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Autosomal Dominant Epilepsy with Auditory Features

Synonyms: ADEAF, Autosomal Dominant Lateral Temporal Epilepsy (ADLTE)

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Summary

Clinical characteristics

Autosomal dominant epilepsy with auditory features (ADEAF) is a focal epilepsy syndrome with auditory symptoms and/or receptive aphasia as prominent ictal manifestations. The most common auditory symptoms are simple unformed sounds including 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 focal to bilateral tonic-clonic seizures, usually accompanied by "focal aware" and "focal impaired-awareness" seizures, with auditory symptoms as a major focal aware seizure manifestation. Some persons have seizures precipitated by sounds such as a ringing telephone. Age at onset is usually in adolescence or early adulthood (range: age 4-50 years). The clinical course of ADEAF is benign. Seizures are usually well controlled after initiation of medical therapy.

Diagnosis/testing

The clinical diagnosis of ADEAF is established in a proband with characteristic clinical features, normal brain imaging (MRI or CT), and family history consistent with autosomal dominant inheritance. Identification of a heterozygous pathogenic variant in *LGI1*, *MICAL1*, *or RELN* by molecular genetic testing establishes the diagnosis if other findings are inconclusive.

Management

Treatment of manifestations: Seizure control is usually readily achieved with anti-seizure medication used routinely in clinical practice (including but not limited to carbamazepine, phenytoin, valproate, and levetiracetam).

Evaluation of relatives at risk: Interviewing relatives at risk to identify those with suggestive findings may enable early treatment in those who develop seizures.

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Genetic counseling

ADEAF is inherited in an autosomal dominant manner. Most individuals with ADEAF have an affected parent; the proportion of cases caused by a *de novo* pathogenic variant is believed to be very low. Each child of an individual with ADEAF has a 50% chance of inheriting the pathogenic variant. The chance that the offspring who inherits the pathogenic variant will manifest ADEAF is between 55% and 78%, depending on the penetrance. While prenatal diagnosis for pregnancies at increased risk and preimplantation genetic testing are possible if the pathogenic variant in the family is known, prenatal testing and preimplantation genetic testing are rarely requested for conditions that (like ADEAF) do not affect intellect and are usually easily treated.

Diagnosis

Suggestive Findings

Autosomal dominant epilepsy with auditory features (ADEAF) **should be suspected** in individuals with the following clinical, imaging, and EEG findings and family history.

Clinical findings

- **A history consistent with focal epilepsy** from the affected individual and witnesses. Other causes of epilepsy (e.g., antecedent illness or injury to the central nervous system, such as severe head trauma, stroke, and brain tumor) must be excluded.
- **Auditory symptoms** that occur in temporal association with seizures as one of the following:
  - An aura immediately preceding generalized tonic-clonic convulsions
  - A component of focal aware or focal impaired-awareness seizures
  - The only ictal symptom

  Note: Auditory symptoms may be underreported; therefore, specific questions to elicit occurrence of auditory symptoms should be included in the clinical history. Since tinnitus and other auditory disturbances may be reported as incidental findings in a person with epilepsy, care should be taken in obtaining the medical history to document a consistent temporal association of auditory symptoms with seizure events or to raise a strong suspicion of the ictal nature of the auditory symptom if not associated with other clinical features.
- **Aphasia** that accompanies seizure onset. Aphasia 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. Note: 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).

Brain imaging (MRI or CT). Normal

Interictal EEG. Often normal. However, focal epileptiform abnormalities (usually localized to the temporal region) are found in up to two thirds of individuals.

Family history is consistent with autosomal dominant inheritance (with reduced and age-dependent penetrance).Two or more family members (including the proband) must have a history of focal epilepsy with either ictal auditory symptoms or ictal aphasia. Other family members may have different seizure types, usually tonic-clonic (undetermined whether focal or generalized).

Establishing the Diagnosis

The clinical diagnosis of ADEAF **is established** in a proband with the above clinical features, normal brain imaging studies (MRI or CT), and family history consistent with autosomal dominant inheritance. Identification of a heterozygous pathogenic (or likely pathogenic) variant in *LGI1*, *MICAL1*, or *RELN* by molecular genetic testing (Table 1) establishes the diagnosis if other findings are inconclusive.

Note: Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous variant of uncertain significance in one of the genes listed in Table 1 does not establish or rule out the diagnosis.

