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Benign familial infantile epilepsy associated with *KCNQ3* mutation: a rare occurrence or an underestimated event?

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ABSTRACT – Benign familial infantile epilepsy (BFIE) is the most genetically heterogeneous phenotype among early-onset familial infantile epilepsies. It has an autosomal dominant inheritance pattern with incomplete penetrance. Although *PRRT2* is the most mutated gene detected in families with BFIE, other mutations in *KCNQ2*, *SCN2A*, and *GABRA6* genes have also been described. To date, *KCNQ*3 mutations have been detected in only four patients with BFIE. Here, we describe the clinical pattern and course of an additional individual with BFIE associated with a novel missense heterozygous *KCNQ3* c.1850G>C variant inherited by his unaffected father. The incidence of *KCNQ3* mutations among BFIE patients is reported to be low in the literature, however, whether this is underestimated is unclear as not all current epilepsy gene panels include *KCNQ3*.

Key words: benign familial infantile epilepsy, BFIE, *KCNQ3*, mutation, incidence

Clinical studies, carried out in the last 20 years, have led to the identification of at least three distinct electroclinical patterns associated with infantile onset, characterized mainly by age at onset but all sharing a favourable outcome, and many individuals share the same phenotype within a family.

These specific clinical traits are highlighted in the respective definitions of benign familial neonatal epilepsy (BFNE), benign familial neonatal-infantile epilepsy (BFNIE), and benign familial infantile epilepsy (BFIE) (Bureau *et al*., 2012).

The early gene sequencing studies showed a distinct phenotype-genotype correlation, in particular

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between BFNE and *KCNQ2*, BFNIE and *SCN2A*, and BFIE and *PRRT2*. In recent years, next-generation sequencing (NGS) panels have led to significant gene discovery related to many disorders including epilepsy. At present, the effort of researchers is aimed at establishing panels of genes as a gold standard to detect as many pathogenic variants as possible (Zara *et al.,* 2013; Zeng *et al.,* 2018). The expansion of NGS technology, mainly for familial infantile epilepsies, has confirmed the existence of three clusters related to the three phenotypes mentioned above. The three phenotypes share certain genetic mutations, albeit at a low incidence. Recent studies indicate that the phenotype associated with BFIE is the most genetically heterogeneous. In recent years, reports in the literature on the relevance of *KCNQ3* gene mutation to the epilepsies have been marginal and a pathogenic role has been recognized in only a small number of patients with typical BFNE and rarely with BFIE (Miceli *et al.,* 2019). Here, we describe a patient with a BFIE phenotype associated with a novel mutation in *KCNQ3*; c.1850G>C (p.Ser617Thr).

Case study

This study was approved by the Ethics Committee Palermo 1 of "Paolo Giaccone" University Hospital of Palermo, Italy. Written informed consent for publication was obtained from the patients' parents. The proband, an Italian 20-month-old male, was born at term following an uneventful pregnancy and delivery. His family history was remarkable for epilepsy; he has a second-degree paternal cousin who has suffered from occasional seizures within his first year and is presently taking phenobarbital. Developmental milestones of our patient were normal: head control, sitting without support, and walking were achieved at three, six and 13 months, respectively. He spoke his first words at eight months. At five months and 15 days, he had a cluster of seizures, lasting for an hour, characterized by deviation of the head and eyes to the left, staring, stertorous breath, and clonic movements of the left upper limb that spread to the upper right limb, evolving into self-limited generalized tonic-clonic seizures lasting for 1.5 minutes. A similar focal seizure recurred at 20 months during a febrile illness. Neurological and EEG examination were normal, as well as brain MRI. He has never been on antiepileptic treatment.

At the last clinical evaluation, performed at 20 months of age, the child was alert, perceptive, and sensitive. He demonstrated a healthy interest in the testing materials with an appropriate level of activity, attention, adaptation to change, and task persistence. He was socially engaged with the examiner, showing good communicative intent and reciprocity. He vocalized in response to the examiner and expressed himself. During the clinical examination, the patient placed items (circle, square, triangle) in designated areas; pointed to objects, pictures, and actions; handled objects; and flicked through a book quickly. He achieved partial thumb opposition, built towers using four cubes, ran with coordination, swung his leg to a kick ball, went up/downstairs using both feet, followed directions, and said 10 different words and spoke a two-word utterance.

As the clinical data suggested BFIE diagnosis, we performed a molecular genetic analysis based on a NGS panel of 149 genes associated with epilepsy. The NGS showed a novel heterozygous missense *KCNQ3* (NM_004519.3) c.1850G>C variant, not previously described in the literature (allele frequency: [ExAC] 0.00001). This nucleotide substitution, inherited by the asymptomatic father, leads to the missense mutation, p.Ser617Thr. The variant affects a residue conserved in the KCNQ2-5 channel subunit, located between helix-C and helix-D of the C-terminal region of the protein. The mutation Ser617Thr is predicted to be "probably damaging", "deleterious", and "disease causing" based on the three in silico models, PolyPhen2, SIFT, and Mutation Taster respectively (*figure 1*).

