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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

seizures were present in some families. Other inclusion criteria were: absence of potentially causative structural brain abnormalities, family history consistent with autosomal dominant inheritance with reduced penetrance, and absence of mutations in the LGI1 gene. Among our Italian families with lateral temporal lobe epilepsy, nine families fulfilled these criteria. Each affected individual was interviewed and directly examined by one of us (RM, AG, ME, FB, OM, CDB, ATG, SB), possibly in the presence of as many family members as possible to ensure complete ascertainment of seizures or other relevant family information. A personal and family history was obtained from each affected and unaffected member along with physical and neurological examination. Medical records describing results of neurophysiological, neuroimaging and history data were collected when possible to supplement the clinical visits. Routine EEGs and magnetic resonance imaging (MRI) were performed in almost all patients.

Sporadic cases

Subjects with partial epilepsy with auditory aura were classified as sporadic IPEAF cases based on absence of first and second-degree relatives with epileptic seizures and of clear-cut neuroradiological abnormalities including temporal structural abnormalities (Bisulli et al., 2004a). These patients exhibited no major differences from ADLTE patients with respect to age at onset, seizure frequency and response to therapy (Bisulli et al., 2004a). Altogether, 104 sporadic patients (55 men; average age at onset 19.2 years) were collected together with 103 healthy controls (45 men) from various geographical regions of Italy, particularly Emilia Romagna and Campania.

Mutation screening

Blood samples were obtained with informed consent from all participants and DNA was extracted using a standard protocol. A mutation search was performed in probands from the 9 ADLTE families by direct sequencing. The coding exons of the potassium channel genes KCNA1, KCNA4, and KCNAB1 and those of ADAM22 were amplified by PCR. All primers (available on request) were designed to be able to sequence each coding exon together with at least 40 bases of flanking introns (KCNAB1 and ADAM22) or overlapping portions of the single coding exon (KCNA1 and KCNA4). The PCR products were sequenced using the Big Dye Terminator Cycle sequencing kit (ABI PRISM, Applied Biosystems).

Analysis of polymorphisms

The population analysis of the nucleotide changes allowing amino acid substitution identified in the sequencing of the four genes was performed, when possible, by restriction fragment length polymorphism (RFLP) or by allele specific oligonucleotide (ASO; details available on request). Statistical significance of allelic and genotypic contingency tables was assessed using the chi-square distribution.

Results

Family description

The pedigrees of the nine Italian families analysed in this study are shown in Fig. 1. Part of them have been described previously: ZN (Michelucci et al., 2000), and I-3, I-4, and I-5 (Michelucci et al., 2003). The clinical features of the other families are briefly summarized in Table 1. In each family, the majority of living affected members experienced auditory auras either isolated or followed by complex partial seizures and/or secondary generalization. Altogether, 22 out of 28 patients (78%) reported auditory symptoms as elementary and unformed sounds, (whistle, buzzing, ringing; 13 subjects), structured voices or music (4 subjects), sudden hearing loss or attenuation (5 subjects). Aphasic manifestations were present in two patients and visual symptoms in four as secondary components of the auras. A history of febrile seizures was reported only in two subjects (PR III-4, and GR III-1) who did not experience any afebrile seizures.

