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Reply

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We agree with the comments of Dr Striano and colleagues regarding the genetic heterogeneity of migrating partial seizures of infancy (MPSI; also called malignant migrating partial seizures of infancy). Our work reporting one cause of MSPI, inherited mutations of *SLC25A22*,[1] certainly falls within this context. The observation of Dr Striano and colleagues of 21 *SLC25A22*-negative cases from among their patients with MPSI is consistent with the many cases we also reported in which 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, as 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 efficiency in the case of an infant with 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] Although 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.

Potential Conflicts of Interest

Nothing to report.

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Questions about Efficacy of Exon-Skipping Therapy for Duchenne Muscular Dystrophy

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Mendell et al[1] report strikingly positive results after treatment of Duchenne muscular dystrophy (DMD) boys with eteplirsen, an exon-skipping antisense morpholino oligonucleotide. The number of dystrophin-positive fibers in muscle biopsy specimens was reported to increase (compared to pretreatment levels) by up to 52% after 48 weeks. Treatment for 48 weeks also showed a statistically significant improvement in walking ability