Reviewer’s report

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

Version: 1 Date: 19 May 2013

Reviewer: Frederic Castinetti

Reviewer’s report:

This study is giving original but very preliminary results on a potential new etiology of CPHD. There are however serious limitations, that are well recognized by the authors in their discussion. I am skeptical about the real interest of this report if the authors do not manage

- to perform additional TF gene sequencing in the patients with BMP’s SNP (to be sure that they are not carrying a mutation of a known TF gene)
- to give additional data about family (and ideally perform sequencing)
- to give more insights on the way BMP4 mutations would lead to a pituitary phenotype without severe organ defects taking into account their early roles in brain/body development (unless there might be a way, maybe by collaboration with another group, to perform functional studies)

To summarize, if the idea is original, the research part in this paper might be too preliminary to lead to a publication currently.

Moreover, to my knowledge, BMPs are not pituitary specific, and this makes me skeptical about the possibility of having isolated pituitary phenotype with such mutations (if they are real mutations)

A few points to consider more in detail as major revisions

1. It is hard to imagine that BMP2 mutations leading to heart defects and very early death in mice could lead to an isolated phenotype of CPHD in Humans. Are there any known mutations of BMP2 lading to isolated organs dysfunction in Humans?

2. How about phenotyping PROP1 and POU1F1 in the 19th patient?

3. Can the authors predict what would be the consequence of BMP4 mutation? It is a highly conserved sequence, but is it located in a functional domain, a DNA interaction zone…

4. Ok to consider that bmp4 mutation could induce the skeletal phenotype. For this reviewer, this is clearly not an evidence for the role of BMP4 mutation in pituitary phenotype.

5. Patient 5 (who seems to be the more interesting) could take benefit from sequencing of other genes coding for TF, taking into account the non specific pituitary phenotype (before considering that BMP4 mutation could lead to the pituitary phenotype)
6. I might have missed it in the paper... Was the BMP4 SNP hetero or homozygous?

Minor revision
Individual data are needed in the manuscript, and not as an additional table. Another possibility could be to include a summarized table with only the patients with BMP SNPs.

**Level of interest:** An article of limited interest

**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