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CORRESPONDENCE

Reply to Pubpeer anonymous contributors: incomplete penetrance and phenotypic variability of 6q16 deletions including *SIM1*

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TO THE EDITOR:

We appreciate the opportunity to reply to the Pubpeer contributors who commented on our paper *'Incomplete penetrance and phenotypic variability of 6q16 deletions including SIM1'* [1]. A series of 15 patients with *de novo* 6q16 deletions was reported in this article, including the first patient with fetopathological data. Using '*Oxychilus pilula*' and '*Haemonchus contortus*' as pseudonyme, Pubpeer contributors raised several questions on the neuropathological examination of this foetus (https://www.pubpeer.com/publications/7DE7D7315929E33A513493198D2B2F#1).

We thank them for their interest in this report and for their suggestion to perform other coloration and specific staining for the neuropathological examination. Immunohistochemistry using anti-MAP2 and anti-GAD67 antibodies as markers of pyramidal neurons and interneurons allowed to confirm a migration delay or defect of pyramidal cells in the cerebral white matter (Supplementary Fig. 1). Cresyl violet coloration and Calbindin immunohistochemistry confirmed the focal neuronal ectopia observed in the cerebellum in the Figure 1 of the article published in 2015 [1] (Supplementary Fig. 2). These results consolidate evidence of cerebellar and cerebral migration defects with neuronal heterotopias in the reported foetus (Patient no. 1 in the paper) [1].

In addition, we would like to apologise for errors in the interpretation of neuropathological sections and in the legend of Fig. 1. We fully agree that the fusion of the anterior caudate nucleus and putamen (Fig. 1c) can be a variation of normal and that the sections presented in Fig. 1c, and Fig. 1f were erroneously indicated as sagittal. The legend should be changed as follows (changes are in bold font):

Fetopathological study of Patient no. 1. (a) Facial features: short straight forehead, marked suborbital folds, broad nasal bridge, prominent philtrum, thin upper lip, micrognathia, and abnormally hemmed ears with a small horizontal fold along the upper edge of the helix. (b) Radiographs of the feet: bilateral calcaneal fragmentation and hypermineralisation. (c) **Coronal** section through the brain: internal capsule dysmorphism with fusion of anterior caudate nucleus and putamen (black arrows). (d) Cerebral white matter containing ectopic neurons (black arrows). (e) Cerebellar grey matter containing ectopic neurons (black arrows). (f) **Horizontal** section through the cerebellum showing focal neuronal heterotopia.

In the Results section, the last paragraph in the description of Patient no. 1 should be changed as follows (changes are in bold font):

Microscopic examination of the brain evidenced fusion of the anterior caudate nucleus and putamen (Fig. 1c), **which can be considered as a variation of the normal**. **There were also** multiple ectopic neurons in the white matter (Fig. 1d) and ectopic Purkinje cells in the **inner** granular layer of the cerebellum (Fig. 1e). Two large heterotopias were identified in the white matter of the paravermis (Fig. 1f).

Of note, Patient no 1 had a large 6q16 deletion (14 Mb) that encompassed several developmental genes, including the (ephrin receptor A7) *EPHA7* gene. Although the known role of *EPHA7* in central nervous system patterning seems compatible with neuronal migration defects observed in neuropathological examination of Patient no 1, no equivalent phenotypic feature was detectable on brain MRI of eight patients with more proximal 6q16 deletions encompassing *EPH7A* but not *SIM1* [2]. The main core phenotype of patients with proximal 6q16 deletion includes a neurodevelopmental disorder with developmental delay, speech delay and behavioural disorders with incomplete penetrance and variable expressivity. Patient no. 1 remains the only one for which neuropathological data are available. Additional patients with *EPHA7* and or *SIM1* haploinsufficiency and functional studies are still necessary to refine the phenotypic description and precise the genotype–phenotype correlation.

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DATA AVAILABILITY

The fetopathological study of Patient no. 1 was previously reported [1]. Genotype and phenotype data can be found in the DatabasE of genomiC varIation and Phenotype in Humans using Ensembl Resources (DECIPHER ID: 292285; https://decipher.sanger.ac.uk/patient/292285). All data analysed for this correspondence are included in the Supplementary Information files.

REFERENCES

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AUTHOR CONTRIBUTIONS

FG performed the additional staining and immunohistochemistry for the neuropathological examination. FG and ADD conceived the Supplementary Figures. LEK, FG and ADD wrote the correspondence. ADD coordinated the work. All authors have approved the final correspondence.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL

Informed consent was obtained from the parents for the autopsy.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41431-022-01110-0.

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