Reviewer's report

Title: POLG1 R722H mutation associated with multiple mtDNA deletions and a neurological phenotype

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Reviewer: Michio Hirano

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Komulainen and colleagues have studied two families with encephalopathies plus other neurological and neuromuscular manifestations due to POLG1 mutations. In the first family, three affected siblings had late-onset dementia, hearing loss, and variable other features including ptosis attributed to a homozygous p.R722H polymorphism, while in the second family, two young adult sisters had ptosis and prominent juvenile-onset encephalopathies manifesting as abnormal behavior. The major novelty of this work is the notion that the p.R722G polymorphism may be pathogenic; however, this point requires further evidence (see below).

Major Compulsory Revisions

Evidence of pathogenicity of the p.R722H POLG1 polymorphism is not entirely convincing. Luoma et al. found this polymorphism in 1% of controls. The authors claim that the mitochondrial abnormalities detected in muscle of patient 1 support pathogenicity; however, muscle of healthy people over age 60 typically shows a few ragged-red fibers and multiple deletions of mtDNA by PCR. What proportion of muscle fibers were ragged-red or cytochrome oxidase deficient? Southern blot analysis should be performed to better assess the levels of the mtDNA deletions. Also, if possible, biochemical activities of mitochondrial respiratory chain enzymes should be measured.

Minor Essential Revisions

The fact that patients 1, 2, and 3 are siblings must be clearly stated in the Abstract or in the descriptions of the patients.

The left basal ganglia infarct in patient 1 is not visible in Figure 1. Is the lesion suggestive of a lacunar infarct?

Additional family history of patients 1, 2, and 3 should be reported. Were there any unaffected siblings? Were parents consanguineous? Did any relative have Parkinson disease?

The p.W748S mutation has been frequently identified in cis with the p.E1143G polymorphism. Did patients 4 and 5 have this second polymorphism?

The manuscript requires editing to correct grammatical errors.
**Level of interest:** An article of limited interest

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.