Discussion

The seizure semiology of our patient mirrors the clinical pattern of typical BFNE (Piro *et al.,* 2019), including incomplete penetrance as the father is an asymptomatic carrier of the *KCNQ3* variant. In addition, the clinical course of our patient demonstrated the occurrence of febrile seizures which have not previously been reported in patients with KCNQ3-BFIE. Indeed, BFIE is usually characterized by brief focal seizures, evolving to bilateral tonic-clonic seizures that occur in clusters at onset, at between three and 20 months of age, mostly between four and seven months, and remit within a year from onset, although some individuals may have seizures later (Vigevano, 2005). Unfortunately, we were not able to directly evaluate the detailed clinical history of our patient's relatives, and therefore we cannot establish whether the current epileptic seizures belong to long-lasting form of BFIE or a new epileptic syndrome. On the other hand, transition between different idiopathic age-related epileptic phenotypes has been reported in the literature, including some features in particular (Mangano *et al.,* 2011, 2013), suggesting the existence of common genetically determined pathophysiological processes that confer susceptibility to seizures. BFIE is a genetically heterogeneous form of epilepsy with autosomal dominant inheritance and incomplete

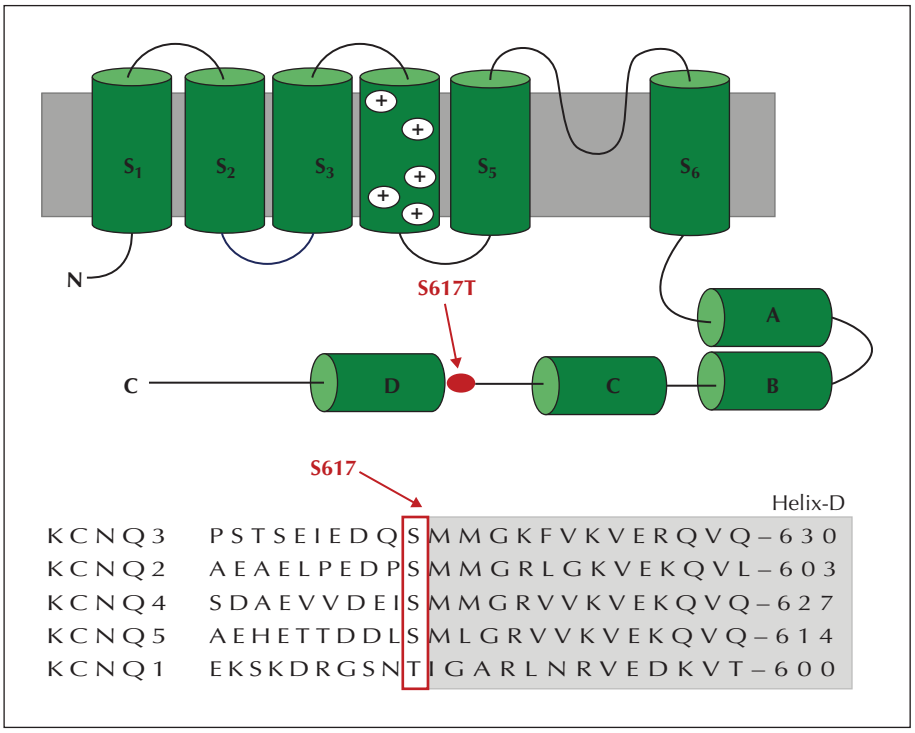

Figure 1. Schematic drawing of a KCNQ subunit and location of the mutation identified in the present case study.

penetrance. Mutations in *PRRT2*, *KCNQ2*, *SCN2A*, and *GABRA6* genes were mainly identified in patients with BFIE phenotype (Zara *et al.*, 2013; Zeng *et al.*, 2018). An additional missense *KCNQ3* p.N468S variant was detected in all of the three siblings of a Chinese family affected with BFIE, but this was considered a polymorphic variant as the mutation did not demonstrate any statistically significant effect on current associated with the heteromeric channel (Singh, *et al.*, 2003). As the data of our patient meet all the clinical criteria for diagnosis of BFIE, we may therefore compare his clinical history with those of the four BFIE cases with pathogenic variants in the *KCNQ3* gene published so far (Zara *et al.*, 2013; Fusco *et al.*,2015). Notably, the proband reported by Zara *et al.*, at the age of three months and 25 days, had a single cluster of seizures characterized by staring, eye deviation, and hypertonus of brief duration. His sibling, at the age of four months, had an isolated secondary generalized focal seizure, and their father, at the age of five and seven months, had had two isolated convulsive seizures. None of the three subjects later had seizure relapse, or neurological or intellectual impairment. The fourth reported patient, a 30-month-old reported by Fusco *et al.*, had benign epilepsy with centrotemporal spikes following benign infantile seizures. Notably, at the age of 10 months, she had several brief ictal events with psychomotor arrest and staring which was not characterized. At two years of age, she had a cluster of hemifacial motor seizures and clonic contractions of the limbs with hypertonia, evolving into generalized tonic-clonic seizures, lasting for one hour and self-limiting. Our patient showed a cluster of focal features evolving into self-limiting generalized tonic-clonic seizures. Taken together, a comparison of the clinical features of seizures and their course between our case and those reported in the literature appears premature given the small sample size reported in the literature and the differences in data collection. Thus, a detailed clinical history associated with accurate description of seizure semiology, possibly supported by video-EEG, and their clinical course would be useful in future studies. We therefore believe, based on our experience, that the *KCNQ3* gene, which is increasingly reported in association with atypical BFNE (Miceli *et al.*, 2015) and other infantile epilepsies, should be further investigated and included in the panel of genes for epilepsy. □

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None of the authors have any conflict of interest to declare.

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TEST YOURSELF

(1) Which of the following genes is most frequently mutated in benign familial infantile epilepsy?
A. KCNQ2
B. PRRT2
C. *SCN2A*

(2) As well as benign familial infantile epilepsy, which other form of epilepsy is associated with mutation of *KCNQ3*?
A. Atypical benign familial neonatal epilepsy
B. Absence epilepsy
C. Lennox Gastaut syndrome

(3) In which age group can benign familial infantile epilepsy occur?
A. Between 21 and 40 months
B. Between 3 and 20 months
C. Between 1 and 2 months

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".