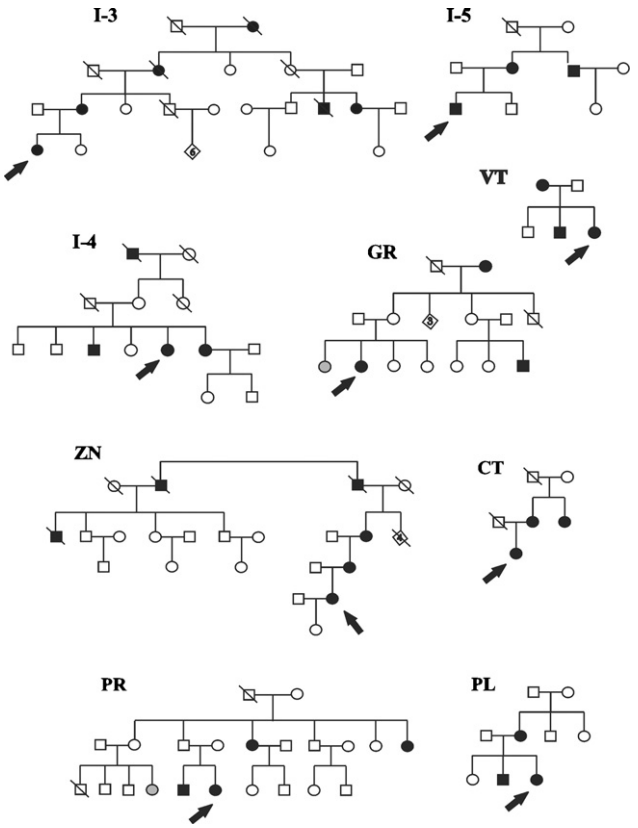

Figure 1 Pedigrees of the ADLTE families analysed in this study. Families ZN, I-3, I-4, and I-5 have already been described (Michelucci et al., 2000, 2003). Circles denote females; squares denote males. Blackened symbols denote subjects with autosomal dominant lateral temporal epilepsy; grey symbols denote patients with febrile seizures. Arrows indicate probands of each family.

Genetic analysis

We sequenced the coding exons of the KCNA1, KCNA4, and KCNAB1 potassium channel genes and of ADAM22 in the probands of our families and detected no mutations linked to ADLTE. During this analysis, however, a total of 25 polymorphisms (11 exonic) were detected (Table 2 and Fig. 2), most of which either had already been reported in public databases or were found in two or more ADLTE families. Four exonic variants giving rise to amino acid substitutions were identified, three in ADAM22 (p.P81R, p.P81G, and p.E128K), and one in KCNA4 (p.S395G). Three of them (p.P81G and p.E128K in ADAM22, and p.S395G in KCNA4), not reported in public databases, were identified each in a single family

Table 1 Main clinical features of novel ADLTE families

Family; patient (sex/age)	Age at onset	Seizure type	Frequency	Aura	EEG	Outcome
CT; II-2 (F/46)	?	SP	Rare	Auditory (whistle)	ND	No treatment
CT; II-3 (F/42)	38	CP, SGTC	Rare	—	Spikes on left parietal lobe	Sz free on CBZ
CT; III-1 (F/19)	16	SP, CP	Rare	Auditory (whistle), vertigo, dreaming state	Slow waves and spikes on left temporal lobe	Sz free on CBZ
GR; I-2 (F/88)	60	SP, CP	Rare	Auditory (whistle)	ND	Sz free on PB
GR; III-2 (F/39)	32	SP, CP, SGTC	Rare	Auditory (whistle)	Spikes on left temporal lobe	Sz free on CBZ
GR; III-7 (M/27)	15	CP, SGTC	Rare	—	Spikes on left temporal lobe	Sz free on VPA
PR; II-5 (F/53)	14	SP, CP, SGTC	Rare	Auditory (multiple voices)	Sharp waves on right temporal lobe	Sz free on CBZ
PR; II-10 (F/44)	16	SP, CP, SGTC	Rare	Auditory (multiple voices)	Sharp waves on right temporal lobe	CBZ, rare Sz
PR; III-5 (M/29)	18	SP, CP, SGTC	Rare	Auditory (voices), visual	Slow waves on right temporal lobe	CBZ, rare Sz
PR; III-6 (F/22)	12	SP, CP, SGTC	Rare	Auditory (whistle), visual	Sharp waves and spikes on right temporal lobe (post)	Sz free on CBZ
PL; II-2 (F/52)	47	SP, CP	Monthly	Auditory (echo, attenuation of sounds) aphasia, vertigo	Slow waves and spikes on left temporal lobe	PB + LEV, monthly Sz
PL; III-2 (M/8)	8	CP	Rare	—	ND	No treatment, Sz free
PL; III-3 (F/23)	23	SP, CP, SGTC	Monthly	Auditory (attenuation of sounds), vertigo	Spikes on right temporal lobe	PB + TPM, monthly Sz
VT; I-1 (F/64)	?	GTC	Rare	—	Secondary bilateral synchronism	VPA, Sz free
VT; II-2 (M/27)	23	CP, SGTC	Monthly	Auditory (music, voices)	Slow waves bilateral temporal lobe	CBZ, rare Sz
VT; II-3 (F/36)	26	SP, CP, SGCT	Monthly	Auditory (acute noise, whistle, attenuation of the sounds)	Slow waves on right temporal lobe	CBZ + PB, monthly Sz

M, male; F, female; Sz, seizure; SP, simple partial seizures; CP: complex partial seizures; SGTC, secondarily generalized tonic-clonic seizures; GTC, generalized tonic-clonic seizures; CBZ, carbamazepine; VPA, valproate; PB, phenobarbital; TPM, topiramate; LEV, levetiracetam; ND, not done.

