Reviewer's report

Title: Novel association of severe neonatal encephalopathy and Hirschsprung disease in a male with a duplication at the Xq28 region

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Reviewer: Maria-Mercedes Garcia-Barcelo

Reviewer's report:

The authors present an excellent and exhaustive study of a patient with severe neonatal encephalopathy and Hirschsprung’s disease. The manuscript is comprehensive, well written and the discussion adequate. I have some minor issues that I would like the authors to clarify for me.

1: Material and Methods/patients:
It is not clear to me how many individuals have been analysed. The authors described the index patients but then I am not sure of how many relatives etc have been submitted to the fully analysis.

2: I am not familiar with the probes used/coverage for the MLPA assay. Perhaps this should be spelt out and a rationale for its differential use given.

3: X inactivation analysis. Authors should explain the necessity of the test in this context

4: from all the genes reported to be duplicated in Xq28 as per the MLPA kits (first paragraph results section), it is not clear to me -or I have not understood- how the authors attribute the phenotype to L1CAM only. On what basis were IRAK1 IDH3G present in the duplicated region excluded? perhaps the authors should comment on this issue.

Level of interest: An article of importance 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'