Reviewer's report

**Title:** Genetic analyses of bone morphogenetic protein 2, 4 and 7 in congenital combined pituitary hormone deficiency

**Version:** 2 **Date:** 10 October 2013

**Reviewer:** Daniel Kelberman

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The manuscript details the molecular screening of three members of the BMP family in a small cohort of individuals with heterogeneous CPHD phenotypes. The manuscript is much improved, however, in the authors' own admission it is difficult to draw firm conclusions from the data presented and it is hard to see how this study in its current form adds much insight into any possible role of these genes in contributing to human disease. In order to truly assess the contribution of these genes to CPHD phenotypes it would be much better to screen larger cohorts of patients, as the current study is very small. This could be achieved through collaboration if necessary.

This study mostly comprises the identification of previously reported common variation in these genes which are unlikely to be contributing in any understandable way to disease. The most interesting variant in BMP4 (c.899C>G) looks worthy of further investigation, but there is no real data presented to draw firm conclusions. The authors state in their rebuttal they are currently conducting functional studies to investigate the consequences of this variant, in which case this data should be included in the same manuscript to strengthen support for any potentially pathogenic role. A second variant that initially looked interesting and may have affected splicing from the original manuscript now appears not to have been real and has been removed from the current version which does bring into question whether electropherogram data should be presented for each variant.

There are other minor points that would improve the manuscript.

1. Correct gene nomenclature is inconsistent throughout the manuscript, gene names should be listed in italics and capitalised in reference to humans. Reference to the gen name PIT1 is incorrect, the official HGNC name for this gene is POU1F1.

2. The column "lack of GH, TSH, LH/FSH, ACTH" in Table 1 is somewhat meaningless and should include details of hormone levels in recognised units with normal ranges.

3. In table 2 it is unclear from the MAF in analyzed cohort column whether this is for the entire cohort of affected and unaffected individuals genotyped or just the 19 affected cases.
Level of interest: An article whose findings are important to those with closely related research interests

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