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Autosomal dominant lateral temporal epilepsy: Absence of mutations in ADAM22 and Kv1 channel genes encoding LGI1-associated proteins

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Summary Mutations in the LGI1 gene are linked to autosomal dominant lateral temporal epilepsy (ADTLE) in about half of the families tested, suggesting that ADLTE is genetically heterogeneous. Recently, the Lgi1 protein has been found associated with different protein complexes

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and two distinct molecular mechanisms possibly underlying ADLTE have been hypothesized: the one recognizes Lgi1 as a novel subunit of the presynaptic Kv1 potassium channel implicated in the regulation of channel inactivation, the other suggests that Lgi1 acts as a ligand that selectively binds to the postsynaptic receptor ADAM22, thereby regulating the glutamate—AMPA neurotransmission. Both mechanisms imply that LGI1 mutations result in alteration of synaptic currents, though of different types. Since their protein products have been found associated with Lgi1, the Kv1 channel subunit genes KCNA1, KCNA4, and KCNAB1 and ADAM22 can be considered strong candidates for ADLTE. We sequenced their coding exons and flanking splice sites in the probands of 9 carefully ascertained ADLTE families negative for LGI1 mutations. We failed to detect any mutation segregating with the disease, but identified several previously unreported polymorphisms. An association study of four non-synonymous variants (three found in ADAM22, one in KCNA4) in a population of 104 non-familial lateral temporal epilepsy cases did not show any modification of susceptibility to this disorder. Altogether, our results suggest that neither ADAM22 nor any of the three Kv1 channel genes are major causative genes for ADLTE.

Introduction

Autosomal dominant lateral temporal epilepsy (ADLTE; OMIM 600512), or autosomal dominant partial epilepsy with auditory features (ADPEAF), is a familial partial epilepsy syndrome characterized by typical auditory auras and/or other less frequent symptoms, such as aphasic or visual auras, which point to a lateral temporal origin of seizures (Ottman et al., 1995; Poza et al., 1999; Brodtkorb et al., 2002). Other features of the syndrome include concordance for lateral temporal epilepsy in at least two affected family members, an average onset in infancy/adolescence, occurrence of secondarily generalized tonic-clonic seizures in most patients, absence of any structural brain abnormality, and benign outcome with good drug response (Winawer et al., 2002; Michelucci et al., 2003). Following genetic mapping to chromosome 10q24 (Ottman et al., 1995; Poza et al., 1999), mutations causing ADLTE were found in the leucine-rich, glioma inactivated 1 (LGI1) gene (Kalachikov et al., 2002; Morante-Redolat et al., 2002). To date, numerous point mutations have been identified in the LGI1 coding region or splice sites, which cause protein truncation or amino acid substitutions (see Ottman et al., 2004). Overall, LGI1 mutations account for about 50% of ADLTE families (Michelucci et al., 2003; Ottman et al., 2004), suggesting the existence of genetic heterogeneity in ADLTE (Bisulli et al., 2002; Michelucci et al., 2003).

Sporadic (non-familial) cases with apparently idiopathic partial epilepsy with auditory features (IPEAF) have been described (Bisulli et al., 2004a). These patients appear to be clinically indistinguishable from ADLTE cases, the only difference from the latter being the lack of family history. Sequence analysis of LGI1 exons in IPEAF patients revealed two de novo LGI1 mutations (Bisulli et al., 2004b; Michelucci et al., 2007), providing a link between familial and sporadic patients with auditory partial epilepsy.

The LGI1 gene is mainly expressed in brain tissues and encodes a protein whose predicted structure consists of a signal peptide, an N-terminal LRR domain (Kobe and Kajava, 2001), and a C-terminal EPTP (beta-propeller) domain (Staub et al., 2002). Both LRR and beta-propeller domains mediate protein—protein interactions, each motif defining a distinct family of proteins exerting a variety of functions. In vitro experiments have shown that the Lgi1 protein produced by transfected cells is secreted (Senechal et al., 2005; Furlan et al., 2006).

The function of LGI1 is still unclear. Recently, immunopurification experiments performed by Schulte et al. (2006) showed that the Lgi1 protein is associated to the rapidly inactivating Kv1 (shaker type) potassium channel, which consists of two alpha subunits, Kv1.1 and Kv1.4, and one beta subunit, Kvbeta1. These authors also showed that, in transfected Xenopus oocytes, Lgi1 selectively prevents inactivation of Kv1 channels mediated by the Kvbeta1 subunit. They proposed Lgi1 as a novel potassium channel subunit and suggested that changes in inactivation gating of the Kv1 potassium channel, which is located mainly in presynapses, may promote epileptic activity. By employing a similar approach, Fukata et al. (2006) immunopurified a postsynaptic protein complex containing PSD-95 and the receptor ADAM22 and found that Lgi1 is bound to ADAM22. They also showed that, as a result of its interaction with ADAM22, Lgi1 potentiates synaptic AMPA currents in hippocampal slices and that the effects of Lgi1 on synaptic transmission are exclusively postsynaptic. These authors proposed that the Lgi1 protein has a role in the control of synaptic strength at excitatory synapses, whose malfunction may result in epilepsy.

Since potassium channels have been involved in other familial epileptic syndromes (Singh et al., 1998; Charlier et al., 1998) and ADAM22 has been shown to cause convulsions in homozygous knock-out mice (Sagane et al., 2005), we regarded the genes KCNA1, KCNA4, and KCNAB1, encoding the Kv1.1, Kv1.4, and Kvbeta1 subunits, respectively, and ADAM22 as strong candidates for ADLTE. A previous study of 18 families with one or more patients with lateral temporal epilepsy revealed no disease-related mutations in ADAM22 (Chabrol et al., 2007). In this work, we analysed the three Kv1 subunit-encoding genes as well as ADAM22 in the probands of 9 Italian ADLTE families.

Patients and methods

Families

Typical ADLTE families included in the study had two or more family members (including the proband) suffering from partial epilepsy with auditory aura; additional affected members with different