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

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Reviewer: Rosa Vargas-Poussou

Reviewer’s report:

In this paper the authors describe a deep characterisation of the region promoter of the CLCN5 gene responsible for Dent-1. The work is complete and well conducted; technical aspects and their interpretation are clear.

Major compulsory revisions

1. The main point is that the clinical relevance of data described in this paper is weak. Indeed, the authors describe previous screening of this region in 30 patients without mutations in the CLCN5 gene. If is not clear whether or not OCRL1 mutations were excluded in these patients. If it is the case, the percentage of patients with Dent-1 explained by molecular abnormalities in the promoter region is quite low (3%). In addition, other authors tested promoter regions in their patients (Ludwig 2003, Hoops 2004, Ludwig 2005 and Ludwig 2006) without detection of sequence variants. Although after description of Dent-2, mutations in the OCRL1 gene were identified in some of these patients, an important percentage of patients without mutations remains, which suggest a supplementary genetic heterogeneity. Do the authors recommend the screening of this region in routine analysis? This point should be discussed.

2. The authors showed a high and similar expression of the CLCN5 mRNA in kidney and colon and suggest that the mechanism of Dent’s disease hypercalciuria could be an absorptive hypercalciuria. Nevertheless the intestinal calcium absorption takes place mainly in small intestine.

3. The authors discussed the presence of several binding sites for transcription factors in the 3 functional promoters. This discussion does not include the HNF1 binding sites. Such sites have been described in the promoter region of mouse and human CLCN5 as well as the regulation of the CLCN5 mouse expression by HNF1-alpha (Tanaka K. AJP 2010).

Minor essential revisions

1. In background section, concerning the characteristics of Dent’s disease: as Fanconi syndrome includes abnormalities of all function of proximal cells, it would be better to write “nephrolithiasis and one or several features of proximal tubular disease (glycosuria, aminoaciduria and phosphaturia, etc) and in some cases Fanconi Syndrome.”
2. Tables 1 to 3 should be presented as supplementary tables.

3. In Figure 4 the novel exon C, between exons 1a and 1b is not represented

**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