This manuscript aims to further characterize the genetic basis of tubular proteinuria in patients with the Imerslund-Grasbeck syndrome (IGS). Patients with IGS have mutations in the genes CUBN or AMN which encode the proteins cubilin and amnionless respectively. Proteinuria is found in many patients with IGS, but not in all of them. Interestingly, a meta-analysis of GWASs, found that a missense variant of CUBN (I2984V) was associated with albuminuria in individuals from European ancestry [Boger CA, JASN 2011]. Evidently, CUBN and its product cubilin are of interest with regard to the pathophysiology of proteinuria and albuminuria.

By mutation analysis of CUBN and AMN, the authors characterized the genetic cause for nine IGS patients of six families. They expanded the present mutations' data by adding one novel CUBN mutation and two novel AMN mutations. In silico + in vitro studies were done to better characterize the deleterious effect of the novel mutations. Tubular proteinuria was assessed by detailed urine testing and the authors describe a genotype-phenotype correlation with regard to proteinuria. The manuscript is well written and all studies were well performed with a convincing presentation.

I highly regard genotype-phenotype correlation studies in rare Mendelian disorders, as it may aid in clinical practice. It can also help us to better understand the function of gene-of-interest and its different domains. However, I find that this manuscript has major weaknesses regarding its importance.

Primarily, the number of patients is very small. Indeed, IGS is a rare syndrome, yet we have hundreds of IGS patients world-wide and the addition of nine patients to the literature may contribute little to our knowledge. A recent mutational analysis of CUBN and AMN in a large cohort of IGS patients added 26 novel CUBN and 19 novel AMN mutations (Tanner SM et al. Orphanet J Rare Dis 2012). It can put into perspective the added-value of the three novel mutations.

The urine analysis in this study was well done. But once again, I find that the small number of patients in this cohort reduces substantially the power of the genotype-phenotype correlation. At most, we have three patients from two families with the same genotype of AMN (homozygous c.208-2A>G). We are left with suggestions about the possible different effects of mutations on the occurrence or absence of proteinuria in IGS patients. It is not a new hypothesis and I do not feel that the findings here contribute greatly to its' validation.
Level of interest: An article of limited interest

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

No