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Identification Of Novel Genes Involved In The Etiology Of Benign Neonatal/Infantile Epilepsy Syndromes And Genetic Epilepsy With Febrile Seizures Plus (GEFS+)

Abstract

Epilepsy is among the most prevalent episodic neurological disorders. Genetic factors play a major role in the etiology of epilepsy. This thesis included analysis of families with distinct epilepsy phenotypes in order to delineate their complex genetic background using advanced and highthroughput current technologies. The first part of the thesis comprised a large family with BFIS phenotype which was analyzed and found to have a synonymous change in the SCN1B gene affecting splicing efficiency as shown in neuronal cell culture and by in silico tools. It was the first time SCN1B gene was shown to be associated with the BFIS phenotype. Several patients in the family also had KCNQ2 gene copy number gain and a frameshift mutation in the PRRT2 gene. The lower penetrance of these two BFIS associated gene mutations indicated the oligogenic nature of the disease. Additional families with BFIS phenotype were also analyzed for point mutations in the SCN1B and PRRT2 genes. A frameshifting 2 bp deletion in the PRRT2 gene was found in one family and rare SNPs in SCN1B genes were identified in other families. Five BFNS patients with neonatal disease onset, on the other hand, had inherited KCNQ2 gene copy number gain mutations suggesting that KCNQ2 duplications mutations may also be implicated in the etiology of BFIS/BFNS phenotypes. In the second part of the study a large multiplex, multigenerational kindred with epilepsy similar to GEFS+ phenotype and with patients having idiopathic generalized or partial epilepsy subtypes was analyzed by current genomic technologies and found to have a VNTR expansion on the mir137 gene in significantly higher numbers in individuals with epilepsy phenotypes. The VNTR expansion disrupts the expression of mir137 that targets all the genes involved in schizophrenia, synapses formation and important ion channel genes involved in epilepsy.

PUBLICATIONS

Journals

1. Sunay Usluer, Melek Asli Kayserili Uluc Yis, Costin Leu, Thomas Sander, S. Hande Çağlayan “A synonymous change affecting splicing efficiency of the SCN1B mRNA is associated with BFIS (Benign Familial Infantile Seizures) in a multiplex family” (in preperation)
2. Seda Salar, Sunay Usluer, Özlem Yalçın Çapan, Bülent Kara, Cihan Meral, Uluç Yiş, Mutluay Arslan, Rıdvan Akın, Aslı Gündoğdu Eken , S. Hande Çağlayan “Exome Sequencing Of The Scn1a Gene In 21 Turkish Patients” (in preperation. * Equal Contribution)
3. Sunay Usluer, Canan Aykut-Bingol, Kadriye Agan, Berrin Aktekin, Naz Berfu Akbaş, S. Hande Caglayan “Genome-Wide Analysis Of A Large Kindred Suggests That Mir 137 May Be A Risk Factor In Epilepsy” (in preparation)
4. Sunay Usluer, Dilşad Türkdoğan, Bülent Kara, S. Hande Çağlayan “A novel PRRT2 mutation in a BFNS family and a novel SCN2A allele associated with BFNS phenotype of five patients” (in preperation)

Conferences

1. Sunay Usluer, Yasemin Şen, S. Hande Çağlayan "Massive Parralel Sequencing Of SCN1A Gene by Amplicon Sequencing Method" The 16th Annual Meeting of Infantile Seizure Society (ISS)" Kapadokya, June 2014, Türkiye (Oral Presentation)

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