Table 2 Exonic and intronic variants

Gene	Location	Accession #	Nucleotide	Amino acid	Family[a]
KCNA1	Exon 1	rs1048500	c.684T>C	p.C228C	I-3, I-5, ZN, CT
	Exon 1	rs2227910	c.804G>C	p.T268T	I-3, I-5, ZN, CT
	Exon 1	rs4766309	c.1440T>A	p.T480T	I-5, ZN, CT, PL
	3′-UTR	rs4766310	c.1488+9A>G	—	I-3, I-4, I-5, PR, GR
KCNA4	Exon 2	—	c.1032C>T	p.G344G	I-4,
	Exon 2	rs3802914	c.1035C>T	p.G345G	VT
	Exon 2	—	c.1185C>G	p.S395G	I-4
KCNAB1	Intron 5	rs2272112	c.428+15A>G	—	GR
	Intron 8	—	c.604+14C>T	—	GR
	Intron 10	rs17317854	c.811+18A>G	—	PR,
	Intron 11	—	c.906+22A>G	—	I-4, I-5, CT, GR
	Exon 13	rs2280031	c.1044T>C	p.N348N	I-4
	3′-UTR	—	c.1206+21A>G	—	PL
ADAM22	Intron 1	—	c.85+18G>A	—	I-3, I-4, I-5
	Exon 2	—	c.241G>C	p.P81G	CT
	Exon 2	rs2279542	c.242C>G	p.P81R	PR, CT, I-3
	Exon 4	—	c.382G>A	p.E128K	ZN
	Intron 7	—	c.607+35G>A	—	VT, PL
	Intron 8	—	c.679−53G>C	—	CT
	Intron 13	—	c.1168+29G>C	—	I-4
	Intron 16	rs3761806	c.1393−3T>C	—	GR
	Intron 25	—	c.2282+73G>A	—	VT, PL
	Intron 26	—	c.2288−55delG	—	GR
	Intron 28	rs2240467	c.2509+35T>C	—	GR
	Intron 29	—	c.2576+21G>A	—	I-4

Nucleotide and protein numbering is according to the reference sequences from the ENSEMBL web site (see legend to Fig. 2).
[a] Families in which variants were identified.

Table 3 Allelic and genotypic distribution of the ADAM22 c.242C > G (p.P81R) and c.382G > A (p.E128K) polymorphisms

Polymorphism	Population	Genotype frequencies[a] (*N*(%))			Allele frequencies[a] (*N*(%))	
		W/W	W/M	M/M	W	M
c.242C > G	Sporadic cases (*n* = 104)	40 (38.4)	46 (44.2)	18 (17.3)	126 (60.5)	82 (39.5)
	Controls (*n* = 103)	40 (38.8)	35 (34.0)	28 (27.2)	115 (55.9)	91 (44.1)
c.382G > A	Sporadic cases (*n* = 104)	100 (96.1)	4 (3.9)	0 (0.0)	204 (98.1)	4 (1.9)
	Controls (*n* = 103)	96 (93.2)	7 (6.8)	0 (0.0)	199 (96.6)	7 (3.4)

[a] W refers to the wild-type allele of each polymorphism; M refers to the mutant allele at that same polymorphism. Absolute numbers of alleles and genotypes are shown; percentages are in parentheses; *p*-values were not significant (p.P81R, alleles: 0.32, genotypes: 0.16; p.E128K, alleles: 0.35, genotypes: 0.63).

(see Table 2), but did not co-segregate with the disease, ruling out any causative relation between these variants and the ADLTE phenotype in our families. The known p.P81R (rs2279542) variant, found in ADAM22 in several families, also did not co-segregate with the disease. We further analysed these four polymorphisms in a cohort of 104 sporadic IPEAF cases (Bisulli et al., 2004a) and in 103 neurologically normal controls of similar age, gender and geographic origin by PCR-RFLP or ASO methods. The ADAM22-p.P81G and KCNA4-p.S395G polymorphisms were not found in both the case and control populations and, therefore, are likely to be rare variants. The ADAM22 p.P81R and p.E128K polymorphisms were present in both populations but their allelic and genotypic frequencies did not differ significantly between sporadic cases and controls (Table 3). All genotypes were in Hardy−Weinberg equilibrium in both the case and control populations.

