**Whole-Exome Sequencing Identifies Rare Coding Variants in Patients with Focal Cortical Dysplasia (FCD)**

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**Introduction:** FCDs are a subtype of MCD which affects greater than 25% of all patients undergoing surgery for the treatment of refractory epilepsy1. Microscopically, FCD is usually associated with cell abnormalities, giant/dysmorphic neurons and balloon cells2 and severe drug-resistant epilepsy. In this study, we examined type II FCD that consists of an isolated lesion characterized by cortical dyslamination and dysmorphic neurons without (Type IIA) or with balloon cells (Type IIB)3. The mechanisms involved in the pathogenesis of type II FCD are not completely understood4 and it has been hypothesized that FCD is caused by brain somatic mutations in affected regions. In this context, the goal of this work is to identify potentially somatic and germline variants in FCD.

**Materials and Methods:** We performed whole-exome sequencing (WES) in four blood-brain paired samples with FCD, including two individuals with FCD type IIA, two with type IIB. All donors provided written informed consent prior to enter the study. Genomic DNA derived from resected brain tissue and peripheral blood leukocytes were isolated by the phenol extraction method. Libraries underwent using the Agilent SureSelect Target Enrichment Kit for sequence capture and paired-end sequencing on an Illumina HiSeq2000 with an average read depth of 100–150×. Comparison of the brain vs blood sequencing results was performed using standardized bioinformatics methods followed by specific filter steps.

**Results**: Histopathology of the resected tissue showed dyslamination, dysmorphic neurons and balloon cells consistent with focal cortical dysplasia type IIA and IIB. To date, our preliminary WES results detected 139 stop-gains variants included 24 novel variants, 227 frameshift variants wherein 66 variants were novel and 62 missense variants. Some of these findings were in homozygous state in at least one individual and we noticed a significant enrichment of rare and rare damaging variants based on our in-house control database of 29 samples as well as in two independents control databases: Exome Variant Server and Exome Aggregation Consortium (ExAC). In addition, we found that variants were present in genes belonging most frequently to specific biological pathways, which were associated with DNA/RNA and protein binding; cell adhesion; cell differentiation, growth and migration further ubiquitination.

**Discussion and conclusion**: WES study has proven to be an efficient strategy to identify
brain somatic and germline mutations in FCD, helping to better clarify the underlying mechanisms responsible for the disorder.

**References:**

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