Reviewer's report

Title: A novel study of Copy Number Variations in Hirschsprung disease using Multiple Ligation-dependent Probe Amplification (MLPA) technique.

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Reviewer: Eli Hatchwell

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A novel study of Copy Number Variations in Hirschsprung disease using Multiple Ligation-dependent Probe Amplification (MLPA) technique.

This is a poorly written and generally weak paper. The English is very weak (see examples below). The authors correctly point out that the standard methods used for mutation detection (sequencing, SSCP, dHPLC) will miss copy number variants and decided to use a commercial kit from MRC-Holland (MLPA-Hirschsprung test kit, P169) to search for deletions and duplications within a set of 4 genes (RET, ZFHX1B, EDN3 and GDNF). While 2 examples were found of decreased dosage, the authors subsequently demonstrated that these represented sequence variations that affected probe annealing, rather than true copy number changes. The authors do not discuss why these sequence variants were not detected during their dHPLC screening prior to the use of MLPA.

Apart from the poor English, my major criticism is that this paper reveals little that is novel, either in terms of results or methodology. The authors used a commercial kit, developed by MRC-Holland. Had they designed their own assay and used this publication to demonstrate it's benefits over an off the shelf kit, I might have been more favorable towards this article.

There is clearly a fine line between routine diagnostics and research and my view is that the contents of this paper fall more on the side of diagnostics. It should be routine, these days, for any condition that results from alterations of known genes to look for copy number variations as well as sequence changes in those genes. As such, it is only novel methods or variations on known methods that should be worthy of publication.

Examples of poor use of English (I have chosen only a few examples – there are too many to list):

Abstract, first sentence: “…during embrionary development.” Should be “…during embryonic development.”

Background, end of 4th para: “Nevertheless, additional studies are required to deep in the real involvement in the disease.” I think I understand what they mean but I am not sure how to correct this!
Level of interest: An article of limited interest

Quality of written English: Not suitable for publication unless extensively edited

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