A multigene panel that includes *LGI1*, *MICAL1*, *RELN*, and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Note: Serial single-gene testing of *LGI1*, *MICAL1*, and *RELN* is impractical given the relatively large number of exons in the latter two genes.

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

Gene [1, 2]	Proportion of ADEAF [3] Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [4] in Gene Detectable by Method	
		Sequence analysis [5]	Gene-targeted deletion/ duplication analysis [6]
LGI1	30% [7]	95%	5% [8]
MICAL1	7% [9]	90%-95%	Unknown
RELN	17%-18% [7]	90%-95%% [10]	Unknown

Table 1. continued from previous page.

Gene [1, 2]	Proportion of ADEAF [3] Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [4] in Gene Detectable by Method	
		Sequence analysis [5]	Gene-targeted deletion/ duplication analysis [6]
Unknown [11]	~50%	NA	

1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. Autosomal dominant inheritance defined as ≥2 family members with idiopathic focal epilepsy with ictal auditory symptoms or receptive aphasia [Michelucci et al 2003, Berkovic et al 2004a, Ottman et al 2004, Michelucci et al 2013].
4. See Molecular Genetics for information on allelic variants detected in these genes.
5. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
7. Michelucci et al [2017]
8. A deletion encompassing the first four exons of *LGI1* was identified in one family [Fanciulli et al 2012], and a deletion encompassing the second exon in another family [Dazzo et al 2015b]. No structural variants were identified by MLPA in 43 other families [Magini et al 2014, Manna et al 2014, Dazzo et al 2015b].
9. Dazzo et al [2018]
10. Dazzo et al [2015a]
11. A locus on 19q13.11-q13.31 likely to harbor a gene associated with ADEAF was identified in a large Brazilian family [Bisulli et al 2014]. In 21 families with ADEAF, 12 rare CNVs were identified by genome-wide SNP microarray analysis that segregated with ADEAF in single families, including rare microdeletions within or near *RBFOX1* and *NRXN1*, and a microduplication in the proximal region of chromosome 1q21.1, where duplications have been associated with various neurodevelopmental disorders and epilepsy [Fanciulli et al 2014]. Deletions/duplications at these loci confer susceptibility to other forms of genetic epilepsy.

Clinical Characteristics

Clinical Description

Autosomal dominant epilepsy with auditory features (ADEAF) is characterized by focal 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, Michelucci et al 2013], 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, ADEAF is also known as autosomal dominant lateral temporal epilepsy (ADLTE).

Epilepsy. Affected individuals have focal to bilateral tonic-clonic seizures, usually accompanied by focal aware or focal impaired-awareness seizures, with auditory symptoms as a major focal aware seizure manifestation occurring in around two thirds of affected individuals. Some individuals have seizures precipitated by specific sounds, such as a telephone ringing [Michelucci et al 2003, Michelucci et al 2004, Michelucci et al 2007].

Although most individuals in families with ADEAF have focal epilepsy, idiopathic generalized epilepsy was reported in four individuals with *LGI1* pathogenic variants in two previously reported families [Ottman et al 2004]. The occurrence of idiopathic generalized epilepsies in these families may be explained either as an effect of *LGI1* on the risk for idiopathic generalized epilepsy, or by the co-occurring pathogenic variant in these families of another (unidentified) gene that specifically influences risk for idiopathic generalized epilepsy.

Febrile seizures do not occur with increased frequency in ADEAF.

Auditory symptoms. 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). Negative auditory symptoms, such as sudden decrease or disappearance of the surrounding noises, are reported by a minority of affected individuals.

Aphasia. 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* pathogenic variant [Brodtkorb et al 2002, Brodtkorb et al 2005a] (although auditory symptoms also occurred) and in a small Japanese family [Kanemoto & Kawasaki 2000]. Aphasia has also been reported in other families with *LGI1* pathogenic variants [Michelucci et al 2003, Ottman et al 2004, Di Bonaventura et al 2009].

Other ictal symptoms. In families with ADEAF, 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, Michelucci et al 2013, Dazzo et al 2015b].

