U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Michelucci R, Pasini E, Dazzo E. Autosomal Dominant Epilepsy with Auditory Features. 2007 Apr 20 [Updated 2024 May 9]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Autosomal Dominant Epilepsy with Auditory Features

Synonyms: ADEAF, Autosomal Dominant Lateral Temporal Lobe Epilepsy, Autosomal Dominant Partial Epilepsy with Auditory Features

Roberto Michelucci, MD, PhD,[1] Elena Pasini, MD,[1] and Emanuela Dazzo, PhD[2]

Created: April 20, 2007; Updated: May 9, 2024.

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. Age at onset is usually in adolescence or early adulthood (age 10-30 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 can be established in a proband with characteristic clinical features, normal brain imaging by MRI, and family history consistent with autosomal dominant inheritance. The molecular diagnosis is established in a proband with characteristic clinical features and a heterozygous pathogenic variant in *LGI1*, *MICAL1*, or *RELN* identified by molecular genetic testing.

Management

Treatment of manifestations: Seizure control is usually readily achieved with standard anti-seizure medications (ASM).

Surveillance: Monitoring of epilepsy as clinically indicated; neurocognitive assessments in individuals suspected to have memory or attention deficits; evaluation by a psychiatrist for any psychiatric comorbidities.

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

Author Affiliations: 1 IRCCS Istituto delle Scienze Neurologiche di Bologna, Neurology and Epilepsy Unit, Bellaria Hospital, Bologna, Italy; Email: roberto.michelucci@isnb.it; Email: elena.pasini@isnb.it. 2 CNR Institute of Neuroscience, Padua, Italy; Email: emanuela.dazzo@cnr.it.

Pregnancy management: 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.

Genetic counseling

By definition, ADEAF is inherited in an autosomal dominant manner. Most individuals diagnosed with ADEAF have an affected parent; the proportion of individuals with ADEAF caused by a *de novo* pathogenic variant is believed to be low. 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. Once the ADEAF-related pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

Consensus clinical diagnostic criteria for autosomal dominant epilepsy with auditory features (ADEAF) have been published by the International League Against Epilepsy (ILAE) [Riney et al 2022].

Suggestive Findings

ADEAF **should be suspected** in individuals with the following clinical, neuroimaging, and EEG findings and family history.

Clinical findings. A history consistent with **focal epilepsy** typically in adolescence/adulthood (age of onset 10-30 years) with no prior history of seizures or developmental delays. Seizure semiology is consistent with focal aware seizures with auditory symptoms and/or receptive aphasia:

- **Auditory symptoms** can occur in a temporal association with seizures as:
  - An aura immediately preceding a bilateral tonic-clonic seizure;
  - A component of focal aware or focal impaired-awareness seizures;
  - The only ictal symptom.
- **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.

Early development and neurologic examination are typically normal.

Brain imaging is typically normal.

Interictal EEG is often normal. However, focal (temporal) or diffuse epileptiform abnormalities are found in up to two thirds of individuals.

Family history is consistent with autosomal dominant inheritance (with reduced penetrance). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The clinical diagnosis of ADEAF can be **established** in a proband based on clinical diagnostic criteria [Riney et al 2022]. The molecular diagnosis is established in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *LGI1*, *MICAL1*, or *RELN* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include 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.

Clinical Diagnosis

Consensus clinical diagnostic criteria for ADEAF have been published by the ILAE [Riney et al 2022].

Mandatory criteria:

- Focal sensory auditory seizures and/or focal cognitive seizures with receptive aphasia
- Normal brain imaging by MRI

Exclusion/alert criteria:

- Generalized-onset seizures or other focal-onset seizures
- Moderate or severe intellectual disability
- Generalized epileptiform discharges
- Focal abnormalities on neurologic examination

Molecular Diagnosis

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determines which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Option 1

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

Option 2

When the phenotype is indistinguishable from many other epilepsy disorders, **comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. To date, the majority of pathogenic variants reported in *LGI1*, *MICAL1*, and *RELN* are within the coding region and are likely to be identified on exome sequencing.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

