SIGNIFICANCE STATEMENT

This manuscript describes a novel mechanism of renal tubular damage and CKD involving the formation of unique intramitochondrial protein aggregates. The disease results from monoallelic mutations in the gene encoding glycine amidinotransferase (GATM), a proximal tubular enzyme in the creatine biosynthetic pathway. All disease-related GATM mutations create an additional interaction interface within the GATM protein, promoting its linear aggregation. Aggregate-containing mitochondria in proximal tubular cells are associated with elevated production of reactive oxygen species, initiation of an inflammatory response, and increased cell death. These data establish a link between intramitochondrial GATM aggregates, renal Fanconi syndrome, and CKD.