Non-epileptic manifestations associated with ADEAF on rare occasion include the following:

- Behavioral problems (e.g., explosive violent behaviors, impulsiveness) and depression (with suicide attempts) have been reported in single pedigrees [Chabrol et al 2007, Kawamata et al 2010]. However, a systematic study investigating a possible shared genetic susceptibility to epilepsy and depression in families with an *LGI1* pathogenic variant did not find such an association; rather, the depression appeared to be related to the epilepsy or anti-seizure treatment [Heiman et al 2010].
- Migraine segregating with occipito-temporal epilepsy resembling ADEAF has been described in one family [Deprez et al 2007].

Prognosis. The clinical course of ADEAF is usually benign. The following are offered as examples.

- In a series of 34 affected individuals in seven Spanish and Italian families, focal to bilateral tonic-clonic seizures occurred only once or twice per year. The frequency of focal aware or focal impaired-awareness 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 [Michelucci et al 2003].
- In a Norwegian family with prominent ictal aphasia, all individuals had been free from focal to bilateral tonic-clonic seizures for two or more years, and focal aware seizures occurred infrequently in most individuals. 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 [Brodtkorb et al 2002].
- In one other family with an *LGI1* pathogenic variant, an unusual clinical picture with high seizure frequency and anti-seizure medication resistance was described [Di Bonaventura et al 2009].

EEG. Interictal (routine and sleep-deprived) EEGs may be normal in persons with ADEAF; however, epileptiform interictal EEG abnormalities are found in up to two thirds 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]. Interestingly, a left predominance of the abnormalities has been observed in some clinical series [Michelucci et al 2003, Di Bonaventura et al 2009].

Ictal EEGs have been reported in three persons [Winawer et al 2002, Brodtkorb et al 2005a, Di Bonaventura et al 2009]. One of these showed left mid- and anterior temporal onset [Winawer et al 2002], and another onset in the left frontotemporal region with bilateral and posterior spreading, documented during a video-recorded aphasic seizure [Brodtkorb et al 2005a]. The third was recorded during a prolonged seizure cluster lasting several hours

in an individual with prominent ictal aphasia; the EEG pattern consisted of low-voltage fast activity followed by delta activity and rhythmic sharp waves located in the anterior and middle left temporal regions [Di Bonaventura et al 2009].

Findings from magnetoencephalography (MEG) with auditory stimuli showed significantly delayed peak 2 auditory evoked field latency in individuals with *LGI1* pathogenic variants [Ottman et al 2008]. Another study using MEG detected significantly large N100m signals in three of five individuals, contralateral to the auditory stimulation [Usui et al 2009].

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

An interictal single-photon emission computed tomographic 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* pathogenic variant [Kobayashi et al 2003]. However, other studies using high-resolution MRI in families with *LGI1* pathogenic variants have not confirmed this finding [Tessa et al 2007, Ottman et al 2008].

Diffusion tensor imaging identified a region of increased fractional anisotropy in the left temporal lobe in individuals with an *LGI1* pathogenic variant [Tessa et al 2007].

In functional MRI with an auditory description decision task, persons with epilepsy in families with an *LGI1* pathogenic variant had significantly less activation than controls [Ottman et al 2008]. These results suggest that individuals with ADEAF have functional impairment in language processing.

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 et al 2005b]. 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, would appear to suggest the existence of some structural abnormalities in the lateral temporal neuronal network.

Genotype-Phenotype Correlations

Auditory symptoms were less frequent with *LGI1* pathogenic variants that predict truncation in the terminal epitempin repeat domain than with other *LGI1* pathogenic variant type/domain combinations [Ho et al 2012].

Phenotypic features are the same in published familial cases with *LGI1*, *MICAL1*, or *RELN* pathogenic variants [Dazzo et al 2015a, Michelucci et al 2017, Dazzo et al 2018].

No significant clinical differences are observed between families with an *LGI1* pathogenic variant and families without an identified pathogenic variant [Michelucci e al 2013].

No phenotypic differences have been found between simplex cases (i.e., a single occurrence in a family) and published familial cases [Bisulli et al 2004a, Bisulli et al 2004b, Flex et al 2005, Michelucci et al 2007, Michelucci et al 2009].

Penetrance

Estimates of penetrance in studies of families with ADEAF range from 54% to 85% [Ottman et al 1995, Poza et al 1999, Ottman et al 2004, Wang et al 2006]. This variability may in part result from the use of different statistical models.

