**Identification of the genetic basis related to familial mesial temporal lobe epilepsy**

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**Introduction:** Mesial temporal lobe epilepsy (MTLE) constitutes the most frequent focal epilepsy in the adult population and it is characterized by epileptic discharges originated from the mesial structures of the temporal lobe. MTLE is also frequently associated with histological abnormalities in the mesial temporal structures, such as the hippocampus, also known as mesial temporal sclerosis (MTS). Although MTLE +MTS were classically considered as sporadic forms of epilepsies in which environmental factors seemed to play a more relevant role, we identified a familial form of MTLE+MTS (FMTLE+MTS) with clear autosomal dominant inheritance presenting a candidate locus on chromosome (ch) 18p11.31. Currently we are developing additional studies in order to identify the genetic variants related to the FMTLE+MTS locus.

**Materials and Methods:** Peripheral blood DNA from all participants in the study was previously collected and it is part of our biobank. All patients in the study were previously diagnosed as having FMTLE+MTS, based on clinical and encephalographic exams, according to International League Against Epilepsy (ILAE) defined criteria. Patients are being prospectively followed and all clinical, neuroimaging and inclusion/exclusion characterization have been previously described by our group [1]. Whole exome sequencing has been carried out in the family known to be linked to ch 18p as well as in additional families, using TruSeq Exome Enrichment Kit in an Illumina Hi Seq 2500 platform. Sequencing data is currently being submitted to bioinformatics packages for genetic elements prospection, such as SNVs, CNVs, exon skipping and transposable elements. Exome data will be validated in all samples by 1) allelic discrimination qPCR 2) Genome-Wide Human SNP Array 6.0 *microarray* chips for CNVs; 3) Sanger sequencing for exon skipping and insertion of transposable elements. Validated genetic elements will be further studied in functional experiments involving induced pluripotent stem cells (iPSC) cultures obtained from patients and non-related healthy controls. In addition, we will use’ biopsy punches’ fibroblasts in order to identify possible morphological, cellular connection and gene expression alterations. Human fibroblasts transformation into iPSCs and neural precursor will follow protocols specific to the generation of telencephalic neural precursors, especially hippocampus granular cells [2].

**Results:** With these approaches, we aim to identify strong genetic candidates for FMTLE+MTS that will be submitted to functional validation in FMTLE iPSCs cultures in order to confirm their role in the development of this type of familial epilepsy.

**Discussion:** The recent revolution in molecular biology techniques allows us to tackle complex diseases presenting clear genetic origin with different, yet sensitive approaches in a more dynamic and complete form. This way, this project was designed to integrate all data already available about FMTLE+MTS individuals and also to collect new genetic information, in an attempt to unequivocally identify the genetic variants responsible for FMTLE+MTS.

**Conclusion:** The data collected in the present project might be crucial for the development of less invasive and more efficient therapies for FMTLE patients and also, improve our knowledge of neural excitability control mechanisms.

**References:** [1] Kobayashy E et al., Neurology 56(2):166-72, 2001; [2] Brennand KJ et al., Nature 473(7346):221-25, 2014.