EDITORIAL OPEN ACCESS

What does a defect in N-glycosylation mean for neuronal migration and function?

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Neurol Genet 2020;6:e490. doi:10.1212/NXG.0000000000000490

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Somatic *SLC35A2* mosaicism correlates with clinical findings in epilepsy brain tissue

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Patients with epilepsy have not benefitted equally from the availability of next-generation sequencing. Although the diagnostic yield in epileptic encephalopathies is up to 50%, it is only approximately 12% in non-acquired focal epilepsies (NAFE).[1] However, somatic mosaicism has emerged as an important cause of genetic causation in NAFE. This is hardly surprising, considering the scale of cellular divisions and differentiations during the human brain development that provides ample opportunities for the occurrence of brain-restricted somatic variation. For example, depending on the developmental timing and a progenitor lineage, pathogenic variants leading to mammalian target of rapamycin pathway activation result in a spectrum of brain malformations, such as focal cortical dysplasia (FCD) type 2 or hemimegalencephaly.[2,3] Of interest, these developmental lesions seem to display a mutant allele gradient and a dose effect; approximately 13% of mutant alleles were observed in FCD type 2 compared with 40% in hemimegalencephaly, and the highest variant allele fraction seems to be in the epicenter of a lesion.[3,4] Although research has elucidated mechanisms underlying some malformations of cortical development, molecular etiology of other FCD types has remained obscured. N-glycosylation defects linked to pathogenic variants in the Solute Carrier Family 35 Member A2 gene (*SLC35A2*) have emerged as causal to an X-linked early onset epileptic encephalopathy typically manifested with infantile spasms or West syndrome in women or in mosaic men and most recently, they were also identified in approximately 30% of NAFE because of FCD type 1.[5,6] *SLC35A2* encodes a uridine diphosphate galactose transporter (UGT). A defect in the UGT results in a reduced galactosylation of N-glycosylated proteins, glycosphingolipids, and proteoglycans, which affects neuronal migration, axon guidance, and synaptic physiology.[7] In this issue of *Neurology® Genetics*, Miller et al.,[8] attempted to explore the impact of *SLC35A2* gene insufficiency on neuronal excitability. Evaluation of a 3-year-old boy with West syndrome and generalized spasms showed that the ictal electrographic correlates demonstrated a consistent emphasis over the left posterior head quadrant, a region further implicated by a subtle signal abnormality on brain MRI and a hypometabolism on a fluorodeoxyglucose positron emission tomography. Invasive monitoring with subdural grids and strips showed a varied density of interictal activity in the sampled areas and a broad ictal involvement of all subdural contacts. The patient underwent a multilobar resection, a neuropathologic examination confirmed FCD type 1c,[2] and exome sequencing identified a somatic, brain tissue-restricted, previously reported pathogenic variant in the *SLC35A2* gene (NM_005660.3: c.634-635delTC, p.Ser212LeufsTer9). The variant allele ranged from 0.6% to 27.7% in an exome and from 4.2% to 19.5% in a targeted variant validation across resected regions. The authors observed a correlation between interictal spike density and the pathogenic allele burden. The highest variant fraction (19.5%) and interictal spike density (32 spikes per minute) were in the hippocampal tissue, whereas the area of the inferior occipital gyrus showed the lowest spike frequency (5.7 spikes per minute) and a lesser variant allele proportion (4.2%–6.5%). This gene identification and validation study underscores the value for genetic diagnostic profiling of a resected brain tissue in patients with a nondiagnostic genetic testing of their peripheral samples. It adds to the growing number of cases where focal, genetically predisposed abnormalities manifest in generalized spasms. This lends some explanation for the surprisingly low (15%) yield of genetic testing of a peripheral DNA in this patient population.[9] A report by Miller et al.[8] further validates the *SLC35A2* gene as causal in FCD type 1 and lends support to experimental data linking

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disordered N-glycosylation to FCD type 1 and neuronal hyperexcitability and seizures.[10] It also attempts to link clinical markers of neuronal hyperexcitability to the burden of *SLC35A2* variation. However, many questions remain; first, there is the currently unresolved relationship between a mutant variant load and the resulting phenotype. In a recent case series, Vals et al. failed to see a correlation between the phenotype severity and the estimated quantity of pathogenic *SLC35A2* variants.[5] Of interest in the current study, variant proportions did not correlate with the messenger RNA expression of the alternative allele, suggesting the possibility of a nonsense-mediated decay. Because the UGT protein was not assessed, relationship among the varied proportions of the alternative allele to UGT quantities or function remain unclear. In addition, the imaging suggested an extensive area of signal abnormality and one would assume a corresponding structural distortion of cortical architecture. Curiously, the interictal spiking was restricted to a few defined areas within much larger regions sampled in this study. Future experimental work will have to clarify the potential impact of different *SLC35A2* pathogenic variants on neuronal structure and cellular and network function. The reported correlation among the spike frequency and the *SLC35A2* pathogenic variant proportions is interesting but will need to be confirmed in a sufficiently large case series with well-defined ictal onset and extended sampling of ictal and interictal data. Future studies will also need to pay attention to the properties and densities of spikes and variants at the margins of the resected lesion and explain their relevance for the outcome. Although it is tempting to ponder the reported relationship among the pathogenic *SLC35A2* variant proportions and the severity of imaging abnormalities, the absence of an unbiased quantification of the visualized lesion makes this correlation problematic to accept. Rather, it poses a research opportunity for the future. In summary, the case report by Miller et al.[8] adds to the growing recognition of brain-restricted somatic mosaicism as causal to infantile spasms and NAFE. It provides additional evidence connecting the *SLC35A2* gene to FCD type 1, thus opening opportunities to study glycosylation pathways in relationship to malformations of cortical development. It is also likely to stimulate future research linking *SLC35A2*-related genetic defects with the development of structural lesions and their functional manifestations on cellular and network levels.

Study funding

No targeted funding reported.

Disclosure

The author reports no relevant disclosures. Go to Neurology.org/NG for full disclosure.

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