Gene identification in Mendelian forms of familial epilepsy

Epilepsy encompasses a heterogeneous group of recurrent seizure disorders affecting 1% of the world's population. Idiopathic generalized epilepsy accounts for 40% of all epilepsy disorders. Genetic factors contribute significantly to the etiology of idiopathic generalized epilepsies. Complex non-Mendelian forms of familial epilepsies comprise the majority of idiopathic generalized epilepsies, where susceptibility genes remain largely unknown. However, rare Mendelian or monogenic familial epilepsies have contributed to our understanding of the genetic heterogeneity and complexity of epilepsy disorders. Recent advances in the genetics of epilepsy have identified most monogenic idiopathic generalized epilepsies as being caused by various channelopathies of which the majority show an autosomal dominant pattern of inheritance. In this study we aim to identify gene(s) responsible for autosomal recessive forms of familial idiopathic generalized epilepsy.

We identified one consanguineous family with idiopathic generalized epilepsy showing an autosomal recessive pattern of inheritance. Age of onset of epilepsy in affected family members was in early adolescence. The majority manifest generalized tonic-clonic seizures and abnormal EEG findings. We performed whole-genome single nucleotide polymorphism genotyping for the five family members using Illumina platform (200,000 single nucleotide polymorphisms). Linkage analysis by homozygosity mapping (Homozygosity Mapper) was performed. We identified one region spanning approximately 10 Mb on the long arm of chromosome 11. The region contains 279 protein-coding genes. Candidate genes were prioritized in-silico based on brain expression and conservation through evolution. The identified candidate genes are re-sequenced (Sanger sequencing, big dye terminator chemistry) and one gene has been excluded up to date. We are currently re-sequencing and pre-forming mutation analysis on the remaining ten candidate genes.