Reviewer's report

Title: Complexity of the 5'UTR region of the CLCN5 gene: eleven 5'UTR ends are differentially expressed in the human kidney

Version: 1

Date: 15 April 2014

Reviewer: Gema Ariceta

Reviewer’s report:

Dear authors:

Your manuscript entitled “complexity of the 5'UTR region of the CLCN5 gene: eleven 5'UTR ends are differentially expressed in the human kidney” by Tosetto et al, provides new evidence about the structural complexity of the CLCN5 5'UTR region, and its impact on the diagnosis, and classification of patients with Dent’s disease. Those findings may better explain patients’ phenotype, and understand mechanisms of the disease in those patients without a confirmed genetic diagnosis, but with prototypic clinical expression. Further, better characterization of the 5'UTR region may explain additional functions of CLCN5, that could also extend the current knowledge in Dent’s disease. Description of different 5'UTR ends distribution among tissues may help to understand different clinical variants of the disease.

This manuscript describes original data, which are correctly presented and discussed. Authors present their results supporting their findings. Mayor limitations are the lack of evidence of which functional consequences are caused by the different expression of those 5'UTR ends in the animal models of the Dent’s disease.

I suggest including the reference detailed below:

A missense mutation in the chloride/proton ClC-5 antiporter gene results in increased expression of an alternative mRNA form that lacks exons 10 and 11. Identification of seven new CLCN5 mutations in patients with Dent’s disease.


In summary, this manuscript provides new light on the variability of CLCN5 gene 5'UTR ends expression in the human kidney, and may support better phenotypic classification and explain new pathogenic mechanisms caused by CLCN5 gene mutations. Therefore I support this manuscript for publication in BMC. Thank you very much for giving me the opportunity to collaborate with your journal.

Sincerely,
Gema Ariceta MD

**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