

## 1. Introduction

Epilepsy is a common neurological disorder that affects approximately 50 million people world wide with a 3% lifetime prevalence (Jallon and Latour 2005). It is characterized by abnormal excessive firing of neurons in the CNS, resulting in behavioral manifestations, often referred to as seizures. Hereditary factors have been implicated to play a major role in its etiology (Ottman 2005). Mutations, in particular in ion channel genes, have been shown to cause rare familial epilepsies (Mulley et al 2005; Turnbull et al 2005); however, for the more common forms, identification of susceptibility factors has been complicated by clinical and genetic heterogeneity, complex mode of inheritance and limitations in study designs (Ferraro and Buono 2006).

In order to overcome some of the obstacles and limitations of studying human epilepsy, the field has employed animal models as a strategy to gain insight into disease mechanisms (Ferraro and Buono 2006). Fundamental advantages include the ability to reproducibly measure seizure threshold and activity in a controlled experimental setting. In addition, genetic engineering and molecular studies of brain tissues are possible, thus facilitating discovery efforts. Even though there is debate to what degree these seizure-related genes derived from animal models can be translated to human epilepsy, they might identify new pathways for future investigations.

While genetically engineered knock-out mice have been used successfully in the past to identify genes involved in seizure disorders (Upton and Stratton 2003), they represent only single gene approaches and do not reflect the polygenic nature of human epilepsy. The use of multigenic animal models therefore represents a promising new strategy for identifying common susceptibility factors in a complex disease.

The set of experiments described in this work were designed to identify candidate genes via a multigenic mouse model and then to test these candidate genes in human case-control association studies. Quantitative trait loci (QTL) mapping in inbred mice, using seizure threshold as outcome measure, identified a critical region on distal mouse chromosome 1 (*Szs1*) which harbors a gene or genes that contribute to both generalized and focal seizure susceptibility (Ferraro et al 2001; Ferraro et al 1997; Ferraro et al 1999). Additional fine mapping and congenic animal studies

narrowed the critical interval to a 6.6Mb region (Ferraro et al 2004). Systematic analysis of candidate genes within this region identified the inward rectifier potassium channel gene *Kcnj10* as a high ranking candidate. The two mouse strains used for mapping differ at *Kcnj10* amino acid position 262, with seizure resistant mice carrying a threonine and seizure sensitive mice carrying a serine. Gene transfer experiment, using a BAC clone that harbors the *Kcnj10* seizure resistant allele, documented a significant “phenotypic rescue” in transgenic animal lines (Ferraro 2007). Based on this animal model, we then investigated *KCNJ10* in human epilepsy. Mutation screening identified a common mis-sense amino acid polymorphism Arg271Cys (rs1130183). Case-control association analysis revealed a significant association with disease (Buono et al 2004). Independent confirmation in a second sample confirmed results (Lenzen et al 2005).

Our experiments demonstrate a successful identification of *KCNJ10* as seizure susceptibility gene using a translational approach. This model might be used for future studies and has the potential to offer new insight into the pathogenesis of human epilepsy.