**NEXT GENERATION SEQUENCING SUCCESSFULLY IDENTIFIES MUTATIONS IN PATIENTS WITH CHILDHOOD EPILEPTIC ENCEPHALOPATHIES**

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**Introduction:** Childhood epileptic encephalopathies (CEE) are severe brain disorders in which abnormal electrical discharges may contribute to progressive psychomotor dysfunction. It is believed that the epileptic brain electrical activity during maturation is a major cause of regression or progressive deterioration in cognitive and neuropsychological development in children and may lead to early death [1]. Recently, genetic studies have identified genes related to the etiology of CEE [2,3]. However, there is still a great need to increase knowledge about the molecular and clinical characteristics of patients with mutations in specific genes. This knowledge can only be acquired if systematic studies are performed on large samples of clinically well characterized patients with CEE. Therefore, the main objectives of this study are i) to identify potentially deleterious changes in genes related to CEEs in a large group of patients and ii) to implement a panel of candidate genes constructed for the molecular diagnosis of these patients.

**Materials and Methods:** We used two different strategies to investigate our cohort of patients with CEE. First, we used a gene panel, which was designed to investigate mutations in the most important gens related to Dravet/Doose syndrome: *CHD2, GABRG2, PCDH19, SCN1A, SCN1B* and *SCN2A*. We used this panel to study 14 patients with Dravet and Doose, as well as 34 additional patients with other types of CEE. For this strategy the SureSelect XT Target Enrichment System for Illumina Paired-End Sequencing Library (Agilent Technologies) kit was used and the sequencing was performed in MiSeq (Illumina®). In addition, whole exome sequencing (WES) was performed in two patients with Dravet syndrome with no mutations in *SCN1A*. For the WES experiment we used the Nextera Rapid Capture Expanded Exome (Illumina®) kit was used and the sequencing was performed on HiSeq (Illumina®).

**Results:** This is an ongoing study and to date the analysis of the sequence data from the gene panel is still under way. As for WES we found six sequencing changes which have the potential to be pathogenic for patient 1 and seven changes for patient 2. All of these changes are predicted to have a deleterious effect on protein function as determined by *in silico* analysis.

**Discussion and Conclusion:** We have successfully constructed and used a gene panel kit for the molecular investigation of patients with CEE. Furthermore, we found 13 putative deleterious changes in two patients with Dravet syndrome. Additional bioinformatics filters as well as validation studies and investigation in control individuals are under way in order to identify the deleterious changes which are most likely related to the phenotype in these two patients. Data from the gene panel is also under analysis. We believe that, when complete, our study will help to establish better clinical and molecular parameters for the diagnostic investigation of patients with CEE.

**References:** [1]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. [2]GONSALES, M. C. et al., Arq Neuropsiquiatr 73 (11):1-13, 2015;[3]Marini C, Mei D, Temudo T, *et al*. Idiopathic epilepsies with seizures precipitated by fever and *SCN1A* abnormalities. Epilepsia. 2007; 9: 1678-1685.

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