Discussion

About half of the ADLTE families have mutations in the LGI1 gene (Michelucci et al., 2003; Ottman et al., 2004). In the absence of a large ADLTE pedigree suitable for genome-wide linkage analysis, a strategy to identify new ADLTE genes relies on testing candidate genes, such as, for example, structurally homologous genes. Recently, we tested the other members of the LGI family, LGI2, LGI3, and LGI4, in several ADLTE families and found no mutations (Ayerdi-Izquierdo et al., 2006). Alternatively, candidate genes for

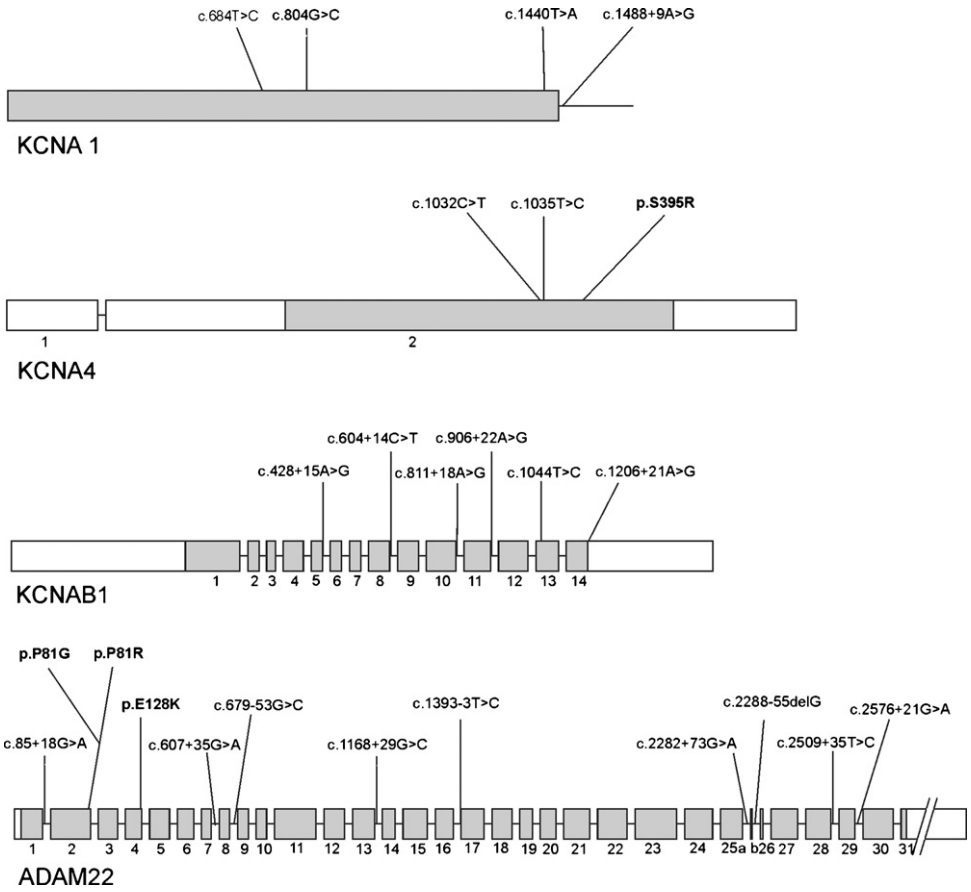

Figure 2 Exon—intron organization of the KCNA1, KCNA4, KCNAB1, and ADAM22 genes. Grey boxes, coding exons; white boxes, non-coding exons; introns (thin lines) are not to scale. Exons of KCNA4, KCNAB1, and ADAM22 are numbered. Sequence variants are illustrated, non-synonymous polymorphisms are in bold. All polymorphic positions are numbered from the start codon of the reference sequences from the ENSEMBL web site (http://www.ensembl.org): KCNA1: OTTHUMT00000103343; KCNA4: ENST00000328224; KCNAB1: OTTHUMT00000266805; ADAM22: OTTHUMT00000059747.

