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Autosomal Dominant Partial Epilepsy with Auditory Features

[*ADLTE, ADPEAF, Autosomal Dominant Lateral Temporal Lobe Epilepsy*]

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Summary

Disease characteristics. Autosomal dominant partial epilepsy with auditory features (ADPEAF) is characterized by localization-related epilepsy with auditory symptoms and/or receptive aphasia as prominent ictal manifestations. The most common auditory symptoms are simple unformed sounds such as humming, buzzing, or ringing; less common forms are distortions (e.g., volume changes) or complex sounds (e.g., specific songs or voices). Ictal receptive aphasia consists of a sudden onset of inability to understand language, in the absence of general confusion. Less commonly, other ictal symptoms may occur, including sensory symptoms (visual, olfactory, vertiginous, or cephalic), or motor, psychic, and autonomic symptoms. Most affected individuals have secondarily generalized seizures, usually accompanied by simple partial and complex partial seizures, with auditory symptoms as a major simple partial seizure manifestation. Some persons have seizures precipitated by sounds such as the telephone ringing. Age at onset ranges from four to 50 years but is usually in adolescence or early adulthood. The clinical course of ADPEAF is benign. After initiation of medical therapy, seizures are well controlled.

Diagnosis/testing. The diagnosis of ADPEAF is based on clinical findings, family history, and normal brain imaging studies (MRI or CT). Mutations in *LGI1* have been identified in approximately 50% of families with ADPEAF; no other loci have yet been reported. Molecular genetic testing is available on a clinical basis.

Management. *Treatment of manifestations:* Seizure control is usually readily achieved with antiepileptic drugs (AEDs) used routinely in clinical practice (e.g., carbamazepine, phenytoin, valproate). *Testing of relatives at risk:* Interviewing relatives at risk to identify those with suggestive symptoms may allow early treatment in those who develop seizures.

Genetic counseling. ADPEAF is inherited in an autosomal dominant manner. Most individuals with ADPEAF have an affected parent; the proportion of cases caused by *de novo* gene mutations is believed to be very low. Each child of an individual with ADPEAF has a 50% chance of inheriting the mutation. The chance that the offspring will manifest ADPEAF ranges from 25% to 43%, depending on the penetrance. Prenatal diagnosis is available.

Diagnosis

Clinical Diagnosis

The diagnosis of autosomal dominant partial epilepsy with auditory features (ADPEAF), also known as autosomal dominant lateral temporal epilepsy (ADLTE), is based on the following:

- **A clinical history consistent with localization-related (partial or focal) epilepsy** from the affected individual and witnesses. Other causes of epilepsy (antecedent illness or injury to the central nervous system, such as severe head trauma, stroke, brain tumor) must be excluded.
- **Family history consistent with autosomal dominant inheritance** (with reduced and age-dependent penetrance).Two or more family members (including the proband) must have a history of localization-related (partial or focal) epilepsy with either ictal auditory symptoms or ictal aphasia; other family members may have different epilepsy types or symptoms.
- **Auditory symptoms** must occur in temporal association with seizures (as an aura immediately preceding generalized tonic-clonic convulsions or as a component of simple partial or complex partial seizures).

  Note: Auditory symptoms may be underreported; therefore, specific questions to elicit occurrence of auditory symptoms should be included in the clinical history.
- **Aphasia** that accompanies seizure onset may be difficult to distinguish from nonspecific confusion or alteration of consciousness; therefore, specific questions to assess the inability to understand spoken language in the absence of general confusion should be included in the clinical history.

Clinical imaging (MRI or CT) is normal.

The interictal EEG is often normal, although epileptiform abnormalities (usually localized to the left temporal region) have been found in approximately 30% of reported cases.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Gene. Mutations in the leucine-rich, glioma-inactivated-1 gene *(LGI1*) have been identified in approximately 50% of families with ADPEAF [Gu, Brodtkorb et al 2002; Kalachikov et al 2002; Morante-Redolat et al 2002; Michelucci et al 2003; Ottman et al 2004].

Clinical testing

Sequence analysis. Sequencing of all coding exons and intron-exon boundaries of *LGI1* detects mutations in approximately 50% of families with autosomal dominant inheritance of ADPEAF [Michelucci et al 2003; Berkovic, Izzillo et al 2004; Ottman et al 2004].