LGI1. Based on analysis of obligate heterozygotes in 24 published families, penetrance of *LGI1* pathogenic variants was estimated at 67% (95% CI 55%-77%) [Rosanoff & Ottman 2008].

More recently, in a study of 33 families in which probands were excluded, penetrance for epilepsy was estimated at 61% in ten families with an *LGI1* pathogenic variant and 35% in families without an identified pathogenic variant, suggesting that inheritance may be complex in some families [Michelucci et al 2013].

All of these estimates are likely to be inflated by ascertainment bias, since they are based on families selected for study because they comprised many affected individuals.

RELN. Twenty (60%) of 33 individuals heterozygous for a *RELN* pathogenic variant (from 7 families) had epilepsy [Dazzo et al 2015a].

MICAL1. Penetrance is unknown.

Prevalence

The prevalence of ADEAF 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 ADEAF.

Whereas Mendelian epilepsy syndromes account for a very small fraction of all epilepsy, findings from one study suggest that among Mendelian forms of focal epilepsy, ADEAF may not be rare as 9/48 (19%) of families with two or more individuals with idiopathic focal epilepsy met criteria for ADEAF (i.e., they comprised ≥2 individuals with ictal auditory symptoms) [Ottman et al 2004].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *LGI1* and *MICAL1*.

Homozygous *RELN* pathogenic variants cause lissencephaly with cerebellar hypoplasia (OMIM 257320), a recessive disorder characterized by severe and widespread neuronal migration defects, delayed cognitive development, and seizures [Hong et al 2000].

Differential Diagnosis

Table 2 summarizes Mendelian focal epilepsy disorders. Distinguishing among these disorders can be challenging because the manifestations in affected family members are variable and no operational criteria for classification of families are yet available [Picard et al 2000]. Moreover, these different forms of focal epilepsy have shared genetic mechanisms; pathogenic variants in *DEPDC5* have been identified in all of them [Poduri 2014], and were found in ten (12%) of 82 families with two or more individuals with focal epilepsy who did not have a detectable structural etiology [Dibbens et al 2013]. However, to date, pathogenic variants in *DEPDC5* have not been identified in families with ADEAF. (See also *DEPDC5*-Related Epilepsy.)

Table 2. Mendelian Focal Epilepsy Disorders

Disorder	Gene(s)	MOI	Clinical Features					
			Localization of epileptogenic zone	Seizure semiology	Age at onset	Neuroimaging	EEG	Other
Autosomal dominant epilepsy w/ auditory features (ADEAF)	*LGI1* *MICAL1* *RELN*	AD	Lateral temporal	• Auditory symptoms are most common. • Autonomic or psychic symptoms occur in <25% of persons. [1]	Usually late adolescence or early adulthood	Normal	• Interictal EEGs may be normal. • Epileptiform interictal EEG abnormalities found in ≤2/3s of affected individuals [2] • Ictal EEGs reported in 3 persons [3]	
Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)	*CHRNA4* *CHRNB2* *CHRNA2* *KCNT1* *DEPDC5* *CRH* [4]	AD	Frontal lobe (rarely from extrafrontal areas – e.g., temporal, insular, & parietal regions)	Asymmetric tonic/ dystonic posturing &/or complex hyperkinetic seizures, mostly during sleep	1st 2 decades of life in ~80% (mean onset age 10 yrs)	Normal	• Interictal & ictal scalp EEG features may be normal. • Prolonged video-EEG recording is best diagnostic test to assess seizure occurrence.	• Characterized by clusters of nocturnal motor seizures, often stereotyped & brief (5 secs - 5 mins) • Clinical neurologic exam normal & intellect usually preserved, but psychiatric comorbidity or cognitive deficits may occur • Manifestations may vary considerably w/in a family.

Table 2. continued from previous page.

