Reviewer's report

Title: A novel GLI3 Mutation Affecting the Zinc Finger Domain Leads to Isolated Polydactyly

Version: 1 Date: 1 June 2014

Reviewer: Tania ATTIE-BITACH

Reviewer's report:

The paper of Huppke and coauthors reports on a novel GLI3 mutation in a single large family described as affected with polydactyly/polysyndactyly. The mutation is located in a C2H2 motif of the Zing Finger domain of the protein, where mutation classically lead to Greig polysyndactyly syndrome (GCPS).

Major revisions

1/ The main statement of the paper is that the patients have no other features, in particular of the spectrum of GCPS. However in this family, 5/8 patients have an OFC at or above the 90° centile, and in unaffected members, the OFC is always beyond the 55° centile. This is the classical range of OFC observed in GCPS where OFC is around +2ds/+3ds. Therefore, the family is not an unusual presentations of the disease and authors should change the title and this statement all over the paper:

- "OF findings are similar in affected and non affected individuals" (page 5, 107)

- "presenting no other syndromic feature"

The authors seem confused themselves about this as they define the family as having "a practically isolated polydactyly syndrome". "isolated" and "syndrome" are contradictory and lead to an inconsistent sentence.

Why not simply presenting the family as a GPCS, with familial variability, including some members (3) with isolated polydactyly?

2/ For a single family report, the clinical data could be better presented and much precise, and would strengthen the paper. The supplementary table contains only OFC and IPD measurements, with no correspondence between the numbering of patients in this table and in the pedigree (figure 1A). The other features are described in the text globally for all patients together. To better appreciate the familial variability, a table should summarize all clinical data of each individual, including the limb features, macrocephaly, intellectual disability, brain imaging if performed. It's quite deceiving not to be able to appreciate the facial dysmorphisms.

3/ In the methods section, page 4 line 83, the authors write "linkage to genes known to be associated with isolated polydactyly was tested using 2 polymorphic
markers flanking each candidate gene: association of the phenotype with SHH, GJA1, HOXD13, LMBR1 and FBLN1 was ruled out". This sentence suggest that mutations in all these genes are associated to isolated polydactyly. However:

- SHH and LMBR1 represent the same locus and isolated polydactyly might result from point mutations in a Sonic hedgehog regulatory element (ZRS) located within intron 5 of the LMBR1 gene, while mutations in the SHH gene itself leads to holoprosencephaly and mutations in the LMBR1 gene result in Acheiropodia.

- To my knowledge, GJA1 mutations are not associated to polydactyly. Could the authors cite a reference?

Minor remarks

- The novel GLI3 mutation is interesting, within the C2H2 motif of the Zinc finger domain, predicting it's pathogenicity as shown by the crystallographic structure modeling of the mutant. The authors might discuss the other GLI3 mutations affecting C2H2 motifs that have been reported previously in GCPS.

- Page 3 line 57: authors present together the consequences of GLI3 germline mutations (GCPS, PHS, PD) and GLI3 somatic loss of heterozygosity (hypothalamic hamartoma). This might be confusing for readers.

- Page 4 line 90: "miss-sense" to correct

- Legends to figures should describe the limb malformation, and indicate to which patient they belong in the pedigree.

**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 no competing interests