Germline mutations in *LGI1* are rarely found in simplex cases (i.e., individuals with symptoms consistent with ADPEAF who do not have a family history) [Bisulli, Tinuper, Avoni et al 2004; Flex et al 2005]. One *de novo* mutation was identified among 40 simplex cases screened (2.5%) [Bisulli, Tinuper, Scudellaro et al 2004].

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Autosomal Dominant Partial Epilepsy with Auditory Features

Test Method	Mutations Detected	Mutation Detection Frequency [1]		Test Availability
		Positive Family History	Negative Family History	
Sequence analysis	*LGI1*	50%	2.5%	Clinical Testing

1. Proportion of affected individuals with a mutation(s) as classified by population group and test method

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Genetically Related (Allelic) Disorders

LGI1 was previously reported to be associated with progression of glial cell tumors [Chernova et al 1998]. However, families with ADPEAF have not been found to have an excess of brain tumors or other malignancies [Brodtkorb et al 2003]. No other disorders have been found to be related to mutations in *LGI1*.

Clinical Description

Natural History

Autosomal dominant partial epilepsy with auditory features (ADPEAF) is characterized by localization-related epilepsy not caused by a previous illness or injury, with auditory symptoms and/or receptive aphasia as prominent ictal manifestations. Age at onset has ranged from four to 50 years in previously reported families [Winawer et al 2000, Brodtkorb et al 2002, Winawer et al 2002, Michelucci et al 2003], but is usually in adolescence or early adulthood. The prominent auditory symptoms and aphasia are thought to reflect a localization of the epileptogenic zone in the lateral temporal lobe; accordingly ADPEAF is also known as autosomal dominant lateral temporal epilepsy (ADLTE).

Affected individuals have secondarily generalized seizures, usually accompanied by simple partial and complex partial seizures, with auditory symptoms as a major simple partial seizure manifestation. The most common auditory symptoms are simple unformed sounds such as humming, buzzing, or ringing. Less frequently, other types of auditory symptoms occur, including complex sounds (e.g., specific songs or voices) or distortions (e.g., volume changes). Some persons have seizures precipitated by sounds such as the telephone ringing [Michelucci et al 2003, Michelucci et al 2004, Ottman et al 2004].

Another distinctive feature is ictal receptive aphasia (i.e., sudden onset of an inability to understand language, in the absence of general confusion). Ictal aphasia was the most prominent symptom in one large Norwegian family with an *LGI1* mutation [Brodtkorb et al 2002; Brodtkorb, Michler et al 2005] (although auditory symptoms also occurred), and in a small Japanese family [Kanemoto & Kawasaki 2000]. Aphasia has also been reported in other families with *LGI1* mutations [Michelucci et al 2003, Ottman et al 2004].

In families with ADPEAF, affected individuals also have other ictal symptoms, either in isolation or accompanying auditory symptoms or aphasia. These occur less frequently than auditory symptoms, and include other sensory symptoms (visual, olfactory, vertiginous, or cephalic) as well as motor, psychic, and autonomic symptoms [Poza et al 1999, Winawer et al 2000, Winawer et al 2002, Michelucci et al 2003, Hedera et al 2004, Ottman et al 2004]. Also, although most individuals in families with ADPEAF have localization-related epilepsy, idiopathic generalized epilepsy was reported in four individuals with *LGI1* mutations in two previously reported families [Ottman et al 2004]. The occurrence of idiopathic generalized

epilepsies in these families may be explained either by an effect of *LGI1* on risk for idiopathic generalized epilepsy, or by a co-occurring mutation in these families in another (unidentified) gene that influences risk for idiopathic generalized epilepsy specifically.

Febrile seizures do not occur with increased frequency in ADPEAF.

The clinical course of ADPEAF is benign. For example, in a series of 34 affected individuals in seven Spanish and Italian families [Michelucci et al 2003], secondarily generalized seizures occurred only once or twice per year. The frequency of simple or complex partial seizures ranged from twice per year to several times per month. After initiation of medical therapy, seizures were well controlled by any of a variety of medications (carbamazepine, phenobarbital, or phenytoin), sometimes at low doses. In the Norwegian family with prominent ictal aphasia [Brodtkorb et al 2002], all individuals had been free from secondarily generalized seizures for two or more years, and simple partial seizures occurred infrequently in most patients. However, two family members with epilepsy died suddenly in their sleep, both at age 28 years; a relationship to seizures was suspected but could not be confirmed.