Disorder	Gene(s)	MOI	Clinical Features					
			Localization of epileptogenic zone	Seizure semiology	Age at onset	Neuroimaging	EEG	Other
Familial mesial temporal lobe epilepsy (FMTLE) (OMIM PS600512)	Unknown	AD AR	Mesial temporal lobe [5]	• Psychic symptoms (esp. déjà vu) most common • Autonomic or special sensory components in ~50% • Auditory symptoms in <10%	Usually late adolescence or early adulthood	Normal	Interictal epileptiform EEG abnormalities in ~20%	• Febrile seizure frequency as in general population • Benign clinical course, w/long remissions & good response to range of therapies (carbamazepine, phenytoin, or valproate)
Familial partial epilepsy w/ variable foci (FPEVF) (OMIM PS604364)	*DEPDC5* *NPRL2* *NPRL3*	AD	• Epileptogenic zone (frontal, temporal, or occipital) differs among family members. [6] • Frontal lobe seizures most common	Auditory symptoms & aphasia not described in families w/FPEVF	Usually middle childhood to early adulthood	Normal	Interictal & ictal EEG abnormalities localized in different areas (frontal, temporal, occipital)	Seizures in FPEVF occur less frequently than in ADNFLE; when they occur it is more often in daytime.

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance

1. Ottman et al [2004]

2. 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]

3. Winawer et al [2002], Brodtkorb et al [2005b], Di Bonaventura et al [2009]

4. Molecular genetic testing reveals pathogenic variants in *CHRNA4*, *CHRNB2*, *CHRNA2*, *KCNT1*, *DEPDC5*, or *CRH* in approximately 20% of individuals with a positive family history and fewer than 5% of individuals with a negative family history.

5. Andermann et al [2005]

6. Scheffer et al [1998], Xiong et al [1999], Callenbach et al [2003], Berkovic et al [2004b]

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with autosomal dominant epilepsy with auditory features (ADEAF), consultation with a clinical geneticist and/or genetic counselor is recommended.

Treatment of Manifestations

ADEAF is benign in the great majority of individuals. No clinical trials of different anti-seizure medications have been carried out, but seizure control is achieved in most individuals with medications used routinely in clinical practice (e.g., carbamazepine, phenytoin, valproate).

Education of parents regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for parents or caregivers of children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Surveillance

No surveillance guidelines for ADEAF have been developed.

- As in any other form of focal epilepsy, routine interictal EEG may be performed to detect focal epileptiform abnormalities.
- Brain MRI may be repeated to rule out structural abnormalities.

Evaluation of Relatives at Risk

It is appropriate to evaluate relatives at risk in order to identify as early as possible those who would benefit from initiation of treatment and measures to minimize risk in the event of seizure onset (e.g., avoidance of unattended swimming).

- If the *LGI1*, *MICAL1*, or *RELN* pathogenic variant in the family is known, molecular genetic testing can be used to clarify the genetic status of at-risk relatives.
- If the pathogenic variant in the family is not known, interview of relatives at risk may identify symptoms possibly related to seizures.

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

Pregnancy Management

In general, women with epilepsy or a seizure disorder from any cause are at greater risk for mortality during pregnancy than pregnant women without a seizure disorder; use of anti-seizure medication (ASM) during pregnancy reduces this risk. However, exposure to ASM may increase the risk for adverse fetal outcome (depending on the drug used, the dose, and the stage of pregnancy at which medication is taken). Nevertheless, the risk of an adverse outcome to the fetus from ASM exposure is often less than that associated with exposure to an untreated maternal seizure disorder. Therefore, use of ASM to treat a maternal seizure disorder during pregnancy is typically recommended. Discussion of the risks and benefits of using a given ASM during pregnancy should ideally take place prior to conception. Transitioning to a lower-risk medication prior to pregnancy may be possible [Sarma et al 2016].

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of 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; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Autosomal dominant epilepsy with auditory features (ADEAF) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with ADEAF have an affected parent.
- A proband with ADEAF may have the disorder as the result of a *de novo LGI1* or *RELN* pathogenic variant; the proportion of cases caused by a *de novo* pathogenic variant is believed to be low (~1%).
  - Three (1%) of 230 simplex cases (i.e., a single occurrence in a family) had a heterozygous *LGI1* pathogenic variant [Bisulli et al 2004a, Bisulli et al 2004b, Flex et al 2005, Michelucci et al 2007, Dazzo et al 2015b]. Two were *de novo* [Bisulli et al 2004b, Michelucci et al 2007]; the origin of the third could not be determined [Dazzo et al 2015b].
  - A *de novo* pathogenic variant was identified in a study of 16 Turkish simplex cases and ten familial cases [Kesim et al 2016].
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include molecular genetic testing of the parents and a medical history to ascertain a history of seizures.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. Though theoretically possible, no instances of germline mosaicism have been reported.
- The family history of some individuals diagnosed with ADEAF 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. Therefore, an apparently negative family history cannot be confirmed unless appropriate evaluations (e.g., molecular genetic testing and/or clinical history) have been performed on the parents of the proband.

