# Epilepsy phenotypes and genotype determinants

## Identical twins teach lessons on complexity

Renzo Guerrini, MD
Jeffrey R. Buchhalter, MD, PhD

Correspondence to Dr. Guerrini: r.guerrini@meyer.it

*Neurology*® 2014;83:1038–1039

Advances in our ability to classify epilepsy syndromes are mainly based on increased knowledge of their genetic causes and pathophysiology.[1] However, the pleiotropic expression of a single-gene mutation, modifying genes, or several genes producing a similar phenotype make the interpretation of genetic determinants of phenotype complex. After all, epilepsy is the end result of the dysfunctional contribution of one among multiple genetically determined elements, subjected to environmental influences and affecting a cascade of events in excitable neural networks. Twin studies can shed light on the weight of genetic variance on a phenotype, especially when complex traits are involved.

Although the characterization of monogenic epilepsies has provided new insights, these have had limited clinical import, as none of the genes involved in rare monogenic epilepsy syndromes has a role in the common idiopathic (now "genetic") epilepsies.[2] In fact, most common epilepsies do not follow a simple Mendelian pattern of inheritance, but are likely generated by the combination of less penetrant alleles with large effect, of polygenic alleles with small effect, and of interactions with environmental factors.[2] In these cases, the causative role of single modifications of gene sequences is often inferred from their presence in patients and functional effects in vitro. In some families with Mendelian inheritance, phenotypic variability has been ascribed to genetic modifiers (genetic variants that can modulate the effect of the genetic mutation) or environmental factors that influence phenotypic expression.

A syndrome category that was not included in the previous proposal for classification of the epilepsies[3] for which strong evidence exists of genetic determinants is genetic (previously "generalized") epilepsy with febrile seizures plus (GEFS+).[4] GEFS+ is a familial syndrome diagnosed on the basis of at least 2 individuals with GEFS+ phenotypes in a family. The GEFS+ spectrum denotes phenotypic heterogeneity in families, including febrile seizures (FS) and FS plus (FS exhibiting some atypical features such as presentation after 6 years of age or co-occurring with afebrile seizures). The course and response to antiepileptic drugs may vary considerably within the same family, including rare FS, afebrile seizures, and drug-resistant epilepsy. GEFS+ was originally recognized because of remarkably large autosomal dominant pedigrees with 60%–70% penetrance.[4] It has been associated with mutations in the *SCN1A* or *SCN1B* (β1) genes in approximately 10% of families.[2] However, the genetics of GEFS+ appear to be more complex than originally thought, as no clear dominant inheritance is apparent in most families and marked phenotypic heterogeneity within and between families is often seen. In addition, many sporadic patients exhibit a phenotype that would fit into the GEFS+ categorization. The twin analysis presented by Vadlamudi et al.[5] in this issue of *Neurology*® confirms clear genetic influences for the GEFS+ spectrum with very high monozygotic (MZ) concordance and provides further evidence indicating that the actual inheritance pattern is complex. As suggested by the authors, this could indicate the contribution of multiple genes "of small effect," the influence of environmental, stochastic factors, or epigenetic modifications. Compelling evidence for a strong genetic influence is also obtained for additional (especially generalized) syndromes that corroborate the validity of the concept of genetic epilepsy and the genetic influence on some nonlesional focal epilepsies.

There are, however, many open questions future studies ought to address about the etiologic classification of epilepsy and the specific ways through which genetic factors act. The category of genetic epilepsy may turn out to be arbitrarily used as what is presumed to be symptomatic today may be revealed as genetic after molecular screening. Likewise, the category structural/metabolic epilepsies is heterogeneous. Different malformations of cortical development, which have a concordance rate of 0.5%,[5] can be caused by postzygotic (somatic mosaic) mutations. Based upon the time of origin, neurons with abnormal migration patterns can affect either the whole brain or just be localized.[6,7] It will therefore be unlikely for epilepsy caused by a focal malformation to show any concordance in identical twins. This suggests the need for a category that includes the genetic defect and interposed structural

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From the Neuroscience Department (R.G.), Children's Hospital A. Meyer–University of Florence, Italy; and the Faculty of Medicine (J.R.B.), University of Calgary, Alberta Children's Hospital, Canada.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the editorial.

abnormality. Some recently characterized genetic disorders challenge the distinction between the "pure" genetic epilepsies and the structural/metabolic disorders in which a separate abnormality is interposed between the genetic defect and the epilepsy. Epilepsy seems to be a primary expression of the genetic defect in patients with *PCDH19* and *ARX* mutations, as all patients have seizures, but no structural lesion is found. Neuropathology and molecular pathology will hopefully provide additional answers in the future.

Twin studies also open new questions. For example, as Vadlamudi et al.[5] state, their study shows no concordance for MZ twins with benign epilepsy with centrotemporal spikes (BECTS), disproving previous assumptions that this common syndrome is largely genetic in origin. However, mutations of the *GRIN2A* gene encoding the α2 subunit of the NMDA glutamate receptor have been identified recently in 5% of patients with BECTS[8] and in up to 20% of individuals with nonlesional continuous spike-waves in slow sleep and Landau-Kleffner syndrome,[9] which may represent discrete expressions of the BECTS phenotypic spectrum. These contradictory results might be explained as either the number of patients with BECTS in the twin cohort is too limited to include rare individuals with monogenic inheritance, or that discordant MZ twins are caused by postzygotic mutations.[10] This suggests that the genetics of BECTS are more complicated than initially conceptualized.[5]

As next-generation sequencing in large cohorts emerges, complexities in the genetic basis of epilepsy, as underlined by twin studies, should be kept in mind.


## STUDY FUNDING

No targeted funding reported.


## DISCLOSURE

R. Guerrini received honoraria from Biocodex, UCB, Eisai, ValueBox, and ViroPharma, and research support from the Italian Ministry of Health, the European Community Sixth and Seventh Framework Thematic Priority Health, the Italian Ministry of Education, University and Research, the Tuscany Region, the Telethon Foundation, the Pisa Foundation, and the Mariani Foundation. J.R. Buchhalter has acted as a consultant to UCB, Upsher-Smith, and Lundbeck. Go to Neurology.org for full disclosures.

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