Reviewer's report

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

Version: 1 Date: 18 May 2013

Reviewer: Shamima Rahman

Reviewer's report:

This is the second report of HUPRA syndrome caused by mutations in SARS2, encoding the mitochondrial seryl tRNA synthetase. This is of interest to nephrologists because the authors provide confirmation of a specific association between SARS2 mutations and a multisystem phenotype including progressive renal failure.

Major Compulsory Revisions

1. It is of note that respiratory chain enzyme activities were found to be normal in skeletal muscle in both cases, which may make it difficult to diagnose this condition. Do the authors consider that this disorder may be under-recognised? Abnormal respiratory chain enzyme activities in skin fibroblasts in the context of normal activities in skeletal muscle is an unusual finding, and worthy of comment. However I am not convinced that the fb activities are truly 'abnormal' (see my comment re Table below). Please can the authors provide more details about the respiratory chain enzymology method performed in kidney, since this is not widely available. How was the renal reference range derived? How many control samples were assayed? And how were these obtained?

2. The presentation of the data in the Table needs to be improved. What does 'Level' mean? If this is the control reference range then please label these columns as such. In the Kidney section what does 'C' refer to? If this is the value obtained in a single control, then this should be explicitly stated, since that greatly reduces the significance of the apparently low respiratory chain enzyme activities observed in the patient. Furthermore, asserting that there were combined complex I and IV deficiencies in the patient's fibroblasts is an overstatement, since the activities are only just below the control range. I think the chevrons may be pointing in the wrong direction in all the control columns – surely normal is greater (>) than a certain vale not less (<)?

3. Why was SARS2 sequenced in these patients? The diagnostic rationale needs to be carefully explained. Was this the only gene sequenced in their patients? Was the mitochondrial DNA studied? Were any other nuclear genes sequenced? Or are they asserting that the HUPRA phenotype is so specific that the SARS2 gene should be targeted as a first line investigation? Have they screened any other patients for SARS2 mutations? Can they estimate how frequently SARS2 mutations may cause infantile onset renal disease?
4. My strongest criticism of this study is that only in silico evidence of pathogenicity is provided. This study would be far more convincing with some functional data to demonstrate mutation pathogenicity.

5. This manuscript would benefit from a more detailed discussion of the function of SARS2, with respect to disease mechanisms in HUPRA. The authors should also postulate reasons for the observed tissue specificity despite a global impairment of mitochondrial translation.

Minor Essential Revisions

Case Presentation
p4, line 5: please provide more details regarding the nature of the anaemia
p4, line 10: HCO# not “HCO#

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 that I have no competing interests