DEBATE: DOES GENETIC TESTING HAVE A ROLE IN EPILEPSY MANAGEMENT? YES

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Recent progress in the genetics of epilepsies provides important insights into biologic processes underlying epileptogenesis. On the other hand, the genetic etiology underlying epilepsy is largely unknown, and the impact of available genetic data on the nosology of epilepsy is still limited. Therefore, the role of the currently available genetic information in clinical practice is controversial. I will briefly summarised the rapid progress in the field of genetics, which allowed the identification of epilepsy-causing gene mutations underlying idiopathic epilepsies and epileptic encephalopathies and resulted in the improvement of classification, prognosis, and counseling.

Genetic anomalies are thought to be responsible for pathogenesis, with a monogenic or polygenic model of inheritance. Over the last two decades, a number of genetic anomalies and encoded proteins have been related to particular idiopathic epilepsies and epileptic encephalopathies. Most of these mutations involve subunits of neuronal ion channels (e.g. potassium, sodium, and chloride channels), and may result in abnormal neuronal hyperexcitability manifesting with seizures. However non-ion channel proteins may also be affected. The primary consequence of the identification of disease genes is the implementation of genetic tests into the routine diagnostic work-up to corroborate or disclaim a diagnosis that is made at the clinical level. Diagnostic genetic tests are regularly exploited for complex genetic syndromes, which include epilepsy as a prominent feature, such as malformations of cortical development, neurocutaneous diseases, and metabolic disorders. However, genetic testing is an increasingly recognized diagnostic tool in some rare inherited idiopathic epilepsies characterized by significant genotype–phenotype correlations such as benign familial neonatal seizures (KCNQ2 and KCNQ3), autosomal dominant partial epilepsy with auditory features (LGI1), and autosomal dominant nocturnal frontal lobe epilepsy (CHRNA4 and CHRNB2). Moreover, it should be emphasized that the genetics of the most common forms of epilepsy is largely unknown and hence the impact of the genetic data in the clinical practice is still limited. In addition, to the diagnostic application of genetic testing in a few rare epileptic conditions, the latest acquisition in genetics provides several clues relevant to the classification of epileptic syndromes and, in turn, to clinical epileptology. Therefore, at present, classification of epileptic disorders should be based mainly on electroclinical features. However, it is possible to speculate that the dissection of the complex genetics of epilepsy will have a strong impact on the classification of epilepsy syndromes. The identification of common genetic and pathophysiologic pathways will eventually bring together clinically different phenotypes. Conversely, homogenous epileptic conditions will turn out to be etiologically heterogeneous. Finally, new phenotypes will be identified through the accurate analysis of familial clusters. Linkage and genome-wide association studies have failed to identify robust or unambiguous associations in large series of patients. It is hoped that, in the near future, other epilepsy-causing genes will be discovered and other genetic and non-genetic factors responsible for the epileptic phenotypes will be clarified.

An additional intriguing and hopeful challenge is the engine of targeted antiepileptic drugs, which may act on the basis of a well-known gene anomaly. For example, ezogabine (retigabine) is a new drug for adjunctive therapy of partial-onset seizures with a novel mechanism of action that consists of the opening of neuronal voltage-gated potassium KCNQ2 and 3 channels, thus promoting membrane repolarisation and opposing rapid repetitive discharges. Correlations between genotype and phenotype are not easy to establish, since genetic and non-genetic factors are likely to play a role in determining the severity of clinical features. The growing number of discoveries on this topic are improving classification, prognosis and counseling of patients and families with these forms of epilepsy, and may lead to targeted therapeutic approaches in the near future.