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Titel des Beitrags: Loss-of-function mutations in MGME1 impair mtDNA replication and cause multisystemic mitochondrial disease.

Abstract: Known disease mechanisms in mitochondrial DNA (mtDNA) maintenance disorders alter either the mitochondrial replication machinery (POLG, POLG2 and C10orf2) or the biosynthesis pathways of deoxyribonucleoside 5’-triphosphates for mtDNA synthesis. However, in many of these disorders, the underlying genetic defect has yet to be discovered. Here, we identify homozygous nonsense and missense mutations in the orphan gene C20orf72 in three families with a mitochondrial syndrome characterized by external ophthalmoplegia, emaciation and respiratory failure. Muscle biopsies showed mtDNA depletion and multiple mtDNA deletions. C20orf72, hereafter MGME1 (mitochondrial genome maintenance exonuclease 1), encodes a mitochondrial RecB-type exonuclease belonging to the PD-(D/E)XK nuclease superfamily. We show that MGME1 cleaves single-stranded DNA and processes DNA flap substrates. Fibroblasts from affected individuals do not repopulate after chemically induced mtDNA
depletion. They also accumulate intermediates of stalled replication and show increased levels of 7S DNA, as do MGME1-depleted cells. Thus, we show that MGME1-mediated mtDNA processing is essential for mitochondrial genome maintenance.