EEG. Although interictal EEGs are frequently normal in persons with ADPEAF, epileptiform interictal EEG abnormalities have been found in about 30% of affected individuals [Poza et al 1999, Winawer et al 2000, Brodtkorb et al 2002, Winawer et al 2002, Fertig et al 2003, Michelucci et al 2003, Pizzuti et al 2003, Hedera et al 2004, Ottman et al 2004, Pisano et al 2005]. When present, interictal EEG abnormalities have almost always been on the left side.

Ictal EEGs have been reported in two persons [Winawer et al 2002; Brodtkorb, Michler et al 2005]. One of these showed left mid- and anterior temporal onset [Winawer et al 2002], and the other onset in the left frontotemporal region with bilateral and posterior spreading, documented during a video-recorded aphasic seizure [Brodtkorb, Michler et al 2005].

Neuroimaging. Findings from routine neurologic examination and routine clinical imaging (MRI or CT) are normal.

An interictal single-photon emission computed tomographic (SPECT) scan in one person identified hypoperfusion in the left temporal lobe [Poza et al 1999].

A left lateral temporal lobe malformation was identified through high-resolution MRI in ten individuals in a Brazilian family with an *LGI1* mutation [Kobayashi et al 2003]. However, a study of seven other families with *LGI1* mutations did not confirm this finding [Ottman et al 2006].

Other investigations. Asymmetry of long-latency auditory evoked potentials (with reduced left N1-P2 amplitudes) was shown in the Norwegian family with aphasic seizures [Brodtkorb, Steinlein et al 2005]. Abnormal phonologic processing was demonstrated in four persons in a Sardinian family by means of a fused dichotic listening task [Pisano et al 2005]. The above data, though based on a small sample size, seem to suggest the existence of some structural abnormalities in the lateral temporal neuronal network.

Genotype-Phenotype Correlations

No genotype-phenotype correlations are known.

Bisulli, Tinuper, Avoni et al (2004) and Flex et al (2005) found no phenotypic differences between simplex cases who did not have *LGI1* mutations and the published familial cases.

Penetrance

Penetrance is incomplete, and is likely to range from 50% to 85%. Penetrance was estimated as 71%, 78%, and 60%-80% in three previously reported large families [Ottman et al 1995, Poza et al 1999, Brodtkorb et al 2002]; however, all three of these estimates are likely to be inflated by ascertainment bias, since they are based on families selected for study because they contained many affected individuals. In a study that attempted to control for ascertainment bias by considering only family members who did not lead to the selection of families for study, penetrance was estimated as 54% (95% confidence interval 34%-71%) [Ottman et al 2004]. An additional study estimated a penetrance of 85% based on a statistical model [Wang et al 2006].

Anticipation

Anticipation has not been found to occur in this syndrome.

Nomenclature

A consensus has not yet been reached regarding the most appropriate term for this syndrome.

Ottman and colleagues have used the term autosomal dominant partial epilepsy with auditory features (ADPEAF) because of its simplicity and utility for identifying families likely to have mutations in *LGI1* [Winawer et al 2000].

Poza et al (1999) proposed the term autosomal dominant lateral temporal epilepsy (ADLTE) because the symptoms that they identified in a large Basque family, including both auditory and visual symptoms, strongly suggest a lateral temporal localization of the epileptogenic zone. Both terms are used widely in the literature.

Prevalence

The prevalence of this disorder is unknown but likely to be very low. Fewer than 3% of persons with epilepsy have a significant family history of epilepsy and only a fraction of these have clinical features consistent with ADPEAF.

Although Mendelian epilepsy syndromes comprise a very small fraction of all epilepsy, findings from one study suggested that among Mendelian forms of localization-related epilepsy, ADPEAF may not be rare [Ottman et al 2004]. In that study, 9/48 (19%) of families with two or more individuals with idiopathic localization-related epilepsy met criteria for ADPEAF (i.e., they contained two or more individuals with ictal auditory symptoms).

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Tinnitus and other auditory disturbances may be reported as incidental findings in a person with epilepsy, so care should be taken in obtaining the medical history to document a consistent temporal association of auditory symptoms with seizure events.