Sibs of a proband. The risk to sibs of a proband depends on the clinical/genetic status of the parents:

- If a parent has clinical characteristics consistent with ADEAF and/or has the pathogenic variant identified in the proband, the likelihood that each sib will inherit the pathogenic variant is 50%. The chance that a sib who inherits the pathogenic variant will manifest ADEAF ranges from 54% to 85%, depending on the assumed penetrance (see Penetrance).
- If a parent has clinical characteristics consistent with ADEAF and does not have the *LGI1*, *MICAL1*, or *RELN* pathogenic variant identified in the proband, the recurrence risk to sibs may be as low as 35%, especially in smaller (nuclear) families (see Penetrance).

- If the proband has a known *LGI1*, *MICAL1*, or *RELN* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the ADEAF-related pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for ADEAF because of the possibility of reduced penetrance in a parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Offspring of an individual with ADEAF who is heterozygous for a pathogenic variant have a 50% chance of inheriting the pathogenic variant; the chance that offspring who inherit the pathogenic variant will manifest ADEAF ranges from 54% to 85% depending on the assumed penetrance.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has phenotypic features consistent with ADEAF or has a pathogenic variant in *LGI1*, *MICAL1*, or *RELN*, the parent's family members may be at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Diagnostic testing for *LGI1*, *MICAL1*, or *RELN* pathogenic variants in individuals with ADEAF has limited clinical utility because identification of a pathogenic variant would not lead to a change in treatment or management [Ottman et al 2010]. On the other hand, identification of the genetic basis of ADEAF enables informed genetic counseling and benefits individuals interested in knowing the cause of their epilepsy.

The utility of presymptomatic testing is limited because:

- Approximately one third of those with a pathogenic variant will remain unaffected due to reduced penetrance;
- Seizures are treatable in most affected individuals;
- No methods have been identified to prevent the development of seizures in those with a pathogenic variant.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing 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. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *LGI1*, *MICAL1*, or *RELN* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **American Epilepsy Society**
  www.aesnet.org
- **Canadian Epilepsy Alliance**
  Canada
  Phone: 1-866-EPILEPSY (1-866-374-5377)
  www.canadianepilepsyalliance.org
- **Citizens United for Research in Epilepsy (CURE)**
  www.cureepilepsy.org
- **Epilepsy Canada**
  Canada
  Phone: 877-734-0873
  Email: epilepsy@epilepsy.ca
  www.epilepsy.ca
- **Epilepsy Foundation**
  Phone: 301-459-3700
  Fax: 301-577-2684
  www.epilepsy.com

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Autosomal Dominant Epilepsy with Auditory Features: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
LGI1	10q23.33	Leucine-rich glioma-inactivated protein 1	LGI1 database	LGI1	LGI1
MICAL1	6q21	[F-actin]-monooxygenase MICAL1		MICAL1	MICAL1
RELN	7q22.1	Reelin	RELN database	RELN	RELN

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Autosomal Dominant Epilepsy with Auditory Features (View All in OMIM)

600512	EPILEPSY, FAMILIAL TEMPORAL LOBE, 1; ETL1
600514	REELIN; RELN
604619	LEUCINE-RICH GENE, GLIOMA-INACTIVATED, 1; LGI1
607129	MICROTUBULE-ASSOCIATED MONOOXYGENASE, CALPONIN AND LIM DOMAINS-CONTAINING, 1; MICAL1
616436	EPILEPSY, FAMILIAL TEMPORAL LOBE, 7; ETL7

Molecular Pathogenesis

The proteins reelin and Lgi1 colocalize in a subset of rat brain neurons, supporting a common molecular pathway underlying ADEAF [Dazzo et al 2015a]. Reelin serves a dual purpose in mammalian brain with critical roles both during embryonic development [D'Arcangelo et al 1995, Lambert de Rouvroit & Goffinet 1998] and postnatally [Niu et al 2004, Beffert et al 2005]. Work on conditional knockout mice suggests that Lgi1, like reelin, could serve different functions during brain development and in adulthood [Boillot et al 2014]. Thus, a functional interplay between the two proteins may be necessary for proper regulation of various neuronal processes during development and in adult life.

