Reviewer’s report

Title: Familial hypomagnesaemia with hypercalciuria and nephrocalcinosis (FHHNC): 2 heterozygous mutations in the claudin 16 (CLDN16) gene.

Version: 1 Date: 6 November 2007

Reviewer: Boris Utsch

Reviewer’s report:

Hampson et al. report on a family with 2 affected siblings with FHHNC. Both children underwent renal transplantation due to CNI. The authors point out that the course of the disease in the boy as well as in his sister is typical for FHHNC without any extra-renal manifestations. By direct sequencing, the authors found two heterozygous mutations in CLDN16 confirming the suspicious diagnosis of autosomal-recessive FHHNC. The authors point out that the 2 reported cases point out the importance of claudin 16 in the renal handling of calcium and magnesium.

Major Compulsory Revisions

The title should better include “compound heterozygous” instead of “two heterozygous mutations”.

The conclusion of the abstract is pretty weak with limited information. Besides the new cases and the detected mutations, the rest of the information given here is mainly general. It is a case report with one compound heterozygous mutation in one family.

The authors should indicate in the results section which sequence (acc. no.) was used for numbering the nucleotides.

Page 8 line 11: something is missing after “…indicate…”.

The missense mutation is already known (www.hgmd.org). The authors write 2 novel mutations on page 7 (seventh last line) and later that one of the detected mutations is already known (page 8, line 10).

The donor splice site mutation is new. Nevertheless, the consequences of the splice site alteration can be predicted in a better way than “…may result in exon skipping or a frame shift…”. By calculating the score of splice sites or using electronic public accessible prediction programs, the consequences of these mutations can be predicted much better! Where is an alternative donor splice site? Can the regular acceptor splice site of the next exon be used? Is there any stop codon due to a frame-shift, which truncates the protein? Do the authors have still access to the patients? Do they have RNA to evaluate the consequences on cDNA level? Instead of just reporting mutations, this information would improve the molecular studies easily by some functional
consequences of a new mutation.

The last paragraph of the discussion: guess that the “…heterozygote carriers of this family…” refers to CLDN16 mutations. The preceding sentences are dealing with CLDN19 mutations. This is somehow confusing.

The conclusion of the abstract and in the main text is somehow different: very general and limited in the abstract and with more molecular aspects in the text.

Minor Essential Revisions

Either BE or AE should be used (e.g. see title: hypomagnesaemia vs. in abstract: hypomagnesemia).

Gene symbols should be used in Italics whereas proteins should be written in normal letters.

CLDN16 should be used consequently instead of CLDN-16.

Even if the MS is well written the authors should look for an adequate orthographic stile and correct punctuation marks (commas, dots, spaces etc.)

“…familial hypomagnesemia…” in the background section, first paragraph, second last line.

Reference section:
Reference 7: hypomagnesemia
Reference 9: familial
Reference 17: renal

Discretionary Revisions

The authors should more focus on the clinical course of both patients from clinical manifestation until transplantation.

The authors should use the corresponding units even in brackets for normal values.

The authors should use the corresponding units even in brackets for normal values.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being
published

**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