The Expanding *SCN8A*-Related Epilepsy Phenotype

The Phenotypic Spectrum of *SCN8A* Encephalopathy.

Larsen J, Carvill GL, Gardella E, Kluger G, Schmiedel G, Barisic N, Depienne C, Brilstra E, Mang Y, Nielsen JEK, Kirkpatrick M, Goudie D, Goldman R, Jähn JA, Jepsen B, Gill D, Döcker M, Biskup S, McMahon JM, Koeleman B, Harris M, Braun K, de Kovel CGF, Marini C, Specchio N, Djémié Y, Weckhuysen S, Tommerup N, Troncoso M, Troncoso L, Bevot A, Wolff M, Hjalgrim H, Guerrini R, Scheffer IE, Mefford HC, Møller RS; for EuroEPINOMICS RES Consortium CRP. *Neurology* 2015;84:480–489.

OBJECTIVE: *SCN8A* encodes the sodium channel voltage-gated α8-subunit ($Na_v1.6$). *SCN8A* mutations have recently been associated with epilepsy and neurodevelopmental disorders. We aimed to delineate the phenotype associated with *SCN8A* mutations. METHODS: We used high-throughput sequence analysis of the *SCN8A* gene in 683 patients with a range of epileptic encephalopathies. In addition, we ascertained cases with *SCN8A* mutations from other centers. A detailed clinical history was obtained together with a review of EEG and imaging data. RESULTS: Seventeen patients with de novo heterozygous mutations of *SCN8A* were studied. Seizure onset occurred at a mean age of 5 months (range: 1 day to 18 months); in general, seizures were not triggered by fever. Fifteen of 17 patients had multiple seizure types including focal, tonic, clonic, myoclonic and absence seizures, and epileptic spasms; seizures were refractory to antiepileptic therapy. Development was normal in 12 patients and slowed after seizure onset, often with regression; 5 patients had delayed development from birth. All patients developed intellectual disability, ranging from mild to severe. Motor manifestations were prominent including hypotonia, dystonia, hyperreflexia, and ataxia. EEG findings comprised moderate to severe background slowing with focal or multifocal epileptiform discharges. CONCLUSION: *SCN8A* encephalopathy presents in infancy with multiple seizure types including focal seizures and spasms in some cases. Outcome is often poor and includes hypotonia and movement disorders. The majority of mutations arise de novo, although we observed a single case of somatic mosaicism in an unaffected parent.

Commentary

Larsen, Carvill, and colleagues report a spectrum of epileptic encephalopathy phenotypes associated with the gene *SCN8A*, relatively recently identified in the epilepsy genetics literature as a gene responsible for epilepsy and intellectual disability. As with many newly emerging genes associated with epilepsy and epileptic encephalopathy, the *SCN8A* spectrum is quite broad and still expanding. Since initial reports often reflect the most severe cases of epilepsy associated with a new gene, it is difficult to predict the full range of this spectrum. Thus, there is great value in the detailed characterization of cases from well-curated cohorts of patients with epilepsy.

Even though it is not a population study, the fact that the seven cases they report derive from an impressive cohort of 683 individuals with epileptic encephalopathy reflects the role of *SCN8A* as one of many important genes for early-onset epilepsy. To those outside the field, this 1% may not seem substantial, but epilepsy—even epileptic encephalopathy—is genetically heterogeneous, with a multitude of genetic causes collectively accounting for the growing list of epileptic encephalopathies with identifiable genetic etiology (1–4). To add to the phenotypic characterization of *SCN8A* encephalopathy, the authors also included ten additional cases referred for this study. The work thus represents the collaborative strength of some of the major groups who have been devoting their careers to epilepsy genetics.

One feature of the genetics of *SCN8A* encephalopathy worth noting is that, as with other epilepsy genes and their mutations, the types and locations of *SCN8A* mutations are varied. The authors outline very reasonable criteria for their assumptions of pathogenicity for each case. Clinical neurologists should take heed that the mere mention of a variant in a gene associated with epilepsy does not necessarily mean that that gene is the cause of a patient's epilepsy. The majority of the mutations are missense variants predicted to be pathogenic, including an apparent mutation hotspot at amino-acid position 1872 (more detail is available in a subsequent review by Wagnon and Meisler [5]). While there is already some functional evidence for gain of channel function and resultant neuronal hyperexcitability for some previously described mutations, additional functional work on some of the mutations is needed and can be correlated with the clinical data presented by these authors.

The phenotypes of the 17 patients considered to have mutations in *SCN8A* are quite variable. While many began

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with focal seizures in the first few months of life, the majority of seizure types eventually seen included many generalized seizure types, including generalized tonic-clonic seizures, epileptic spasms, myoclonic seizures, and absence seizures. A main discussion point concerns differences between patients with mutations in *SCN8A* and Dravet syndrome, a more distinct sodium channel–related epilepsy. Indeed, patients with *SCN8A* encephalopathy seem to have an earlier and more varied onset, perhaps a broader range of seizure types, and less association between fever and seizures than patients with Dravet syndrome. While medications such as carbamazepine and its derivatives would be a common first choice of treatment for focal seizures, as was the case for some of the patients, the presence of generalized seizure types that could worsen with carbamazepine seemingly complicates the treatment choices for patients with *SCN8A* encephalopathy.

The *SCN8A* phenotypes presented raise some important questions that can be answered as more patients are diagnosed with *SCN8A* encephalopathy, which they undoubtedly will be:

1) The MRI atrophy seen in three cases is interesting, and over time we will see if this is a feature specific to a subset of patients with mutations in *SCN8A* and is disease-related as opposed to being referable to medications or other causes.

