

## ROLE OF SCN1A GENE IN CHILDHOOD EPILEPTIC ENCEPHALOPATHIES

ISCIA LOPES-CENDES (PQ)<sup>1</sup>, MARINA C GONSALES (PQ)<sup>1</sup>; MARILISA GUERREIRO (PQ)<sup>2</sup>, MARIA AUGUSTA MONTENEGRO (PQ)<sup>2</sup>, CAMILA V SOLER (IC)<sup>1</sup>, MAIARA F TERRA(IC)<sup>1</sup>.

<sup>1</sup>Department of Medical Genetics - UNICAMP, Campinas, SP; <sup>2</sup>Department of Neurology - UNICAMP, Campinas, SP; and The Brazilian Institute of Neuroscience and Neurotechnology (BRAINN)

### Abstract

Childhood epileptic encephalopathies (CEEs) are severe brain disorders in which epileptic electrical discharges may contribute to progressive psychomotor dysfunction in children. One of the most relevant genes in the etiology of some forms of epilepsy is *SCN1A*, which encodes the  $\alpha 1$ -subunit of the neuronal voltage-dependent sodium channel. Mutations in this gene can cause abnormal neuronal excitability. Therefore, our objective is to search for mutations in *SCN1A* in a large group of patients with different forms of CEE.

**Key words:** Genetic epilepsies; DNA sequencing; ion channel mutations; neurogenetics

### Introduction

The epilepsies are a group of diseases in which there is a predisposition to recurrent seizures without metabolic or toxic-febrile conditions (1). These seizures are transient clinical events caused by abnormal, excessive electrical discharges of the nerve cells, as a result of abnormal ion movement across the cell membrane<sup>1</sup>.

Childhood epileptic encephalopathies (CEEs) are serious brain disorders in which epileptic electrical discharges may contribute to progressive psychomotor dysfunction. It is believed that abnormal brain electrical activity during brain maturation is a major cause of cognitive and neuropsychological regression or progressive deterioration<sup>2</sup>.

Currently, one of the most relevant genes in the etiology of different types of epilepsy is *SCN1A*, whose mutations were initially identified on the spectrum of Generalized Epilepsies with Febril Seizures Plus (GEFS+), mainly associated with the phenotype of Dravet syndrome<sup>3</sup>.

Recent studies have suggest that mutations in *SCN1A* may be present in patients with the phenotype outside the boundaries of typical Dravet syndrome.

The main objective of this study is to evaluate the presence of mutations *SCN1A* in a large group of well characterized patients with different types of CEEs.

### Results and Discussion

Mutation screening was performed by Sanger sequencing in *SCN1A* in 44 patients with CEE and 12 patients with GEFS+. Missense mutations were analyzed by prediction algorithms to estimate the deleterious effects on the coded proteins.

Overall we observed potentially deleterious changes in *SCN1A* in 14% of our patients (Table 1). In addition, deleterious prediction analyzes reached a consensus for most missense mutations found. Most importantly, of the eight patients with deleterious changes, seven did not show clinical feature of Dravet syndrome.

**Table 1.** Potentially deleterious changes identified in *SCN1A* gene in patients with EE and GEFS+.

MUTATION TYPE	NUCLEOTIDE CHANGE	PROTEIN CHANGE	PHENOTYPE
Missense	c.301C>T	p.Arg101Trp	CEE
	c.3830A>C*	p.Gln1277Pro	GEFS+
	c.4244T>C*	p.Phe1425Ser	CEE
	c.4435A>T*	p.Ile1479Phe	CEE
	CM076495	p.Thr1658Arg	CEE
	c.4915C>T	p.Arg1639Cys	GEFS+
Frameshift	c.1693_1694nsTT*	p.Ser565PhefsX59	CEE

\* unpublished changes

### Conclusions

Our findings indicate the importance of studying *SCN1A* in patients with CEE even in the absence of typical clinical features of Dravet syndrome.

### Acknowledgement

This study is developed within The Brazilian Institute of Neuroscience and Neurotechnology (BRAINN). Financial Support: PIBIC/CNPq and FAPESP

1.Guerreiro CAM, Guerreiro MM, Cendes F, Lopes-Cendes I. Epilepsia. São Paulo: Lemos Editorial. 2000. 1-3; 71-74.

2.Panayiotopoulos CP. The Epilepsies: Seizures, Syndromes and Management. Oxfordshire (UK): Bladon Medical Publishing; 2005. Chapter 7: Epileptic Encephalopathies in Infancy and Early Childhood in Which the Epileptiform Abnormalities May Contribute to Progressive Dysfunction.

3.Marini C, Mei D, Temudo T, et al. Idiopathic epilepsies with seizures precipitated by fever and *SCN1A* abnormalities. Epilepsia. 2007; 9: 1678-1685..