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

Gene [1, 2]	Proportion of ADEAF Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] in Gene Identified by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
LGI1	~30% [6]	95%	5% [7]
MICAL1	~7% [8]	~95%-100%	None reported to date
RELN	~17%-18% [6]	~99% [9]	~1% [10]
Unknown [11]	~50%	NA	

1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on variants detected in these genes.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. 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. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.
6. Michelucci et al [2017]
7. Several partial and total gene deletions involving *LGI1* have been identified in families with ADEAF in which exome sequencing did not reveal any pathogenic sequencing alterations [Fanciulli et al 2012, Magini et al 2014, Manna et al 2014, Dazzo et al 2015b, Monlong et al 2018, Coppola et al 2019, Truty et al 2019]
8. Dazzo et al [2018]
9. Dazzo et al [2015a]
10. Martinez-Granero et al [2021]
11. A locus on 19q13.11-q13.31 likely to contain a gene associated with ADEAF was identified in a large Brazilian family [Bisulli et al 2014]. In 21 families with ADEAF, 12 rare copy number variants (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 syndromes.

Clinical Characteristics

Clinical Description

Autosomal dominant epilepsy with auditory features (ADEAF) is characterized by adolescence/adulthood onset of focal aware seizures with auditory symptoms and/or receptive aphasia in individuals with normal cognitive and neurologic development [Michelucci et al 2009, Riney et al 2022].

Table 2. Autosomal Dominant Epilepsy with Auditory Features: Frequency of Select Features

Feature	% of Persons w/Feature	Comment
Epilepsy	100%	Most commonly reported seizure types include: • Focal to bilateral tonic-clonic seizures accompanied by focal aware or focal impaired-awareness seizures, w/auditory symptoms (~88%-92%) • Reflex seizures (in response to sudden noises or a noisy environment) (~8%-13%)
Auditory features	~57%-71%	Can be simple (e.g., hearing a monotone sound such as humming or buzzing as in tinnitus) or complex (e.g., hearing voices or music)

Table 2. continued from previous page.

Feature	% of Persons w/Feature	Comment
Aphasia	~17%-20%	Typically receptive
EEG abnormalities	~ 57%-80%	Focal (temporal) or generalized

Michelucci et al [2009], Michelucci et al [2013], Michelucci et al [2017]

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 4 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 to the Heschl gyrus or Wernicke area. Typically, individuals have normal neurologic examination and intellectual development.

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 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].

Febrile seizures do not appear to 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.

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. Another distinctive feature of ADEAF 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* and *RELN* pathogenic variants [Michelucci et al 2003, Ottman et al 2004, Di Bonaventura et al 2009, Michelucci et al 2020].

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 of consciousness).

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 occasions 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, depression appeared to be related to either the epilepsy or anti-seizure medication (ASM) [Heiman et al 2010].
- Migraine headaches segregating with occipitotemporal epilepsy resembling ADEAF has been described in one family [Deprez et al 2007].

Prognosis. The clinical course of ADEAF is usually benign. Several studies have reported on variable outcomes, as summarized below.

- In a series of 34 affected individuals from 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 were seizure-free (from focal or 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 ASM resistance was described [Di Bonaventura et al 2009].
- In one family with ADEAF caused by a pathogenic *RELN* variant, the proband had a long history of refractory focal seizures. Interestingly, brain MRI showed left temporal lobe abnormalities suggestive of focal cortical dysplasia [Michelucci et al 2020].
- In a large retrospective cohort study investigating a heterogeneous group of individuals with epilepsy with auditory features (EAF), prognosis seems to be more variable, ranging from mild to severe intractable epilepsy. However, in this cohort familial cases represented 32% of individuals, with a clear autosomal dominant inheritance pattern of ADEAF identified only in 12% [Bisulli et al 2018]. Furthermore, some of these ADEAF cases were reported to be due to pathogenic *DEPDC5* variants and could therefore be better considered to have familial focal epilepsy with variable foci (see *DEPDC5*-Related Epilepsy).

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, 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 rare cases [Winawer et al 2002, Brodtkorb et al 2005a, DiBonaventura et al 2009, Michelucci et al 2020]. One of these showed left mid- and anterior temporal onset [Winawer et al 2002], and another showed 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]. More recently an ictal EEG in a familial case with a pathogenic *RELN* variant has been described, showing – at least in the longer seizures (up to 20-30 seconds) – rhythmic focal discharges in the left temporal region [Michelucci et al 2020].