ADLTE can be inferred from biochemical/functional studies. Proteins interacting or functionally associated with Lgi1 may potentially carry themselves ADLTE-causing mutation, as in other familial epilepsies (Singh et al., 1998; Charlier et al., 1998). Recent work by Schulte et al. (2006) suggested that the Lgi1 protein may act as a subunit of the presynaptic, rapidly inactivating Kv1 potassium channel complex, which consists of three known subunits, Kv1.1, Kv1.4, and Kvbeta1. Mutations in the gene for the Kv1.1 subunit, KCNA1, are known to cause episodic ataxia type 1 (EA1), an autosomal dominant disorder (Browne et al., 1994). However, in some families carrying mutations in KCNA1 episodic ataxia is associated with epilepsy (see Rajakulendran et al., 2007); in addition, a mouse knock-out of KCNA1 has been described to have an epilepsy phenotype (Smart et al., 1998). Thus, KCNA1 mutations could be the causative factors in some epilepsy families, and the possible functional relationship with Lgi1 proposed by Schulte et al. (2006) suggests that KCNA1 may be implicated in ADLTE together with KCNA4 and KCNAB1. On the other hand, Fukata et al. (2006) provided experimental evidence suggesting that Lgi1 serves as a ligand for the postsynaptic receptor ADAM22, the function of which is still unclear. This finding and the epileptic phenotype displayed by ADAM22-deficient mice (Sagane et al., 2005) suggest that ADAM22 is a plausible candidate for ADLTE.

The nine families included in the study were selected on the basis of strict clinical criteria previously defined in studies of ADLTE families with LGI1 mutations: (1) concordance for lateral temporal epilepsy with auditory aura or aphasia in at least two affected members of each family; (2) compatibility with autosomal dominant inheritance with reduced penetrance; (3) absence of MRI-detectable brain structural anomalies (Morante-Redolat et al., 2002; Michelucci et al., 2003). Families fulfilling these criteria and lacking mutations in LGI1 are more likely to carry ADLTE-causing mutations in other major genes and are best suited to search for these genes. Multiplex families with a single member suffering from auditory partial epilepsy and those with uncertain mode of inheritance were excluded from analysis.

On the basis of the above considerations, we sequenced the coding regions of the candidate genes KCNA1, KCNA4, KCNAB1, and ADAM22 in the probands of our ADLTE families lacking LGI1 mutations and failed to identify any mutations co-segregating with the disease. These results suggest that neither the Kv1 subunit-encoding genes nor ADAM22 have a major causative role in ADLTE, though the presence of genomic rearrangements or deletions undetectable by

sequencing cannot be excluded. The lack of ADAM22 mutations in our families is in agreement with the data recently reported by Chabrol et al. (2007), who found no mutations in this gene in 18 families with lateral temporal epilepsy among which 8 were diagnosable as typical ADLTE. Our results combined with the findings by Chabrol et al. strongly suggest that ADAM22 is not a major gene implicated in ADLTE.

During our sequencing work, we found four non-synonymous polymorphisms in ADAM22 and KCNA4 which did not segregate with the ADLTE syndrome. We investigated these coding variants in a case-control study of sporadic lateral temporal epilepsy. Two of these polymorphisms had allelic and genotypic frequencies similar to those found in the control population, whereas the other two turned out to be rare variants absent in the study population. Our limited association study, however, does not rule out the possibility that these or other polymorphisms of these genes may confer a risk of lateral temporal epilepsy or that they may modify the susceptibility to other forms of idiopathic epilepsy.

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References

Ayerdi-Izquierdo, A., Stavrides, G., Sellés-Martínez, J.J., Larrea, L., Bovo, G., López de Munain, A., Bisulli, F., Martí-Massó, J.F., Michelucci, R., Poza, J.J., Tinuper, P., Stephani, U., Striano, P., Striano, S., Staub, E., Sarafidou, T., Hinzmann, B., Moschonas, N.K., Siebert, R., Deloukas, P., Nobile, C., Pérez-Tur, J., 2006. Genetic analysis of the LGI/Epitempin gene family in sporadic and familial lateral temporal lobe epilepsy. Epilepsy Res. 70, 118—126.

Bisulli, F., Tinuper, P., Marini, C., Avoni, P., Carraro, G., Nobile, C., 2002. Partial epilepsy with prominent auditory symptoms not linked to chromosome 10q. Epileptic Disord. 4, 183—187.

Bisulli, F., Tinuper, P., Avoni, P., Striano, P., Striano, S., d'Orsi, G., Vignatelli, L., Bagattin, A., Scudellaro, E., Florindo, I., Nobile, C., Tassinari, C.A., Baruzzi, A., Michelucci, R., 2004a. Idiopathic partial epilepsy with auditory features (IPEAF): a clinical and genetic study of 53 sporadic cases. Brain 127, 1343—1352.

