Reviewer's report

Title: Novel SCARB2 mutation in Action Myoclonus-Renal Failure syndrome and evaluation of SCARB2 mutations in isolated AMRF features

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Reviewer: Alessandro De Lca

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In this manuscript the authors analyze for mutations in SCARB2 gene a previously reported family with action myoclonus renal failure syndrome (AMRF) with additional signs of demyelinating polyneuropathy and dilated cardiomyopathy and identify a novel homozygous mutation. In addition, they extended the analysis to patients with isolated AMRF syndrome features including 103 cases with epilepsy, 192 with renal failure, 102 with demyelinating polyneuropathy (PNP) and 85 with dilated cardiomyopathy (DCM). Mutation analysis detected a previously reported SCARB2 mutation (Y222XfsX) in 2 cases with PNP. SCARB2 mutations were not found in any of the other selected cohorts.

- Major compulsory revision

Homozygous SCARB2 mutations have been found in patients with AMRF and in patients with progressive myoclonus epilepsy (PME) without renal failure. More recently, Dibbens and coworkers (Arch Neurol. 2011 Jun;68(6):812-3.) reported the identification of 2 different SCARB2 mutations in a patient with progressive myoclonus epilepsy and demyelinating peripheral neuropathy (originally described by Costello et al. (Arch Neurol. 2009 Jul;66(7):898-901)). The authors should include both these papers in the references. In the current study mutation analysis of patients with isolated AMRF features was conducted by high resolution melting technique, which is not 100% sensitive by definition. Considering that SCARB2 heterozygous carriers are often asymptomatic, and the limited sensitivity of HRM, and the fact that the heterozygous mutation reported here in PNP (Y222XfsX) was previously detected in an homozygote patient with PME (Ann Neurol. 2009 Oct;66(4):532-6.), I strongly encourage the authors to rule out the possibility that these 2 PNP heterozygous cases are compound heterozygotes for an undetected HRM mutation, deletion, or duplication. This task would be easily accomplished by simply analyzing the 2 cases with the Y222XfsX mutation using the same mutation strategy they have been using for the AMRF family (Sanger sequencing for mutation detection and real-time quantitative PCR analysis of all exons to find deletions).

Methods

In the original work of Dibbens and coworkers (Ann Neurol. 2009 Oct;66(4):532-6.) all the PME patients with mutations in the SCARB2 gene were phenotypically resembling Unverricht-Lundborg disease (ULD-like type), while
SCARB2 mutations were not found in the remaining PME cases (not ULD-like). For a better comparison between previous and current findings, it would be useful to know how many PME patients of the present cohort were “ULD-like type” without CSTB mutations.

- Minor essential revisions

- Discretionary revisions
A number of idiopathic DCM cases have mutations in sarcomeric proteins (MYH7, 5-8%; LMNA, 7-8%; TNNT2, 2-4%, etc.). The authors may want to consider the opportunity to mention if their patients had been previously tested for any DCM causative genes.

Regards,
Alessandro De Luca

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