Findings from magnetoencephalography (MEG) with auditory stimuli showed significantly delayed peak 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], suggesting a plausible hyperexcitability in the pathologic temporal cortex in ADEAF.

Neuroimaging. Routine brain imaging studies (MRI or CT) are typically normal.

A left lateral temporal lobe malformation was identified by high-resolution MRI in ten individuals in a Brazilian family with an *LGI1* pathogenic variant, but this neuroradiologic finding did not segregate entirely with the genotype [Kobayashi et al 2003]. 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 eight individuals with ADEAF with an *LGI1* pathogenic variant [Tessa et al 2007], indicating a link between pathogenic *LGI1* variants and a focal structural abnormality that could be epileptogenic.

Using functional MRI with an auditory description decision task, individuals 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.

An interictal single-photon emission computed tomography scan in one person identified hypoperfusion in the left temporal lobe [Poza et al 1999], whereas a left mesial temporal hypometabolism in a F-fluorodeoxyglucose positron emission tomography (FDG-PET) scan was found interictally in an individual with a pathogenic *RELN* variant [Michelucci et al 2020], suggesting a more complicated epileptogenic network.

In another study, two individuals with ADEAF in the same family underwent stereoelectroencephalography (SEEG) investigation and subsequent SEEG-guided radiofrequency thermocoagulation and in one case surgical resection. Fast activities recorded with deep electrodes originated from the right superior temporal gyrus with rapid spreading to other network's nodes. Despite a normal cerebral MRI, an FDG-PET scan showed hypometabolism in the superior temporal gyrus. Genetic findings were incomplete [Wei et al 2022].

Other investigations. Asymmetry of long-latency auditory evoked potentials (with reduced left N1-P2 amplitudes) was shown in a Norwegian family with aphasic seizures [Brodtkorb et al 2005b]. Abnormal phonologic processing was demonstrated in four individuals 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, 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 epilepsy-associated (epitempin) domain than with other *LGI1* pathogenic variant types / domain combinations [Ho et al 2012]. No significant clinical differences were observed between families with an *LGI1* pathogenic variant and families without an identified pathogenic variant [Michelucci et al 2013].

Phenotypic features were similar in published familial cases with *LGI1*, *MICAL1*, or *RELN* pathogenic variants [Dazzo et al 2015a, Michelucci et al 2017, Dazzo et al 2018]. Further, no phenotypic differences have been found between simplex cases (i.e., a single occurrence in a family) and published familial cases of epilepsy with auditory features [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 across these studies.

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

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 these estimates are likely to be inflated by ascertainment bias, as they are based on families selected for analysis because they comprised many affected individuals.

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

MICAL1. Penetrance is unknown.

Nomenclature

The term "epilepsy with auditory features (EAF)" refers to all individuals with a diagnosis of EAF, encompassing individuals with a known family history of EAF ("familial EAF [FEAF]") and individuals who appear to represent simplex cases (i.e., the only family known to be affected with EAF). EAF has been proposed to replace the family history-dependent terms – "autosomal dominant lateral temporal lobe epilepsy (ADLTE)" and "autosomal dominant partial epilepsy with auditory features (ADPEAF)" – used previously to refer to the disorder [Furia et al 2022, Riney et al 2022]. However, this terminology change is questionable, since the term "EAF" includes a more heterogeneous group of individuals with variable prognosis and etiology. Indeed, genetic advances in this field have been obtained by studying only clinically defined families with a dominant inheritance pattern.

"Autosomal dominant epilepsy with auditory features (ADEAF)" refers to individuals with EAF whose family history is consistent with autosomal dominant inheritance (e.g., affected family members in multiple generations) and/or individuals with EAF known to be caused by a heterozygous pathogenic variant. (Note: An individual with ADEAF may appear to represent a simplex case due to the possibility of reduced penetrance in asymptomatic, heterozygous family members.) The alternative term of ADLTE may be preferred, since some ictal symptoms of this condition (such as aphasia, vertiginous and complex visual auras, high propensity to generalize) indicate a clear localization over the lateral temporal cortex.