Bisulli, F., Tinuper, P., Scudellaro, E., Naldi, I., Bagattin, A., Avoni, P., Michelucci, R., Nobile, C., 2004b. A de novo *LGI1* mutation in sporadic partial epilepsy with auditory features. Ann. Neurol. 56, 455—456.

Brodtkorb, E., Gu, W., Nakken, K.O., Fischer, C., Steinlein, O.K., 2002. Familial temporal lobe epilepsy with aphasic seizures and linkage to chromosome 10q22—q24. Epilepsia 43, 228—235.

Browne, D.L., Gancher, S.T., Nutt, J.G., Brunt, E.R.P., Smith, E.A., Kramer, P., Litt, M., 1994. Episodic ataxia/myokymia syndrome is associated with point mutations in the human potassium channel gene KCNA1. Nat. Genet. 8, 136—140.

Chabrol, E., Gourfinkel-An, I., Scheffer, I.E., Picard, F., Couarch, P., Berkovic, S.F., McMahon, J.M., Bajaj, N., Mota-Vieira, L., Mota, R., Trouillard, O., Depienne, C., Baulac, M., LeGuern, E., Baulac, S., 2007. Absence of mutations in the LGI1 receptor ADAM22 gene in autosomal dominant lateral temporal epilepsy. Epilepsy Res. 76, 41—48.

Charlier, C., Singh, N.A., Ryan, S., Lewis, T.B., Reus, B.E., Leach, R.J., Leppert, M., 1998. A pore mutation in a novel KQT-like potassium channel gene in an idiopathic epilepsy family. Nat. Genet. 18, 53—55.

Fukata, Y., Adesnik, H., Iwanaga, T., Bredt, D.S., Nicoll, R.A., Fukata, M., 2006. Epilepsy-related ligand/receptor complex LGI1 and ADAM22 regulate synaptic transmission. Science 313, 1792—1795.

Furlan, S., Roncaroli, F., Forner, F., Vitiello, L., Calabria, E., Piquer-Sirerol, S., Valle, G., Perez-Tur, J., Michelucci, R., Nobile, C., 2006. The LGI1/Epitempin gene encodes two protein isoforms differentially expressed in human brain. J. Neurochem. 98, 985—991.

Kalachikov, S., Evgrafov, O., Ross, B., Winawer, M., Barker-Cummings, C., Martinelli Boneschi, F., Choi, C., Morozov, P., Das, K., Teplitskaya, E., Yu, A., Cayanis, E., Penchaszadeh, G., Kottmann, A.H., Pedley, T.A., Hauser, W.A., Ottman, R., Gilliam, T.C., 2002. Mutations in LGI1 cause autosomal-dominant partial epilepsy with auditory features. Nat. Genet. 30, 335—341.

Kobe, B., Kajava, A.V., 2001. The leucine-rich repeat as a protein recognition motif. Curr. Opin. Struct. Biol. 11, 725—732.

Michelucci, R., Passarelli, D., Pitzalis, S., Dal Corso, G., Tassinari, C.A., Nobile, C., 2000. Autosomal dominant partial epilepsy with auditory features: description of a new family. Epilepsia 41, 967—970.

Michelucci, R., Poza, J.J., Sofia, V., de Feo, M.R., Binelli, S., Bisulli, F., Scudellaro, E., Simionati, B., Zimbello, R., D'Orsi, G., Passarelli, D., Avoni, P., Avanzini, G., Tinuper, P., Biondi, R., Valle, G., Mautner, V.F., Stephani, U., Tassinari, C.A., Moschonas, N.K., Siebert, R., Lopez de Munain, A., Perez-Tur, J., Nobile, C., 2003. Autosomal dominant lateral temporal epilepsy: clinical spectrum, new Epitempin mutations, and genetic heterogeneity in seven European families. Epilepsia 44, 1289—1297.

Michelucci, R., Mecarelli, O., Bovo, G., Bisulli, F., Testoni, S., Striano, P., Striano, S., Tinuper, P., Nobile, C., 2007. A de novo LGI1 mutation causing idiopathic partial epilepsy with telephone-induced seizures. Neurology 68, 2150—2151.

