Reviewer’s report

Title: A new mutation in the gene encoding mitochondrial Seryl-tRNA Synthetase as a cause of HUPRA syndrome.

Version: 1 Date: 10 June 2013

Reviewer: Daniel Gale

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Rivera et al describe two siblings presenting with progressive and fatal multisystem disease. The clinical presentation and course described is very similar to that of the patients described in HUPRA syndrome by Belostotsky et al 2011, and sequencing of SARS2 (the gene implicated by Belostotsky et al) demonstrated a homozygous missense mutation of a highly conserved residue that is exceedingly rare in the general population. In addition, there is evidence of impaired mitochondrial function in one of the patients. Together this constitutes strong evidence that the homozygous SARS2 mutation is the molecular defect responsible for the disease, although in the absence of functional data proving that there is an underlying mitochondrial aminoacyl-tRNA synthetase defect this is circumstantial.

Minor essential revisions
1. Table 1 is difficult to interpret. The authors should explain what is meant by “Level” and “C” in the header and exactly what the significance is of the values that appear in red.
2. Lactic acid levels were normal in both patients described here. Elevated blood lactate levels are described in all previous cases of HUPRA and in patients with other defects of mitochondrial aminoacyl-tRNA synthetases and also other mitochondrial disorders. Its absence in this report is somewhat surprising and should be discussed.
3. In previous cases of HUPRA muscle biopsy showed COX deficiency which was absent in the current case. The authors should comment on the significance of this discrepancy.
4. The authors should provide an explanation for the normal mitochondrial metabolic profile of skeletal muscle compared with those of kidney and skin cells.
5. “Cardiomyopathy” should replace “myocardioopathy” on page 5 para 1.
6. “Heterozygosity” should replace “heterozygous” on page 7 line 1.

Discretionary revisions
1. If available the authors should report the magnesium levels. Hypomagnesaemia was observed in all 3 previous patients with HUPRA syndrome and implicated dysfunction of the thick ascending limb.
2. An electron micrograph of a kidney tubule showing the abnormal mitochondrial
morphology alluded to in the text would be of interest.

**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