

## NEUROBIOLOGY

# Localization of a novel epilepsy susceptibility locus at 3q21, in a large south Indian family with idiopathic epilepsy syndrome

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Epilepsies are one of the most common neurological disorders characterized by unprovoked recurrent seizures. Among all human epilepsies, idiopathic epilepsies are most common and are known to have an underlying genetic etiology. These are categorized as idiopathic in the absence of any detectable structural and metabolic abnormalities. Idiopathic epilepsies are further categorized into generalized, where seizures involve the entire brain from the outset, or focal, where seizures begin in a localized brain region. Identification of genes that underlie predisposition to common idiopathic epilepsies has been hindered by the existence of clinical and genetic heterogeneity of the disease and complex mode of inheritance. However, genetic studies of large pedigrees with a clear pattern of inheritance are extremely useful in identifying genes involved in epilepsy pathogenesis. Here, we describe a large three-generation family from South India, in which idiopathic epilepsy, with members having both generalized and focal seizures, segregates as an autosomal dominant trait. Eleven family members had epilepsy, 5 exhibiting generalized seizures, 2 focal seizures with secondary generalization, 1 member with questionable diagnosis of epilepsy, 3 deceased, and remaining 7 members were normal. Although generalized and focal idiopathic epilepsies are well defined and are considered as distinct clinical entities, there is emerging evidence of co-existence of generalized and focal seizures in a single affected individual in an age-dependent manner as well as clustering of the two subtypes in multiple-affected families. With an aim to identify the underlying common genetic predisposing factor for generalized and focal seizures, we performed a genome-wide linkage analysis of the all autosomes to identify the putative locus associated with idiopathic epilepsy in this family. 10cM density genome-wide linkage analysis was carried out using 382 autosomal markers. Parametric linkage analysis was performed with autosomal dominant mode of inheritance, 0.0001 disease allele frequency, equal marker allele frequencies, 90% penetrance, 1% phenocopy and no difference in male and female recombination rates. Evidence of genetic linkage to chromosome location 3q21 was obtained, with a maximum lod score of 3.05 at  $q = 0$  for the marker *D3S1267*. The sub-genomic region encompassing *D3S1267* is syntenic in mouse and human and harbors several potential candidate genes such as *SLC12A8*, *SLC15A2*, *DRD3*, *LSAMP*, *SEMA5B*, *GABABL* and *GAP43*. These genes are expressed in the central nervous system and play role in solute transport, axonal guidance, neurogenesis and signal transduction. Further exploration of the sub-genomic segment is underway to identify the patient-specific mutation. Our work has identified a novel genetic locus at 3q21 and these results suggest that there may be overlapping molecular etiology for idiopathic generalized and idiopathic focal epilepsies.