Reviewer's report

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

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Reviewer: Daniel Kelberman

Reviewer's report:

The authors present data in mutation screening of three BMP genes (BMP2, 4 and 7) in a small cohort of 19 patients with a broad range of combined pituitary hormone deficiencies variably associated with other abnormalities. The authors have identified a number of previously reported and novel genetic variants, however the contribution of these variants to the pathogenesis of the conditions manifested by the patients is unclear. Although studies of this nature providing interesting insight into human genetic variation, the cohort size is very small and limited firm conclusions can be drawn from the data as presented with no functional or family data.

There are a few major concerns with regard to the manuscript

1. The major concern relates to the nomenclature used to describe the variants which is of paramount importance to avoid any confusion as to the specific variant bases and amino acid changes. The authors have stated Ensembl gene accession numbers for each of the three genes, however BMP7 in particular has multiple transcripts and it is unclear as to which the stated variants c.611+3366C>T and c.959-2T>C are referring to. The numbering used should be clearly defined for each variant relative to the accession number for a given transcript so there is no ambiguity. The latter change in particular should be checked carefully as it appears to this reviewer that base c.959 is the first base of exon 5, therefore the variant c.959-2 should refer to the invariant AG splice acceptor site preceding this exon. Seeing as any variation at this position is likely to affect splicing these details need to be checked and clarified. I would recommend checking the naming of all variants with the Mutalyzer program. On a similar note, all amino acid variation should be prefixed "p." in the manuscript.

2. The authors acknowledge the limitations of bioinformatic prediction tools, however there are a wealth of alternative programs that assess other aspects of genetic variants beyond sequence conservation. I would recommend, in the absence of any experimental data, using a variety of different programs available to try to assess pathogenicity (eg. Mutpred, SNPs&GO, mutation taster, fathmm) to obtain a consensus from multiple different models. It would also be good to provide parental genotype information, but I appreciate this is not always possible.

Minor revisions
1. The PCR primers used for screening should be made available in the manuscript or supplementary information rather than being available "on request."

2. It would be interesting if the authors included information on the genetic variation identified in the patients in the screening of other genes listed in the Additional information. The authors state this analysis did not reveal any aberrant results but it would be good to include in the table the variation that was observed.

3. Page 5, the term "infinite omega" with regard to PAML analyses should be defined.

**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