The protein MICAL1 has an enzymatic oxidoreductase activity that induces disassembly of actin filaments, thereby regulating the organization of the actin cytoskeleton in developing and adult neurons and in other cell types. Dysregulation of the actin cytoskeleton dynamics in neurons is a likely mechanism underlying *MICAL1*-related ADEAF [Dazzo et al 2018].

LGI1

Gene structure. The longest *LGI1* transcript variant (NM_005097.2) has eight exons. *LGI1* is a member of a subfamily of leucine-rich repeat (LRR)-encoding genes, denoted *LGI1*, *LGI2*, *LGI3*, and *LGI4* [Gu et al 2002b]. See Table A, **Gene** for a detailed summary of gene and protein information.

Pathogenic variants. Pathogenic variants have been found throughout the gene; they were found to cluster in the LRR domain (exons 3-5) [Ho et al 2012].

Of the reported pathogenic variants, two thirds are missense variants and one third are frameshift variants that predict premature translation termination leading to unstable mRNA or truncated protein. Three intronic pathogenic variants have been reported, each predicting protein truncation [Kalachikov et al 2002, Kobayashi et al 2003, Chabrol et al 2007]. Almost all of the identified pathogenic variants have been unique to an individual family. The exceptions:

- p.Cys46Arg, identified in one Norwegian and one Italian family without known shared antecedents [Gu et al 2002a, Pizzuti et al 2003, Pizzuti & Giallonardo 2003]
- p.Ala253ValfsTer32, identified in two Spanish families from the same region [Morante-Redolat et al 2002, Michelucci et al 2003]
- p.Ser473Leu, identified in one Australian and one Japanese family [Berkovic et al 2004a, Kawamata et al 2010]
- p.Arg474Ter, identified in a Basque family and in a simplex case from Italy, as a *de novo* pathogenic variant [Morante-Redolat et al 2002, Bisulli et al 2004b]

In addition, two of the reported pathogenic missense variants, c.124T>C and c.124T>G, changed the same nucleotide [Berkovic et al 2004a, Ottman et al 2004].

Deletions encompassing one or more exons of *LGI1* were identified in families with ADEAF in which exon sequencing revealed no pathogenic variant [Fanciulli et al 2012, Dazzo et al 2015b].

Table 3. *LGI1* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.124T>C	p.Cys42Arg	NM_005097.2 NP_005088.1
c.124T>G	p.Cys42Gly	
c.136T>C	p.Cys46Arg	
c.758delC	p.Ala253ValfsTer32	
c.1418C>T	p.Ser473Leu	
c.1420C>T	p.Arg474Ter	
Deletion of ~81 kb [1]		

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Deletes exons 1-4 and maps between rs11187602 and rs7099034 [Fanciulli et al 2012]

Normal gene product. The longest transcript NM_005097.2 is predicted to encode the longest isoform, the 557-amino-acid leucine-rich glioma-inactivated protein 1 (Lgi1) (NP_005088.1) [Nobile at al 2009]. See Molecular Pathogenesis.

Abnormal gene product. The function of the normal gene product Lgi1 and the mechanism by which alterations in the protein cause epilepsy remain poorly understood; multiple lines of evidence have been investigated.

Interestingly, there are two protein isoforms, with different expression patterns in human brain [Furlan et al 2006]. The long isoform (NP_005088.1) is secreted [Sirerol-Piquer et al 2006]. Most pathogenic variants are defective for secretion, whereas a few pathogenic variants allow protein secretion but reduce the binding ability of the Lgi1 long form to its neuronal receptors ADAM22 and ADAM23 [Sirerol-Piquer et al 2006, Dazzo et al 2016].

One study suggested that Lgi1 may influence the risk for epilepsy through a glutamatergic mechanism: through its interaction with ADAM22, Lgi1 controls the synaptic content of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors, thereby modulating synaptic transmission as well as regulating the maturation of excitatory synapses [Lovero et al 2015].

Studies in transgenic mice showed that overexpression of an *Lgi1* pathogenic variant, homologous to one known to cause ADEAF in humans, causes epilepsy by impairing the postnatal development of glutamatergic circuits in the hippocampus [Zhou et al 2009].

Cancer and benign tumors. Cancerous tissues obtained from normal individuals show that *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 ADEAF.

