

CISD2 MEDIATED MITOCHONDRIAL INTEGRITY AND AGING IN MAMMALS

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CISD2, the causative gene for Wolfram syndrome 2 (WFS2), is a previously uncharacterized novel gene. Significantly, the *CISD2* gene is located on human chromosome 4q where a genetic component for longevity maps. We had demonstrated for the first time that *CISD2* is involved in mammalian lifespan control. *Cisd2* deficiency in mice causes mitochondrial breakdown and dysfunction accompanied by cell death with autophagic features and these events precede the two earliest manifestations of nerve and muscle degeneration; together, they lead to a panel of phenotypic features suggestive of premature aging. Our study also reveals that *Cisd2* is primarily localized in the mitochondria and that mitochondrial degeneration appears to have a direct phenotypic consequence that triggers the accelerated aging process in *Cisd2* knockout mice; furthermore, mitochondrial degeneration exacerbates with age and the autophagy increases in parallel to the development of the premature aging phenotype. Our work effectively links *Cisd2* gene function, mitochondrial integrity and aging in mammals. Additionally, our *Cisd2* knockout mouse work provides strong evidence supporting an earlier clinical hypothesis that Wolfram syndrome is in part a mitochondria-mediated disorder; specifically, we propose that mutation of *CISD2* causes the mitochondria-mediated disorder WFS2 in humans. Thus, this mutant mouse provides an animal model for mechanistic investigation of *Cisd2* protein function and help with a pathophysiological understanding of WFS2.