Reviewer's report

Title: Genotype-phenotype correlation of proximal tubular function in Imerslund-Grasbeck Syndrome

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Reviewer: C Böger

Reviewer's report:

This is a well-written manuscript on rare mutations causing Imerslund-Graesbeck syndrome by a group that is among the leaders of research in this disease. The manuscript present important new aspects to the disease, and provides genotype-phenotype correlations. However, the manuscript is missing some important information.

Major Compulsory Revisions:

1. Since this paper promises to present genotype-phenotype-correlation, it is astonishing that so little phenotypic information is presented:
   a) The authors need to present more phenotypic detail of the affected patients: age, sex, body weight, body height, body surface area, age diagnosis of idease, general health, kidney function (serum creatinine, eGFR, albuminuria), degree of anemia, vit b12 and folate levels, treatment of anemia if any. This is important information since this manuscript will serve as an important reference for geneticists. Ideally, the authors can also present eGFR and albuminuria values of the parents carrying the causative mutations.
   b) Methods and Table 3 provide too little information on the proteinuria. What urine samples were collected -- spot, first morning void, timed or 24h collection? Was a dipstick test done to exclude urinary tract infection? Please provide the concentrations of all urinary proteins in mg per g creatinine. simply showing "x" or "(x)" is not informative. Please provide the reference normal values for each protein and a citable reference of the reference value.
   c) Shedding of cubilin (and megalin) into the urine has been shown for patients with diabetes (thrailkill et al Diabetes Care 2009). It would be interesting to know if this is observed for any of the affected patients with AMN or CUBN mutations.

2. The functional consequences of the novel mutations are not clarified with equal detail:
   a) Whereas protein expression is analysed beautifully for the G1112E mutation, similar analyses are not shown for the novel AMN mutations. This would be interesting and would complement the nice data on altered AMN transcription for the mutation in family 3 (c.1006+11_1008del). Also, it would be important to see transcription experiments for the novel c.1041_1042delinsCTC mutation in AMN, and for the novel CUBN mutation.
   b) in table 2, last column, it should be indicated what analyses the "yes" and "no"
is based on, or what type of experiments (transcription, protein expression, in silico prediction tools).

Minor Essential Revisions
1. Does the novel CUBN mutation lead to a G1112E or G112E mutation. This is inconsistent in the ms.
2. the authors should include GWAS findings of albuminuria in their discussion of differential phenotypic effects of CUBN and AMN variants on pages 18 and 19, since these extend into the general population and have a more general relevance (Boger et al JASN 2011). Also, the localisation of the mutation in the CUBN gene (which CUB domain) should be discussed.

Discretionary Revisions
Given their authoratitive standing in the field, it would be helpful if they provided a table of all known mutations of AMN and CUBN and their published phenotype correlation, thus providing the reader with an excellent reference.

Level of interest: An article of outstanding merit and interest 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