MICAL1

Gene structure. The main *MICAL1* transcript has 25 exons (NM_022765.4). *MICAL1* is a member of a family of genes that includes two more human genes: *MICAL2* and *MICAL3*. See Table A, **Gene** for a detailed summary of gene and protein information.

Pathogenic variants. Two pathogenic variants have been identified in two families with ADEAF [Dazzo et al 2018]. A missense variant, p.Gly150Ser, was found in the enzymatically active oxidoreductase domain, and a

two-base pair frameshift deletion, p.Ala1065fs, in the C-terminal domain, resulting in truncation of the terminal portion of the protein.

Table 4. *MICAL1* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.448G>A	p.Gly150Ser	NM_022765.4 NP_073602.3
c.3189_3190del	p.Ala1065fs	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. *MICAL1* encodes [F-actin]-monooxygenase MICAL1, a protein of 1,067 amino acids (NP_073602.3) that contains an enzymatically active oxidoreductase domain and three other domains that mediate protein-protein interactions. For a review see Vanoni [2017].

Abnormal gene product. Both pathogenic variants were shown to significantly increase the oxidoreductase activity of MICAL1 and induce cell contraction in cultured cells, which likely resulted from deregulation of actin cytoskeleton dynamics. MICAL1 oxidoreductase activity is autoinhibited by the C-terminal domain, so that the wild type protein is nearly inactive. A small deletion like p.Ala1065fs that alters the structure of the C-terminal domain reduces its ability to suppress the oxidoreductase activity, which is therefore increased (gain of function). The p.Gly150Ser variant affects a highly conserved glycine residue, the substitution of which with a polar serine may result in a local perturbation of domain conformation that partially releases inhibition by the C-terminal domain.

RELN

Gene structure. The longest *RELN* transcript has 65 exons and is primarily expressed in the brain [Dazzo et al 2015a]. Two transcript variants encoding distinct isoforms have been identified for this gene. Other transcript variants have been described but their full length nature has not been determined. See Table A, **Gene** for a detailed summary of gene and protein information.

Pathogenic variants. Seven pathogenic variants have been identified in seven Italian families with ADEAF [Dazzo et al 2015a]. All were missense variants that affected structurally important amino acids or likely affected protein folding. Four pathogenic variants – p.Asp763Gly, p.His798Asn, p.Gly2783Cys, and p.Glu3176Lys – were shown to reduce serum levels of reelin, suggesting a loss-of-function effect due to impaired protein secretion [Dazzo et al 2015a].

Table 5. *RELN* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.2015C>T	p.Pro672Leu	NM_005045.3 NP_005036.2
c.2168A>G	p.Tyr723Cys	
c.2288A>G	p.Asp763Gly	
c.2392C>A	p.His798Asn	
c.2531C>T	p.Pro844Leu	
c.8347G>T	p.Gly2783Cys	
c.9526G>A	p.Glu3176Lys	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. *RELN* encodes reelin, a very large secreted protein of 3,460 amino acids. See Molecular Pathogenesis and D'Arcangelo [2014] for a review.

Abnormal gene product. Pathogenic variants in *RELN* were associated with decreased serum levels of reelin, suggesting an inhibitory effect on protein secretion [Dazzo et al 2015a]. Reduced levels of serum reelin are observed in heterozygous *reeler* mice [Smalheiser et al 2000], which have apparently normal brains but display functional and molecular defects at the synapse [Ventruti et al 2011]. Similar synaptic defects may also be associated with the heterozygous pathogenic variants in *RELN* in ADEAF, eventually giving rise to epilepsy.

In humans, homozygous *RELN* pathogenic variants cause autosomal recessive lissencephaly with cerebellar hypoplasia (LCH) (OMIM 257320) [Hong et al 2000]. In three small consanguineous families with LCH reported, clinically normal heterozygotes (carriers of one *RELN* pathogenic variant) exhibited reduced serum reelin [Hong et al 2000, Zaki et al 2007]. The apparently normal carrier phenotype is consistent with the relatively low penetrance of *RELN* pathogenic variants in families with ADEAF. Thus, as in other genetic epilepsy syndromes, *RELN*-related disorders may be genetically and clinically heterogeneous, with pathogenic variants resulting in ADEAF in heterozygotes and the more severe LCH in homozygotes.

Chapter Notes

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