Reviewer’s report

Title: Novel compound heterozygote mutations of TJP2 in a Chinese child with progressive cholestatic liver disease

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Reviewer: Emma Andersson

Reviewer's report:

The authors present a case report of a 23-month-old Chinese female patient with a low GGT cholestasis, identified as a carrier for two novel TJP2 heterozygous mutations. The case report is interesting, and in line with previous findings showing that TJP2 mutations result in a form of progressive familial intrahepatic cholestasis.

The authors suggest that the splice site disruption and frame shift mutation both abolish translation. It would be interesting to show from cells, or biopsies, or in overexpression experiments, that these mutations indeed abolish translation (western blot, compared to wild type TJP2 translation). Perhaps this is beyond the scope of a publication in BMC Genetics, from what I can see of other case reports, but I think it would strengthen the claims substantially.

It is unclear whether informed consent was provided by one of two parents/guardians (line 169 and line 173), or whether there is only one parent/guardian that is relevant. This should be clarified and ensure that the study complies with all applicable ethics guidelines.

Availability of data: "available upon reasonable request". This is unfortunately often used as a phrase to avoid sharing data (at least has been with other groups). The sequencing of the other genes should be available upon request, or deposited.

I could not find a methods section. - what sample was sequenced (blood, saliva.. other?) More information on the targeted sequencing would be helpful (see especially comments for line 95).

Moderate comments:

Line 79 The imaging of the patient's condition could be put into a figure, especially the biliary obstruction should be represented.

Line 82: It could be mentioned that the biochemical profile discussed is at 23 months of age

Line 92 should the treatment not be more specifically described? (doses?)

Line 95: How was the selection of the 396 genes done? MYO5B is missing from the list, while it is also described as a mutation observed in low GGT cholestasis (Qiu, Hepatology 2017)
Also, why is the table listing genes with mRNA accession numbers rather than gene IDs? Does this mean that genes with different transcript variants were assessed for only one transcript variant?

Line 100 Figure 1 is of poor quality and should be replaced by a figure of higher resolution

Line 111 of note: Byler's disease is specifically referring to PFIC1

Minor comments:

In general, the English language could be improved in this manuscript.

Line 28 replace by "decades"

Line 35 "which WERE inherited"

Line 37 should be "neither has" instead of "none have"

Line 48 "disorders THAT are characterized"

Line 51 "leads RAPIDLY to end stage liver disease in untreated…”

Line 52 rephrase

Line 61 remove "of"

Line 64 "identified AS responsible"

Line 67, Line 119, Line 140, Line 153 "heterozygous mutations"

Line 68 "ARE described"

Line 71 replace "a special face" by "particular facial features"

Line 72: PROTRUDING instead of FORWARD

Line 74: "since the age of 6 months"

Line 75: when hospitalized

Line 78 rephrase, suggestion "No signs were found that the lungs and heart are affected" (the phrase "no positive signs were found" is very ambiguous)

Line 81: "showed a normal thoracic spine"

Line 92 replace "given" by "treated"
Line 100 reword "damaging", could be replaced by "detrimental"

Line 109 "NR1H4, which linked to PFIC, were…"

Line 116: "Elevated levels of serum bile acid AND…"

Line 118: "when admitted at the age of 23 months."

Line 120 "patients, which WERE…"

Line 134: "It was shown that"

Line 137 replace "that" by "to be"

Line 142 "causING PFIC 4"

Line 143: use "neither has" instead of "none have"

Line 145: "Animal studies have shown that loss of Zo-2 protein led to early…"

Line 147: Use treated instead of administrated

Line 150 "AS TJP2 mutations may…"

Line 151 "of HCC, patients should be monitored closely…"

Line 152 replace "firstly" by "for the first time"

Line 169, Line 173 I believe it should state "parentS" (or is there only one caretaker? In either case, it is important to ascertain whether only one parent gave consent? - If there are two parents, I imagine both should give consent)

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

No

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes
Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

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Please indicate the quality of language in the manuscript:

Needs some language corrections before being published

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