SIGNIFICANCE STATEMENT

APOL1 variants are associated with kidney diseases in African ancestral populations; yet, the underlying mechanisms are unknown. Although APOL1 is normally expressed in podocytes, data from cell culture and animal models suggest *APOL1* variant-dependent cytotoxicity mediates kidney disease. This study shows that APOL1 cytotoxicity is variant-independent and related to APOL1 expression levels. At expression levels that are cytotoxic, APOL1 assembles pH-sensitive cation channels on plasma membranes. Stable APOL1 expression is achievable in model systems without variant-dependent differences in cytotoxicity, autophagy, or channel activity. Absence of variant-dependent cell death or cytotoxicity at physiologic expression levels suggests increased cytotoxicity of APOL1 variants does not drive disease progression in humans and alternative mechanisms should be explored.