Persons with epilepsy may report the inability to comprehend speech at the onset of seizures as a result of nonspecific confusion or alteration in consciousness; thus, care should be taken in obtaining the medical history to distinguish this confusion from specific symptoms of aphasia (i.e., an inability to understand language in the absence of alteration in consciousness).

The following three other forms of Mendelian localization-related epilepsy have been identified. Distinguishing among these disorders can be challenging because the symptoms in

affected family members are variable and no operational criteria for classification of families are yet available [Picard et al 2000].

- **Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)** is characterized by clusters of nocturnal motor seizures varying from simple arousals from sleep to dramatic, often bizarre, hyperkinetic events with tonic or dystonic features. A minority of individuals experience daytime seizures. In contrast, the seizures in ADPEAF are most often associated with auditory or other sensory symptoms, and usually occur during the day (although nocturnal seizures have been observed in some cases). The diagnosis of ADNFLE is made on clinical grounds. A detailed history from the affected individual and witnesses, supplemented if necessary by video-EEG monitoring, is the key to diagnosis. In ADNFLE, molecular genetic testing reveals mutations in *CHRNA4* or *CHRNB2* in approximately 20%-30% of individuals with a positive family history and fewer than 5% of individuals with a negative family history. Such testing is available on a clinical basis.

- **Familial mesial temporal lobe epilepsy (FMTLE)** is characterized by seizures with symptoms suggesting a mesial temporal lobe localization of the epileptogenic zone [Andermann et al 2005], in contrast to ADPEAF, in which symptoms are more suggestive of a lateral temporal localization. In the initial description of the syndrome by Berkovic et al (1996), affected individuals had simple and complex partial seizures, and less commonly, secondarily generalized seizures. The seizure semiology most often involved psychic symptoms, with déjà vu the most common among them. Autonomic or special sensory components were observed in about half of cases; auditory symptoms were found in fewer than 10% of cases.

  As with ADPEAF, age at onset was usually in late adolescence or early adulthood; neuroimaging results were normal; interictal epileptiform EEG abnormalities were found in a minority (about 20%) of cases; febrile seizures were not more common than in the general population; and the clinical course was benign, with long remissions and good response to a range of therapies (carbamazepine, phenytoin, or valproate).

  Subsequent studies demonstrated clinical heterogeneity in FMTLE, with some families having hippocampal atrophy and a less benign clinical course [Cendes et al 1998, Kobayashi et al 2001]. Families with temporal lobe epilepsy and prominent febrile seizures have also been described [Baulac et al 2001, Depondt et al 2002]. Because of the similarities between ADPEAF and FMTLE and the great intrafamilial variability of symptoms in both syndromes, differential diagnosis is challenging and relies mainly on the semiology of seizures observed in affected family members. In ADPEAF, auditory symptoms are most common, and autonomic or psychic symptoms occur in fewer than 25% of cases [Ottman et al 2004], whereas in FMTLE, psychic symptoms (particularly déjà vu) are most common, and auditory symptoms are seldom seen. In FMTLE, mutations in *LGI1* have not been found [Berkovic, Izzillo et al 2004], and no genes have yet been identified although evidence for linkage to several different regions has been reported [Baulac et al 2001, Claes et al 2004, Hedera et al 2007].

- **Familial partial epilepsy with variable foci (FPEVF)** is characterized by autosomal dominant inheritance of localization-related epilepsy, with different localization of the epileptogenic zone (frontal, temporal, or occipital) in different family members [Scheffer et al 1998; Xiong et al 1999; Callenbach et al 2003; Berkovic, Serratosa et al 2004]. Frontal lobe seizures are the most common type. However, in FPEVF the seizures occur less frequently and more in the daytime than in ADNFLE. Auditory symptoms and aphasia have not been described in families with FPEVF. Linkage to

chromosome 22q12 has been found in five families with FPEVF; the causative gene has yet to be identified [Xiong et al 1999; Callenbach et al 2003; Berkovic, Serratosa et al 2004].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with autosomal dominant partial epilepsy with auditory features (ADPEAF), the following are recommended:

- A clinical history from the patient and witnesses to establish seizure types and their frequencies, and symptoms associated with each seizure type
- Routine interictal EEG
- Routine clinical imaging to rule out structural abnormalities

Treatment of Manifestations

ADPEAF is a benign syndrome in the great majority of cases. No clinical trials of different antiepileptic medications have been carried out, but most patients have been readily able to achieve seizure control with medications used routinely in clinical practice (e.g., carbamazepine, phenytoin, valproate).

