Reviewer's report

Title: Compound heterozygous mutations in glycyl-tRNA synthetase are a proposed cause of systemic mitochondrial disease

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Reviewer: Gregory M Enns

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McMillan and colleagues report an association between compound heterozygous GARS mutations detected by WES and systemic mitochondrial disease in a 12-year-old girl. Glycyl-tRNA synthetase has been associated with neurological phenotypes in a dominant fashion. This is an interesting case because of the novel mode of inheritance, as well as the description of novel phenotypic findings.

Minor Essential Revisions

1) To clarify, both ubiquinone and ubiquinol were started at age 10 years?

2) The case report could be condensed without losing substantial meaning.

3) It appears that the brothers did not carry either mutant allele, but this is not stated explicitly.

4) If the brothers do not harbor a mutant allele, why was nerve conduction testing done? How old are they?

5) Was electron microscopy performed on the muscle biopsy sample?

6) How common is it to have normal mitochondrial ETC functional studies in muscle biopsies from patients with either dominant GARS mutations or mutations in other ARS? How do you explain the normal ETC function as GARS mutations might be expected to affect multiple complexes?

7) Did the parents undergo echocardiography?

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

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.