Dear Editors:

We agree with Dr. Striano and colleagues’ comments regarding the genetic heterogeneity of migrating partial seizures of infancy (MPSI, also called malignant migrating partial seizures of infancy, MMPSI). Our work reporting one cause of MMPSI, inherited mutations of SLC25A22,\(^1\) certainly falls within this context. Dr. Striano and colleagues’ observation of 21 SLC25A22-negative cases from among their patients with MPSI is consistent with the many cases we also reported in whom we did not find mutations in this gene.

Given this established genetic heterogeneity, the approach they suggest for the evaluation of an individual patient with MPSI is logical, with evaluation first for KCNT1 and then for other associated genes. We would include in such an evaluation PLCB1, TBC1D24, and SLC2A22, especially but not exclusively in consanguineous cases since the mode of inheritance is recessive, and SCN1A sequencing and deletion/duplication testing in all cases. Depending on the availability of options for genetic testing in the clinical setting, evaluation of these “MPSI genes” may be best achieved with a panel that would provide sequencing and copy number data for all of them simultaneously, rather than serially, for the sake of the efficiency when faced with an infant with a devastating epilepsy.

Our experience with a more common epileptic encephalopathy, infantile spasms, has revealed a rapidly expanding range of genetic causes for this condition.\(^2\) We anticipate a similar phenomenon for MPSI. Earlier data have suggested that MPSI may have a distinct set of genetic causes compared to other epilepsy syndromes.\(^3\) Though the elegant work of Barcia and colleagues has shown KCNT1 to be a major gene for MPSI,\(^4\) we nonetheless anticipate additional genes for MPSI to emerge. Thus, it would be prudent to evaluate patients with MPSI with as broad a list as possible for epilepsy-associated genes, particularly all genes associated with epileptic encephalopathies. In situations involving parental consanguinity, autozygosity mapping followed by targeted sequencing, or targeted analysis of exome sequencing data, will also help to identify new genes.\(^5\)

It remains to be seen whether the genes associated with MPSI are distinct from those associated with other severe early onset epilepsies, why that might be, and what the implications will be for treatment of children with MPSI. The current era of accelerated gene discovery in epilepsy brings the prospect of diagnostic clarity for our patients as well as an opportunity to translate these gene discoveries into gene-specific treatments for our patients with MPSI and other severe epilepsies.

Sincerely,

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References