Author's response to reviews

Title: Variable expressivity of FGF3 mutations associated with deafness and LAMM syndrome

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Responses to reviewers’ comments

Thank you for providing the reviewer’s minor concerns regarding our revised manuscript. Below we provide a point by point response to Dr. Frei’s three comments. Changes are highlighted in the the second revision of our text.

1. “Abstract page 4 Results

A possible semi-dominant effect of the mentioned mutation is highly speculative and not shown in the paper. The statement in the abstract is leading to a wrong suggestion.”

We observed conductive hearing loss in the three carriers of a presumably recessive mutant allele of FGF3. We suggested possible explanations for this observation, and indicated that we could not exclude the possibility of otitis media. How much more careful can one be in interpreting the data? There is nothing misleading about one speculative comment in the context of alternative explanations, which we provide.

Nevertheless, in order to avoid a third review of our manuscript, we have revised the abstract and explicitly state the alternative explanations in the abstract. We now state

“We also observed a mild to moderate bilateral conductive hearing loss in three carriers of p.R95W, suggesting either a semi-dominant effect of this mutant allele of FGF3, otitis media, or a consequence of genetic background in these three
family members.”

-Background page 6 line 4 compared to discussion page 15

The two different statements concerning the mouse model are still not changed: normal or mildly abnormal inner ears versus highly variable inner ear phenotype.

We have changed the statement on the page 6, line 4. It now reads “Mice deficient for FGF3 do not model LAMM syndrome but rather have abnormal inner ears with variable penetrance and expressivity on a uniform genetic background.”

-Throughout the paper, the dental status is weakly described and discussed.

In the previous version of this manuscript, we crafted our statements regarding the dental phenotypes so as not to overstate what we observed, and we provided a figure showing photos of teeth. We clearly stated in the Results section of the first revision of our manuscript that

“Affected members of families PKDF295 and PKDF887 showed microdontia with conical, sharp and pointed lateral incisors (white arrow, Figure 2) and widely spaced teeth. In contrast, many of the affected members of PKDF817 had a subtle dental phenotype (Figure 2C). PKDF817 V-3, V-4 and V-5 individuals did not show wider interdental distances compared with those from a heterozygous carrier of the missense mutation. Individuals V-8 and V-10 from family PKDF817 showed neither malformed lateral incisors nor unusually wide interdental spaces (Figure 2C).