Reviewer's report

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

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Reviewer: Fernando Scaglia

Reviewer's report:

McMillan and collaborators have submitted a manuscript entitled "Compound heterozygous mutations in glycyl-tRNA synthetase are a proposed cause of systemic mitochondrial disease" to be considered for publication in BMC Medical Genetics.

The authors report the case of a patient who presented with clinical and biochemical features of a systemic mitochondrial disease including exercise-induced myalgia, non-compaction cardiomyopathy, persistent elevation of blood lactate and alanine, and MRI evidence of mild periventricular leukomalacia. Using exome sequencing, the subject was found to harbor two compound heterozygous variants within the glycyl-tRNA synthetase (GARS) gene; c.1904C>T; p.Ser635Leu and c.1787G>A; p.Arg596Gln. Each variant occurred at a highly conserved site within the anticodon binding domain. The authors state that their findings suggest that recessive mutations in GARS cause systemic mitochondrial disease. This phenotype is distinct from patients with previously reported dominant mutations in this gene who present with either a CMT or a distal SMA phenotype, thereby expanding the spectrum of disease associated with GARS dysregulation.

The manuscript is interesting but the authors need to answer major compulsory revisions in a revised manuscript.

Major compulsory revisions:

1. Dominant mutations in the anticodon binding domain seem to be associated with a worse phenotype associated with early onset as reported by Eskuri et al in J Peripher Nerv Syst. 2012 Mar;17(1):132-4. Since both parents carry variants that occur at a highly conserved site within the anticodon binding domain, could the authors speculate why both parents (and in particular the mother) present with such a mild phenotype? The normal clinical and neurological phenotype of the mother is puzzling (although no EMG was performed). It would have been useful to do an EMG to provide her with better counseling. In some cases the phenotype can present in the last decades of life but typically mutations in this domain tend to be associated with a worse outcome.
2. The authors do not expand on the potential association between the left ventricular left compaction and the presence of these two variants in the GARS gene. Could there be another gene in the exome sequencing data that could be responsible for the presence of left ventricular non-compaction independently of the GARS variants? Exome sequencing data are currently showing that several patients may have complex phenotypes due to the presence of mutations in several genes.

3. Although the authors state that there was subjective improvement with the addition of creatine monohydrate, there was no comment whether clinical improvement was observed with the addition of B50 complex, carnitine and coenzyme Q10.

Minor essential revisions:

1. Please in background section change name of disease: CMT2A2 should be changed to CMT2A

2. Why was ubiquinol used at the same of ubiquinone? Is this a mistake?

**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 declare I have no competing interests.