Testing of Relatives at Risk

Interview of relatives at risk to identify symptoms possibly related to seizures is advisable, so that early treatment may be initiated in those who develop seizures.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Genetics clinics, staffed by genetics professionals, provide information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section may include disease-specific and/or umbrella support organizations.

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Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Autosomal dominant partial epilepsy with auditory features (ADPEAF) is inherited in an autosomal dominant manner, with reduced and age-dependent penetrance.

Risk to Family Members

Parents of a proband

- Most individuals with ADPEAF have an affected parent. However, the family history may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of seizures, late onset of the disease in the affected parent, or reduced penetrance.
- A proband with ADPEAF may have the disorder as the result of a *de novo* gene mutation, although the proportion of cases caused by *de novo* gene mutations is believed to be very low.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include include offering molecular genetic testing of the parents and taking a careful history to rule out a history of seizures.

Sibs of a proband

- The risk to sibs of a proband depends upon the genetic status of the parents.
- If one parent has clinical characteristics consistent with ADPEAF or carries a mutation in *LGI1*, the likelihood that each sib will inherit the mutant allele is 50%. The chance that the sib will manifest ADPEAF ranges from 25% (i.e., 50% x 50%) to 43% (i.e., 50% x 85%), depending on the assumed penetrance.
- The risk to sibs of a proband whose parents are asymptomatic and do not carry a mutation is difficult to estimate.

Offspring of a proband. Each child of an individual with ADPEAF has a 50% chance of inheriting the mutation. The chance that the offspring will manifest ADPEAF ranges from 25% to 43%, depending on the penetrance.

Other family members of a proband. The risk to other family members depends upon their genetic relationship to a family member who has phenotypic features consistent with ADPEAF or carries a mutation in *LGI1*. For example, if one of the proband's parents is affected or carries a mutation, the risk to his or her siblings (the aunts and uncles of the proband) is the same as the risk to the sibs of the proband (i.e., 25%-43%). In general, the risk is 25%-43% for any first-degree relative of a family member who has phenotypic features consistent with ADPEAF or who carries a mutation. The risk to a second-degree relative of a family member who has phenotypic features consistent with ADPEAF or who carries a mutation is half of this amount (13%-22%).

Related Genetic Counseling Issues

See Management: Testing of Relatives at Risk for information on testing at-risk relatives for the purpose of early diagnosis and treatment.

Family planning. The optimal time for determination of genetic risk is before pregnancy. It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. The disease-causing allele of an affected family member must be identified or linkage established in the family before prenatal testing can be performed.

Note: (1) Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements. (2) It is the policy of *GeneReviews* to include clinical uses of testing available from laboratories listed in the GeneTests Laboratory Directory; inclusion does not necessarily reflect the endorsement of such uses by the author(s), editor(s), or reviewer(s).

Requests for prenatal testing are uncommon in conditions such as ADPEAF that do not affect intellect and are usually easily treated. Perspectives may vary among affected individuals and families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, careful discussion of these issues is advisable.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Autosomal Dominant Partial Epilepsy with Auditory Features

Gene Symbol	Chromosomal Locus	Protein Name
LGI1	10q24	Leucine-rich glioma-inactivated protein 1

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Autosomal Dominant Partial Epilepsy with Auditory Features

600512	EPILEPSY, LATERAL TEMPORAL LOBE, AUTOSOMAL DOMINANT; ADLTE
604619	LEUCINE-RICH GENE, GLIOMA-INACTIVATED, 1; LGI1

Table C. Genomic Databases for Autosomal Dominant Partial Epilepsy with Auditory Features

Gene Symbol	Entrez Gene	HGMD
LGI1	9211 (MIM No. 604619)	LGI1

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Normal allelic variants: *LGI1* has eight exons. The longest full length transcript includes all eight exons, a 224-bp 5' untranslated region, a 1674-bp coding region (spanning 225-1898 bp including stop-codon "TGA"), and a 356-bp 3' untranslated region.

LGI1 is a member of a subfamily of leucine-rich repeat (LRR)-encoding genes, denoted *LGI1*, *LGI2*, *LGI3*, and *LGI4* [Gu, Wevers et al 2002]. *LGI1* is expressed primarily in the brain [Chernova et al 1998], and in situ hybridization studies in mouse showed that expression is predominantly neuronal [Kalachikov et al 2002].

