Reviewer's report

Title: A donor splice site mutation in CISD2 generates multiple truncated, non-functional isoforms in Wolfram Syndrome type 2 patients

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Reviewer: Lisbeth Tranebjærg

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A donor splice site mutation in CISD2 generates multiple truncated, non-functional isoforms in Wolfram syndrome type 2 patients

By Catteneo M et al

The authors report a splice mutation in two Italian sisters suffering from the rare Wolfram type 2 syndrome. Only four mutations have so far been reported. They applied molecular and biochemical studies in order to investigate the consequences of this mutation.

They provide convincing data supporting that the mutation causes the production of multiple splice variants, including skipping exon 1, leading to premature stop codon, and subsequent either non-functional isoforms of products being targeted by NMD.

The studies are based on the mutation reported in 2015 by Rondinelli M et al, and aims at providing mechanistic insight in the effects of this mutation.

Based on several methods and experiments they conclude that there is a complete loss of functional CISD2 protein in the patients and a reduction to about 50% in the heterozygous parents. Mouse data from the KO mouse model are in accordance with their findings, and further experiments on the mouse model to analyze the aberrant mitochondrial homeostasis created by non-functional CISD2 protein are very likely to reflect similar mechanistic conditions in human patients with CISD2 mutations.
The paper is well written and legends are appropriate in clarity and number. The applied methods are outside my expert area and must be judged by another reviewer. Please rewrite this text when adding your comments to the authors.

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