Abstract

Epilepsy is a chronic neurological disease affecting millions of people worlwide. The etiology of epilepsy is heterogenous. Published studies confirm a strong genetic basis. While the genetic causes play a huge role in the development of epilepsy, the etiology remains unclear in many patiens.

We present a cohort of 400 patients with epilepsy, who underwent whole genome testing focused on the detection of copy number variants (CNVs). The main criterion for inclusion into the group was manifestation of epilepsy in isolated form or in combination with other neurodevelopmental disorder or congenital anomalies. Genome-wide analysis was performed using two different platforms of array CGH (array comparative genome hybridization): SurePrint G3 CGH ISCA platform 4x180K and 8x60K (Agilent Technologies). For evaluation of clinical impact of detected CNVs different databases (DGV, ClinVar, OMIM, DECIPHER) and relevant articles were used.

In our cohort we have detected 2730 CNVs in total and 86 of them (detected in 76 individuals), were evaluated as possibly clinically relevant - 82 CNVs were evaluated as a possible cause of epilepsy and 4 of them were evaluated as secondary finding without relationship to the patients´ phenotype. Regarding to the current classification, 21/86 CNVs have been refered as pathogenic, 12/86 as likely pathogenic, 39/86 CNVs as unclear and 10/86 CNVs were concluded as "high frequency, low penetrance variants" (HFLP). The origin of the aberration was confirmed in 46/76 (61 %) of cases.

In our cohort we have detected recurrent CNVs located in known epilepsy hot spots, as well as nonrecurrent CNVs. This CNVs were located in regions of the genome that are not currently associated with epilepsies and their clinical significance remains unclear, but contains genes, with possible impact in central nervous system function and development. In several cases, the interaction between two or more suspicious genomic variants, so called „*second hit*" model, was observed. Diagnostic algorithm was set up to increasing efficiency of diagnostic odyssey. We present and introduce custom array CGH platform that allows verification of CNVs detected by massive parallel sequencing, which has been complicated until now. Clinical classification of variants is still not easy and does not always bring the expected results. Expanding the cohort of patients with CNVs of unknown clinical significance could be therefore benefical. Reanalysis of such CNVs, based on new information is a necessary and may contribute to clarifying the genetic impact of these variant in patients with epilepsy

Keywords: epilepsy, neurodevelopmental disorders, copy number variants, aCGH