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LETTER TO THE EDITOR

Reply: Expanding the clinical and genetic spectrum of *PCYT2*-related disorders

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We read the letter by Vélez-Santamaría *et al.* (2020) describing two new cases of *PCYT2* deficiency with great interest. We recently described, for the first time, a new form of complex hereditary spastic paraplegia (HSP) caused by CTP: phosphoethanolamine cytidylyltransferase deficiency (Vaz *et al.*, 2019). CTP: phosphoethanolamine cytidylyltransferase, encoded by *PCYT2*, is the rate-limiting enzyme of the CDP-ethanolamine pathway and is involved in the synthesis of phosphatidylethanolamine and related ether lipid analogues. *PCYT2* deficiency is now indexed in OMIM as spastic paraplegia type 82 (MIM 618770).

One patient in our previous report had compound heterozygous missense variants, while the other four patients had a last exon frameshift homozygous variant [NM_001184917.2:c.1129C>T p.(Arg377Ter)] where the gene product escapes nonsense-mediated decay (Vaz *et al.*, 2019). In all five patients, mutations resulted in reduced, but not absent, PCYT2 enzyme activity. This observation, in conjunction with results of our zebrafish experiments, prompted us to propose that *PCYT2* deficiency is caused by hypomorphic mutations and that complete inactivation is likely to be incompatible with life in vertebrates. Although enzyme activities were not measured by Vélez-Santamaría *et al*, it is clear that neither of their patients would be expected to have a complete enzymatic deficiency of *PCYT2*. Hence, this broadening of the genetic spectrum further supports our hypothesis regarding the hypomorphic nature of the disease-causing *PCYT2* variants. Also, the NM_001184917.2:c.1129C>T p.(Arg377Ter) variant has now been described in 9/14 mutant alleles in patients with *PCYT2* deficiency and interestingly, patients with this variant come from varying ethnicities (British, Turkish, Caucasian American and African American). Further work will be required to uncover if this is a recurrent variant or if it has a common ancestral origin.

Clinically, the first of the two new cases described by Vélez-Santamaría *et al.* (2020) had a normal cognition and is best described as a pure HSP in contrast to the other, more severe, patients that are characterized as having a complex HSP. The second, Case 2, had bilateral cataracts and bilateral optic atrophy, which was also observed in the first patient cohort we described. These new case reports thus expand the clinical phenotype of *PCYT2* deficiency at the milder end of

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the spectrum and also point to a prominent role for optic nerve and eye pathology in disorders of the CDP-ethanolamine pathway. In this respect it is noteworthy that disturbed ether lipid metabolism, either a deficiency of ether lipids [as seen in different types of rhizomelic chondrodysplasia punctata and peroxisome biogenesis disorders (Gorgas *et al.*, 2006)] or an imbalance of ether lipid metabolism [as seen in *EPT1* deficiency (Ahmed *et al.*, 2017; Horibata *et al.*, 2018) and *PCYT2* deficiency] both give rise to similar ocular pathology. This suggests that a balanced ether lipid homeostasis is important for normal development of the eye.

At the biochemical level, Vélez-Santamaría *et al.* show that the plasma lipidomic profile in Case 1 is similar to what we found in our patients, although his phenotype was much milder. This supports our proposed role for plasma ether lipids as diagnostic biomarkers for *PCYT2* deficiency (Vaz *et al.*, 2019) even in milder cases. It will be interesting to perform studies to determine if lipidomic profiles can help predict the severity of the disease, its prognosis or response to treatment.

In summary, the study by Vélez-Santamaría and colleagues makes an important contribution to the further characterization of *PCYT2* deficiency and emphasizes the need for further research to understand the role of (ether) lipid biosynthesis in the pathophysiology of disorders of the CNS.

Data availability

Data sharing is not applicable to this article as no new data were created or analysed in this study.

Competing interests

The authors report no competing interests.

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