Reviewer's report

Title: Rare recessive loss-of-function methionyl-tRNA synthetase mutations presenting as a multi-organ phenotype

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Reviewer: Hudson H Freeze

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Van Meel et al

The manuscript entitled, “Rare recessive loss-of-function methionyl-tRNA synthetase mutations presenting as a multi-organ phenotype” is an important contribution to the rapidly expanding field of solving rare genetic disorders through exome sequencing and biochemical confirmation of the defect. This is the first patient reported with this deficiency. The work is well done, thorough and with sufficient clinical detail to enable others to search for such patients.

Questions remain that cannot be answered with this single patient such as the surprising improvement on TPN. The authors pose important fundamental science questions about the location of the mutations on the modeled structure of the protein and they provide a welcomed calculation of the expected rate of appearance of the disorder using the frequency of deleterious mutations from the ESP database.

MAJOR REVISIONS
None

MINOR ESSENTIAL REVISIONS
None

DISCRETIONARY REVISIONS

1. At the top of page 12, the authors state they looked at a cohort of patients with rare phenotypes. Please state an approximate number.

2. Please provide an estimate of the transfection efficiency of the control and mutant constructs in HEK293 cells.

Declaration of competing interests:

I declare that I have no competing interests