Morante-Redolat, J.M., Gorostidi-Pagola, A., Piquer-Sirerol, S., Saenz, A., Poza, J.J., Galan, J., Gesk, S., Sarafidou, T., Mautner, V.F., Binelli, S., Staub, E., Hinzmann, B., French, L., Prud'homme, J.F., Passarelli, D., Scannapieco, P., Tassinari, C.A., Avanzini, G., Marti-Masso, J.F., Kluwe, L., Deloukas, P., Moschonas, N.K., Michelucci, R., Siebert, R., Nobile, C., Perez-Tur, J., Lopez de Munain, A., 2002. Mutations in the LGI1/Epitempin gene on 10q24 cause autosomal dominant lateral temporal epilepsy. Hum. Mol. Genet. 11, 1119—1128.

Ottman, R., Risch, N., Hauser, W.A., Pedley, T.A., Lee, J.H., Barker-Cummings, C., Lustenberger, A., Nagle, K.J., Lee, K.S., Scheuer, M.L., Neystat, M., Susser, M., Wilhelmsen, K.C., 1995. Localization of a gene for partial epilepsy to chromosome 10q. Nat. Genet. 10, 56—60.

Ottman, R., Winawer, M.R., Kalachikov, S., Barker-Cummings, C., Gilliam, T.C., Pedley, T.A., Hauser, W.A., 2004. LGI1 mutations in autosomal dominant partial epilepsy with auditory features. Neurology 62, 1120—1126.

Poza, J., Saenz, A., Martinez-Gil, A., Cheron, N., Cobo, A.M., Urtasun, M., Marti-Masso, J.F., Grid, D., Beckmann, J.S., Prud'homme, J.F., Lopez de Munain, A., 1999. Autosomal dominant lateral temporal epilepsy: clinical and genetic study of a large Basque pedigree linked to chromosome 10q. Ann. Neurol. 45, 182—188.

Rajakulendran, S., Schorge, S., Kullmann, D.M., Hanna, M.G., 2007. Episodic ataxia type 1: a neuronal potassium channelopathy. Neurotherapeutics 4, 258—266.

Sagane, K., Hayakawa, K., Kaj, J., Hirohashi, T., Takahashi, E., Miyamoto, N., Ino, M., Oki, T., Yamazaki, K., Nagasu, T., 2005. Ataxia and peripheral nerve hypomyelination in ADAM22-deficient mice. BMC Neurosci. 6, 33.

Schulte, U., Thumfart, J.O., Klocker, N., Sailer, C.A., Bidl, W., Biniossek, M., Dehn, D., Deller, T., Eble, S., Abbass, K., Wangler, T., Knaus, H.G., Fakler, B., 2006. The epilepsy-linked Lgi1 protein assembles into presynaptic Kv1 channels and inhibits inactivation by Kvbeta1. Neuron 49, 697—706.

Senechal, K.R., Thaller, C., Noebels, J.L., 2005. ADPEAF mutations reduce levels of secreted LGI1, a putative tumor suppressor protein linked to epilepsy. Hum. Mol. Genet. 14, 1613—1620.

Singh, N.A., Charlier, C., Stauffer, D., DuPont, B.R., Leach, L.J., Melis, R., Ronen, G.M., Bjerre, I., Quattlebaum, T., Murphy, J.V., McHargh, M.L., Gragnon, D., Rosales, T.O., Peiffer, A., Anderson, V.E., Leppert, M., 1998. A novel potassium channel gene, KCNQ2, is mutated in an inherited epilepsy of newborns. Nat. Genet. 18, 25—29.

Smart, S.L., Lopantsev, V., Zhang, C.L., Robbins, C.A., Wang, H., Chiu, S.Y., Schwartzkroin, P.A., Messing, A., Tempel, B.L., 1998. Deletion of the Kv1.1 potassium channel causes epilepsy in mice. Neuron 20, 809—819.

Staub, E., Perez-Tur, J., Siebert, R., Nobile, C., Moschonas, N.K., Deloukas, P., Hinzmann, B., 2002. The novel EPTP repeat defines a superfamily of proteins implicated in epileptic disorders. Trends Biochem. Sci. 27, 441—444.

Winawer, M.R., Martinelli Boneschi, F., Barker-Cummings, C., Lee, J.H., Liu, J., Mekios, C., Gilliam, T.C., Pedley, T.A., Hauser, W.A., Ottman, R., 2002. Four new families with autosomal dominant partial epilepsy with auditory features: clinical description and linkage to chromosome 10q24. Epilepsia 43, 60—67.