Reviewer’s report

Title: Hypotonia and intellectual disability without dysmorphic features in a patient with PIGN-related disease

Version: 2 Date: 30 Jun 2017

Reviewer: Romain Peanne

Reviewer’s report:

Thiffault and colleagues describe the identification of a new patient with mutations in the PIGN gene. This gene encodes glycosylphosphatidylinositol (GPI) ethanolamine phosphate transferase 1 (PIGN), a protein involved in GPI-anchor biosynthesis. PIGN is expressed in various tissues, and pathogenic variants in PIGN have been reported to be associated with a broad range of clinical phenotypes, including multiple congenital anomalies, dysmorphic features, developmental delay, hypotonia and epilepsy.

Here is reported the identification of a 2 years old male with hypotonia, global development delay, and focal epilepsy. Trio-whole exome sequencing revealed heterozygous variants in PIGN, as well as a heterozygous variant in the SCNA1 gene. This variant was already identified when the patient was around 5 months of age, after that targeted NGS analysis for an epilepsy gene panel was performed. In addition, the authors performed flow-cytometry analysis on blood granulocytes, after staining for both FLAER and CD59, to investigate the expression of GPI anchors and GPI-anchored proteins, respectively. Based on all of their observations, Thiffault and colleagues interpreted the reported case as a PIGN-related disease, although dysmorphic features were not present. Nevertheless, as they report it themselves, this observation is in line with recent reports describing a genotype-phenotype correlation for PIGN-deficiency, even suggesting that major congenital abnormalities might not be a core feature of PIGN disorders.

After reading and evaluation of this manuscript, I'm glad to recommend this manuscript to be approved for publication. I only have minor comments, mostly concerning the language. A very few corrections are still needed.

Abstract:

Page 02, lane 28: 'FLAER and anti-CD59 by flow-cytometry'. Please correct by 'ANALYSIS OF FLAER and anti-CD59 STAINING by flow-cytometry'.

Background:

Page 03, lane 55-61: please reformulate this paragraph. The way it is currently written is very confusing.
Case presentation:

Page 05, lane 99: ' [...] focal epilepsy, hypotonia, developmental delayS, [...]'. Please correct 'delayS' by 'delay'.

Page 06, lane 125: ' [...] of the type expected to be pathogenic, the mRNA produced [...]'. Please modify by ' [...] of the type expected to be pathogenic, SINCE the mRNA produced [...]'.

Page 07, lanes 143-144: 'Such studies (Figure 2) demonstrated a shift in this patient's granulocytes, [...]' . Please correct by 'Such studies (Figure 2) demonstrated a shift IN ANTI-CD59 AND FLAER STAINING IN THE patient's granulocytes, [...]' .

Conclusion:

Page 07, lane 151: 'In addition, 22 so-called "PIG genes" are required for synthesis [...]'. Please correct by 'In addition TO THOSE, 22 so-called "PIG genes" are required for synthesis [...]'.

Page 09, lanes 182-184: 'More recently, Fryns syndrome can be caused by recessive mutations in PIGN [...] heterogeneity'. Please replace by 'More recently, recessive mutations in PIGN WERE ALSO DESCRIBED TO CAUSE Fryns syndrome, [...] heterogeneity'.

General comment: please check for spelling mistakes, punctuation errors, and typos.

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

Yes

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
Quality of written English
Please indicate the quality of language in the manuscript:

Needs some language corrections before being published

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