Reviewer's report

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

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**Reviewer:** Rita Horvath

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The manuscript by Komulainen et al. describes 5 patients from 2 independent families homozygous or compound heterozygous for the p.R722H mutation in POLG. This mutation is currently known as a polymorphism on the POLG mutation database (http://tools.niehs.nih.gov/polg/index.cfm?do=main.view ). I think the data provided by the authors suggest, that this mutation is actually a pathogenic mutation, causing symptoms by an autosomal recessive inheritance. This is an important observation and worth to publish.

I have a few suggestions:

1. I think, that for proving the pathogenic role of the p.R722H mutation it would be important to exclude mutations in other possible nuclear genes causing multiple mtDNA deletions (PEO1, ANT1, POLG2).

2. The patients with homozygous p.R722H had a late onset mild phenotype for an autosomal recessive POLG defect. Memory impairment, dementia and psychiatric symptoms were the main presenting features in these patients. I think the authors should make a point for the discussion about this as well, since this is not typical for other POLG mutations.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

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

**Declaration of competing interests:**

I have no competing interests