2) The original proband in the 2012 Veeramah et al. study died with a diagnosis of SUDEP (6), and a question raised by that report is whether *SCN8A*-related epilepsy really confers a higher rate of SUDEP than other refractory epilepsies, a matter of clinical concern when families face a new diagnosis of *SCN8A*-related epilepsy. Since two patients in this series are deceased, and because one patient died with seizures and the other was considered SUDEP, the authors raise the point that this association bears further study as more *SCN8A* cases emerge (3). Some patients had normal development prior to seizure onset, while others were already delayed; by the time of reporting, all were moderately or severely intellectually disabled—one might conclude that this reflects the natural history of *SCN8A*-related epilepsy, but the fact that some appeared normal at onset raises the possibility that earlier intervention in future cases, identified more quickly in the modern genomic medicine era, could exact some benefit not only on seizures but on developmental outcome.

At this point, though we do not yet have evidence supporting specific treatment on the basis of *SCN8A* diagnosis, in this era of precision medicine, we strive to find such treatments. Having our patients identified with their mutations, and ideally having functional data or strong predictors of the functional consequences of mutations, will be the first step to designing clinical trials for genetically defined conditions. This is a major argument in favor of the authors' "genotype first" approach. These authors show that "genotype first, then carefully phenotype" is an effective strategy in the research realm that should quickly translate into the clinical realm. The practice of genetic testing in epilepsy will continue to increase, not only in children with severe, early-onset epilepsy and epileptic encephalopathy but also in older children with perhaps less severe epilepsy but clinically significant comorbidities and even in adults with epilepsy and intellectual disability. In this setting, one would predict more cases of *SCN8A*-related epilepsy to emerge over time, perhaps with a milder phenotype than described by Larsen, Carvill, and colleagues. Treatments targeting one set of *SCN8A* mutations and epileptic encephalopathy will likely have applicability to a much larger group of patients. These authors have provided an excellent example of a phenotyping strategy that can be applied in the future to these additional *SCN8A* mutation-positive patients.

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References

1. Epi4K Consortium; Epilepsy Phenome/Genome Project, Allen AS, Berkovic SF, Cossette P, Delanty N, Dlugos D, Eichler EE, Epstein MP, Glauser T, Goldstein DB, Han Y, Heinzen EL, Hitomi Y, Howell KB, Johnson MR, Kuzniecky R, Lowenstein DH, Lu YF, Madou MR, Marson AG, Mefford HC, Esmaeeli Nieh S, O'Brien TJ, Ottman R, Petrovski S, Poduri A, Ruzzo EK, Scheffer IE, Sherr EH, Yuskaitis CJ, Abou-Khalil B, Alldredge BK, Bautista JF, Berkovic SF, Boro A, Cascino GD, Consalvo D, Crumrine P, Devinsky O, Dlugos D, Epstein MP, Fiol M, Fountain NB, French J, Friedman D, Geller EB, Glauser T, Glynn S, Haut SR, Hayward J, Helmers SL, Joshi S, Kanner A, Kirsch HE, Knowlton RC, Kossoff EH, Kuperman R, Kuzniecky R, Lowenstein DH, McGuire SM, Motika PV, Novotny EJ, Ottman R, Paolicchi JM, Parent JM, Park K, Poduri A, Scheffer IE, Shellhaas RA, Sherr EH, Shih JJ, Singh R, Sirven J, Smith MC, Sullivan J, Lin Thio L, Venkat A, Vining EP, Von Allmen GK, Weisenberg JL, Widdess-Walsh P, Winawer MR. De novo mutations in epileptic encephalopathies. *Nature* 2012;501:217–221. doi:10.1038/nature12439.
2. Veeramah KR, Johnstone L, Karafet TM, Wolf D, Sprissler R, Salogiannis J, Barth-Maron A, Greenberg ME, Stuhlmann T, Weinert S, Jentsch TJ, Pazzi M, Restifo LL, Talwar D, Erickson RP, Hammer MF. Exome sequencing reveals new causal mutations in children with epileptic encephalopathies. *Epilepsia* 2013;54:1270–1281. doi:10.1111/epi.12201.
3. EuroEPINOMICS-RES Consortium; Epilepsy Phenome/Genome Project; Epi4K Consortium. De novo mutations in synaptic transmission genes including DNM1 cause epileptic encephalopathies. *Am J Hum Genet* 2014;95:360–370. doi:10.1016/j.ajhg.2014.08.013.
4. Carvill GL, Heavin SB, Yendle SC, McMahon JM, O'Roak BJ, Cook J, Khan A, Dorschner MO, Weaver M, Calvert S, Malone S, Wallace G, Stanley T, Bye AM, Bleasel A, Howell KB, Kivity S, Mackay MT, Rodriguez-Casero V, Webster R, Korczyn A, Afawi Z, Zelnick N, Lerman-Sagie T, Lev D, Møller RS, Gill D, Andrade DM, Freeman JL, Sadleir LG, Shendure J, Berkovic SF, Scheffer IE, Mefford HC. Targeted resequencing in epileptic encephalopathies identifies de novo mutations in CHD2 and SYNGAP1. *Nat Genet* 2013;45:825–830. doi:10.1038/ng.2646.
5. Wagnon JL, Meisler MH. Recurrent and non-recurrent mutations of SCN8A in epileptic encephalopathy. *Front Neurol* 2015;6:104. doi:10.3389/fneur.2015.00104.
6. Veeramah KR, O'Brien JE, Meisler MH, Cheng X, Dib-Hajj SD, Waxman SG, Talwar D, Girirajan S, Eichler EE, Restifo LL, Erickson RP, Hammer MF. De novo pathogenic SCN8A mutation identified by whole-genome sequencing of a family quartet affected by infantile epileptic encephalopathy and SUDEP. 2012;90:502–510. doi:10.1016/j.ajhg.2012.01.006.