Reviewer’s report

Title: Primary Ciliary Dyskinesia in Japan: Systematic review and meta-analysis

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Reviewer: Robert Anthony Hirst

Reviewer’s report:

This paper describes a meta-analysis of previously published data on PCD cases in Japan. It gives an excellent overview of the landscape of PCD diagnostic testing and the known cases in Japan.

A total of 316 patients with PCD have been identified and stratified by their TEM phenotype and clinical findings. The incidence of PCD in Japan is suggested in the paper to be 1 in 8000 which is higher than in the west.

Also, there seems to be a large proportion of PCD due to defects in isolated inner dynein arm defects. At the time of review, the genes for isolated IDA defects in PCD are unknown.

One thing that is missing is a geographical representation of where in Japan the PCD cases live?

Also which TEM phenotypes are found in specific Japanese regions? For example, are the isolated IDA defects found in a particular isolated community?

The authors have quite rightly stated a number of limitations in this study. These being that clinical symptoms may be underestimated, TEM analysis may be inaccurate, and not standardised.

In addition to these, there are other limitations to interpreting the findings from the literature analysis:

1. The papers cover a period of time when the diagnosis of PCD was evolving rapidly so some of the early testing may have been inaccurate.

2. Clinical awareness of PCD has also increased rapidly and more recent studies may have greater clinical detail and insight.

3. The experience of the diagnostic scientists in the Japanese test centres is likely to be hugely variable and this may also influence the TEM results.

The authors state that undiagnosed PCD in Japan may be hidden and as such the authors suggested that in future, a joined up approach to diagnostic testing in Japan needs adopting. I think that this is essential and due to Japan’s size and population, I would recommend following
the ERS guidelines for PCD testing (Lucas et al, 2017, https://www.ncbi.nlm.nih.gov/pubmed/27836958) over the US recommendations (Shapiro, 2018, https://www.ncbi.nlm.nih.gov/pubmed/29905515). High speed video analysis has recently been shown (Rubbo et al 2019, https://www.ncbi.nlm.nih.gov/pubmed/30826306) as an excellent tool for detecting PCD cases and would easily be adopted in Japan. The other major strength of the ERS guidelines over the US based gene panel and nNO based approach is that cross centre audit and standards can be unified between close diagnostic centres. Also, because the US guidelines depend heavily on known PCD gene panel testing as a primary approach, a high incidence of PCD in Japan may mean that many undiscovered genes for PCD exist in the population. Genetic screening using a whole exome approach is the only way to discover these novel genes.

**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.

Unable to assess

**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.

I am able to assess the statistics

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