Pathologic allelic variants: Disease-causing mutations have been found throughout the gene, without apparent clustering in any region. Two-thirds of the reported mutations have been missense, and the remaining one-third have been truncating. Three intronic mutations have been reported, in each case leading to protein truncation [Kalachikov et al 2002, Kobayashi et al 2003, Chabrol et al 2007]. Almost all of the identified mutations have been unique to an individual family. The exceptions were 136T>C, which was identified in one Norwegian and one Italian family without known shared antecedents [Gu, Brodtkorb et al 2002; Pizzuti et al 2003; Pizzuti & Giallonardo 2003]; 758delC, which was identified in two Basque families [Morante-Redolat et al 2002, Michelucci et al 2003] who shared a common haplotype and are thus likely to be related (although no connection was established through genealogy); and 1420C>T, which was identified in a Basque family and in a sporadic case from Italy, as a *de novo* mutation [Morante-Redolat et al 2002; Bisulli, Tinuper, Scudellaro et al 2004]. In addition, two of the reported missense mutations affected the same nucleotide (124T>C and 124T>G) [Berkovic, Izzillo et al 2004; Ottman et al 2004]. See Table 2 (pdf).

Normal gene product and possible pathogenic mechanism: The main transcription product is predicted to encode a protein, Lgi1, of 557 amino acids, with a structure consisting of an amino-terminal signal peptide sequence and two distinct structural domains, each spanning about half of the protein. The N-terminal half consists of 3.5 LRR sequences flanked on both sides by typical cysteine-rich repeat sequence clusters [Kobe & Kajava 2001]. The C-terminal half consists of seven copies of a novel repeat of about 45 residues, named the epitempin (EPT) [Staub et al 2002] or epilepsy-associated repeat (EAR) [Scheel et al 2002] region, which is reminiscent of the beta-propeller structural domain [Paoli 2001]. This domain is shared with the protein encoded by the *MASS1* gene, which is mutated in the Frings mouse model of audiogenic epilepsy [Skradski et al 2001]. The four paralogs of the LGI subfamily all have the same structure of LRRs and EAR domains [Gu, Wevers et al 2002; Scheel et al 2002; Staub et al 2002]. LRR and beta-propeller motifs are found in many other proteins and often mediate protein-protein interactions.

Abnormal gene product: The function of the normal gene product and the mechanism by which mutations cause epilepsy remain poorly understood, but there are several important new findings. Based on protein homology, initially Lgi1 was hypothesized to influence risk for

epilepsy through a mechanism related to central nervous system development [Kalachikov et al 2002].

A recent study showed that Lgi1 interacts with presynaptic Kv1 potassium channels, selectively removing rapid inactivation mediated by the Kvβ1 subunit; truncated proteins encoded by mutations found in human families failed to slow inactivation by Kvβ1 [Schulte et al 2006]. However, another study demonstrated that Lgi1 is secreted and mutations lead to defects in secretion [Senechal et al 2005]. The establishment of Lgi1 secretion is difficult to reconcile with a potassium channel mechanism.

Recent evidence shows that there are two protein isoforms, with different expression patterns in human brain [Furlan et al 2006]. The long isoform is secreted, whereas the short isoform is retained in an intracellular pool [Sirerol-Piquer et al 2006]. ADPEAF-related mutants of the long form are defective for secretion, and the normal secreted protein specifically binds to the cell surface of differentiated PC12 cells [Sirerol-Piquer et al 2006].

Another study suggested that Lgi1 may influence risk for epilepsy through a glutaminergic mechanism: Lgi1 binds selectively to ADAM22, a neuronal membrane protein, and this binding facilitates glutamate-AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptor-mediated neurotransmission [Fukata et al 2006, Snyder 2006].

LGI1 expression is absent or significantly downregulated in many high-grade but not low-grade gliomas, suggesting a role for *LGI1* in glial tumor progression [Chernova et al 1998, Somerville et al 2000], although no excess of brain tumors or other malignancies has been found in families with ADPEAF.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

American Epilepsy Society
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Fax: 301-577-4941
Email: webmaster@efa.org
www.efa.org

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Suggested Readings

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Chapter Notes

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