Author’s response to reviews

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

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Author’s response to reviews: see over
Dear Editor,

Within the known extreme phenotypic variability of GLI3 mutations, it has been suggested that ZFD mutations cause a Greig Cephalopolysyndactyly Syndrome (GCPS) phenotype. We now demonstrate a novel GLI3 mutation affecting the ZFD domain in a large kindred, and suggest that the findings, within the very large scope of GCPS, demonstrate a mild phenotype of the syndrome, in some of the cases affecting only the limbs.

**Detailed response to the reviewers' comments is below.**

Conflict of interest: The authors have no conflict of interest to declare.

The study has been approved by the Soroka Medical Center IRB, and all DNA samples have been obtained following signed informed consent.

All contributors have read and approved the submission to the AJMG journal.

We are submitting black and white figures for print and a color version for the online edition.

Sincerely,

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**Detailed response to the reviewers' comments:**

I. Reviewer 1 (Yiping Shen):
   1. Recent references regarding effects of GLI3 mutations (including Sethi et al 2013, Wang et al 2014) have been added.
   2. A short discussion has been added (Discussion) regarding possible effects of variations in other genes leading to variable phenotypic consequences of a single GLI3 mutation.
   3. Reference was added for the sentence stating that "mutations affecting the ZDF domain specifically cause GCPS". (now lines 63-66).

II. Reviewer II (Tania Attie-Bitach):
1. It is now clearly stated that 5/8 patients have OFC above 90% while 3 have an isolated limb phenotype. Sentences requested to be removed in that respect – were removed, namely:
   - "its appears that macrocephaly is not a hallmark of this family's phenotype"
     (previously page 4),
   - "OFC findings are similar in affected and non-affected individuals (previously page 5)
   - "presenting no other syndromic feature".
2. As suggested the family is now presented as one with a variable phenotype, ranging from GPCS with large OFC to cases of isolated limb defects.
3. Clinical data are now presented in greater detail, with the table now extended and containing reference to relevant family members in the pedigree. The table now contains clinical data of each individual, including the limb features, macrocephaly and intellectual disability when present (there were no brain imaging data).
4. In the Methods section, the text was fully adjusted in line with the referee's comments. The claim that GJA1 mutations are associated with polydactyly was removed.
5. Minor comments:
   - GLI3 somatic mutation (hypothalamic hamartoma) is now not mentioned to avoid confusion.
   - Miss-sense corrected
   - Legends to figures now describe the limb malformations demonstrated and specify the patients in the pedigree.

III. Reviewer III (Sajid Malik):
1. The mutation is now mentioned in the abstract
2. The clinical data are now presented in a table with significantly more detail.
3. Title: has been amended as suggested.
4. The phrase "isolated polydactyly does not appear now in the abstract or text.
5. Minor comments:
   - Recent references were added (14, 15)
   - The table now specify which of the patients in the pedigree are referred to
   - Missense now spelled correctly
   - Non affected – changed to unaffected