SIGNIFICANCE STATEMENT

X-linked Alport syndrome (XLAS) is a progressive hereditary nephropathy caused by mutations in the *COL4A5* gene. Previous studies have shown genotype-phenotype correlations, but this study is the first to demonstrate that splicing mutations that create a premature stop codon and a truncated transcript are associated with worse prognosis. The investigators also find that, for splicing mutations, transcriptional analysis is necessary to accurately estimate renal prognosis and *in silico* predictive tools are not often useful. The findings suggest consideration of therapeutic approaches to changing truncating mutation into nontruncating transcription for XLAS.