Genetic epilepsies are a large group of disorders with heterogeneous etiologies and clinical features. Over the last two decades, a number of genetic anomalies and encoded proteins have been related to specific forms of idiopathic epilepsies and epileptic encephalopathies (Striano and Zara, 2011; Nicita et al., 2012). 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 epilepsy. However, non-ion channel proteins may also be affected. Mutations may be de novo, or, when inherited, show reduced penetrance and variable expressivity. Phenotypes may include, in addition to epilepsy, variable degrees of intellectual disability, elements of autism spectrum disorders, other psychiatric disorders, and motor impairment. However, 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 is improving classification, prognosis and counselling of patients and families with these forms of epilepsy and may lead to targeted therapeutic approaches in the near future.

Next generation sequencing (NGS) technologies now offer the possibility to map entire genomes at affordable costs, thus allowing coping with the complex diagnosis of genetically heterogeneous disorders. However, significant concerns relate to the management of too many DNA changes with unpredictable meaning and incidental findings that can cause ethical and clinical dilemmas. On the other hand, the technology of enrichment makes also possible to focus the sequencing to the exome or to a more specific DNA target and this is being used to set up cost-effective diagnostic tests.

Severe myoclonic epilepsy in infancy or Dravet syndrome is a form of infantile onset epilepsy characterized by multiple seizure types, prolonged convulsive seizures and frequent episodes of status epilepticus (Dravet and Oguni, 2013). Seizures precipitated by fever are a main characteristic. Patients may show a familial history of febrile seizures or epilepsy (Mancardi et al., 2006; Dravet and Oguni, 2013).

Dravet syndrome is one of the most deleterious epilepsy syndromes during childhood and its treatment remains challenging. Moreover, some antiepileptic drugs, such as phenytoin, carbamazepine, and lamotrigine can worsen seizures and should be avoided (Striano et al., 2008). This condition is commonly caused by de novo mutations in the SCN1A gene, encoding the alpha1-subunit of the neuronal voltage-gated sodium channel (SCN1A), which is the most clinically relevant among all the known epilepsy genes. The majority of SCN1A mutations arise de novo. However, SCN1A mutations have been documented in a spectrum of epilepsy syndromes, ranging from the benign ‘genetic epilepsy with febrile seizures plus’ (GEFS+) to some catastrophic epileptic encephalopathies (Dravet and Oguni, 2013). Over 300 mutations have been so far identified with missense mutations being most common in GEFS+ and more deleterious mutations (nonsense, frameshift, deletions) representing the majority of Dravet syndrome mutations (Marini et al., 2009).

In the first issue of the Journal of Epileptology, Sugawara and colleagues (2013) evaluated the efficiency and the diagnostic impact of a DNA array (called EpiGene) for the genetic diagnosis of patients with epilepsy. This array includes 14 epilepsy-related genes (SCN1A, SCN1B, CHRNA4, CHRNA7, CHRN B2, GABRA1, GABRD, GABRG2, CACNB4, CLCN2, KCNQ2, KCNQ3, CACNA1A, CACNA1H). In particular, the authors compared mutation data generated by this DNA array sequencing in a series of patients with Dravet syndrome to that of data generated by SCN1A capillary sequencing. They showed that this method identified SCN1A mutations with an overall accuracy of 99% and a false-positive rate of 1.1%. Moreover, DNA array analysis was largely consistent with the results of capillary sequencing analysis.

These findings indicate that this DNA array is likely to be a useful tool in clinical settings.

Recently, other studies have showed that the applica-
tion of NGS techniques in large series of patients with epilepsy or epileptic encephalopathies is extremely effective in the identification of pathogenic mutations in already known or indeed novel epilepsy genes (Lemke et al., 2012; Carvill et al., 2013) and it is therefore reasonable to suggest that NGS applications will soon become the first approach in genetic diagnostic laboratories.

However, there are important caveats that should be highlighted. First, the clinical diagnosis of Dravet syndrome can be difficult to achieve at a very early stage. Laboratory tests and neuroimaging are often unremarkable (Striano et al., 2007; Guerrini et al., 2011; Dravet and Oguni, 2013). In addition, SCN1A mosaicism (Gennaro et al., 2006) as well as genic deletions or duplications (Madia et al., 2006; Marini et al. 2009) may be missed by screening methods with important consequences on genetic counseling. Finally, despite intensive investigations, the genetics of up 30% of Dravet syndrome remains unknown.

The use of high-throughput approaches to sequence DNA is revealing a landscape of mutations in genetic epilepsies, affecting a variety of genes involved in neuronal excitability, synaptic transmission, neuronal metabolism, or network development. Early understanding of the genetics of these conditions will improve diagnosis, reveal pathogenic mechanisms, and eventually lead to better treatment. However, epileptologists should never forget that the ‘right diagnosis’ is only one step in the medical pathway, which include counselling and guiding treatment decisions.

CONFLICT OF INTEREST
The authors have no conflicts of interest to declare.

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