomerular permselectivity. However, breeding just one copy of this mutation onto the Alport mouse background dramatically increased the rate of progression to ESRD, suggesting a genetic interaction. Thus, variants in a noncollagen GBM protein can affect progression of Alport syndrome. This could explain in part the variation in disease presentation and progression observed in patients with Alport syndrome.