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EDITORIAL

The "plus" side of epilepsy phenotyping

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The first clinical description of generalized epilepsy with febrile seizures plus (GEFS+) by Scheffer and Berkovic[1] in their landmark *Brain* article of 1997 represented a major step forward in the understanding of the genetic basis of the epilepsies. Coming 2 years after their identification, with collaborators, of the genetic basis for a relatively homogenous syndrome, autosomal dominant nocturnal frontal lobe epilepsy, the detailed phenotypic description of a single large Australian family with heterogeneous febrile seizure plus epilepsy phenotypes and a clear dominant pattern of inheritance put a novel perspective on genotype–phenotype relationships in the epilepsies.[2] Shortly after, the *SCN1A* and *SCN1B* genes were linked to the syndrome, and subsequently the last 2 decades has confirmed that the majority of epilepsy genes show phenotypic heterogeneity and the majority of syndromes reveal genetic heterogeneity.[3] Why one individual in a GEFS+ family has a severe developmental and epileptic encephalopathy such as Dravet syndrome and another has simple self-limited febrile seizures is unknown, but is likely to be determined by other genetic factors influencing the *SCN1A*, or other major genes identified in a family.

Twenty years later, the Melbourne group has revisited GEFS+ and further refined the classification and boundaries of this relatively common familial epilepsy syndrome. In this issue of *Neurology*®, Zhang et al.[4] analyzed the phenotypic spectrum in over 400 affected individuals in 60 (31 previously unreported) families. Clinical information was obtained from parents, spouses, or other eyewitnesses using a validated seizure questionnaire. Previous medical records were reviewed, including EEG, video-EEG monitoring, and MRI studies. Blood samples and genetic analysis was performed in the probands and family members where possible. Then the authors performed detailed electroclinical phenotyping on available affected families and compared their phenotypic and genetic data to those published in the literature over the last 19 years. By doing so, they have expanded the GEFS+ spectrum and identified new phenotypes, namely focal seizures without preceding febrile seizures and classic genetic generalized epilepsies. As about 9% of affected individuals have focal epilepsies, the authors suggest that GEFS+ be renamed genetic epilepsy with febrile seizures plus. This change in terminology is already widely accepted following several articles reporting focal seizures and epilepsies in GEFS+ families.[5,6] In addition, the phenotypic overlap between GEFS+ and the classic generalized epilepsies is considerably greater than previously reported. The authors coin the term early-onset genetic generalized epilepsies for a small subset of patients. Whether this term has clinical and research utility will require further validation.

In their study, the authors report genetic variants in 11/31 GEFS+ families. *SCN1A* was reported in 3 families and the relevance of some of the other variants, notably *SCN9A*, in terms of pathogenicity in GEFS+ remains debatable. The report of *SCN8A* and *PRRT2* is worthy of scrutiny. The *PRRT2* variants segregate with self-limited infantile seizures in this family and are not seen with other phenotypes. The *SCN8A* variant segregates within a family to a child with a severe *SCN8A* developmental and epileptic encephalopathy and to a mosaic father.

The 2017 International League Against Epilepsy Classification of Seizure Types and the Epilepsies reflects scientific advances over the last 3 decades by incorporating an etiologic classification alongside the electroclinical phenotype.[7,8] This approach focuses the clinician on stratifying treatment when possible based on etiology. Well-described epilepsy syndromes, such as Ohtahara and Lennox-Gastaut syndromes, which had established electroclinical phenotypes, are now regarded as of diminished clinical utility unless they are also classified by their structural or genetic etiology. Zhang et al. present a large house for GEFS+ and it is likely that to define prognosis for the individual and aid genetic counseling, detailed genetic classification will be needed alongside precision phenotyping; at present, this is only possible for a minority of GEFS+ cases. This article is an important addition to the literature, providing clarification on several details of the phenotypic spectrum and

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raising more questions about the role and relevance of genetic heterogeneity.

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