Prevalence

The prevalence of ADEAF is unknown but likely 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. Further, isolated auditory symptoms, especially when simple, might not be adequately recognized as pertaining to a disease and especially epilepsy. Therefore, a precise estimate of the incidence of EAF is currently not available.

Whereas genetic epilepsy syndromes account for a 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 germline pathogenic variants in *LGI1* and *MICAL1*.

Biallelic pathogenic variants in *RELN* are associated with lissencephaly with cerebellar hypoplasia (LCH; OMIM 257320), an autosomal recessive disorder characterized by severe and widespread neuronal migration defects, delayed cognitive development, and seizures [Hong et al 2000, Di Donato et al 2022]. In several consanguineous families with LCH reported, clinically normal heterozygotes (carriers of one *RELN* pathogenic variant) exhibited reduced serum reelin [Hong et al 2000, Di Donato et al 2022]. The apparently normal carrier phenotype is consistent with the relatively low penetrance of *RELN* pathogenic variants in families with autosomal dominant epilepsy with auditory features (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.

Differential Diagnosis

Selected genes associated with focal epilepsy in the differential diagnosis of autosomal dominant epilepsy with auditory features (ADEAF) are listed in Table 4.

Table 3. Selected Genes of Interest in the Differential Diagnosis of Autosomal Dominant Epilepsy with Auditory Features

Gene(s)	Disorder	Proportion of Disorder Attributed to Pathogenic Variants in Listed Genes	Clinical Features					
			Localization of epileptogenic zone	Seizure semiology	Age at onset	Neuroimaging	EEG	Other
CABP4 *CHRNA4* *CHRNA2* *CHRNB2* *CRH* *DEPDC5* *KCNT1* *NPRL2* *NPRL3* *STX1B*	Autosomal dominant sleep-related hypermotor (hyperkinetic) epilepsy (ADSHE)	• 19% (persons w/family history of SHE) • 7% (persons w/ negative family history)	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 most persons, typically in adolescence	Usually 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 to 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.
Unknown (*DEPDC5*) [1]	Familial mesial temporal lobe epilepsy (FMTLE)	Rare [1]	Mesial temporal lobe [2]	• 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)

Table 3. continued from previous page.

Gene(s)	Disorder	Proportion of Disorder Attributed to Pathogenic Variants in Listed Genes	Clinical Features					
			Localization of epileptogenic zone	Seizure semiology	Age at onset	Neuroimaging	EEG	Other
Multiple genes incl: *DEPDC5* *NPRL2* *NPRL3* *TSC1* *TSC2*	Familial focal epilepsy w/ variable foci (FFEVF) (OMIM PS604364)	Unknown	• Epileptogenic zone (frontal, temporal, or occipital) differs among family members. [3] • 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.

SHE = sleep-related hypermotor (hyperkinetic) epilepsy

1. Pathogenic variants in *DEPDC5* are a rare cause of FMTLE (see *DEPDC5*-Related Epilepsy). The molecular basis of FMTLE is unknown in most affected individuals.

2. Andermann et al [2005]

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

Management

No clinical practice guidelines for autosomal dominant epilepsy with auditory features (ADEAF) have been published. In the absence of published guidelines, the following recommendations are based on the authors' personal experience managing individuals with this disorder.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with autosomal dominant epilepsy with auditory features (ADEAF), the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Autosomal Dominant Epilepsy with Auditory Features: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Neurologic	Assessment by neurologist for eval of suspected seizures as indicated	To incl EEG, high-resolution brain MRI, cerebral FDG-PET; depending on seizure semiology, severity, & ASMs
Neurocognitive	Assessment by developmental pediatrician &/or neuropsychologist	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Psychiatric	Assessment by psychiatrist	For any psychiatric comorbidities or complications
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of ADEAF to facilitate medical & personal decision making

ADEAF = autosomal dominant epilepsy with auditory features; ASM = anti-seizure medication; MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves care by specialists in relevant fields (see Table 5).

Table 5. Autosomal Dominant Epilepsy with Auditory Features: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Epilepsy	Standardized treatment w/ASM by epileptologist or experienced neurologist	• Most persons are responsive to standard ASMs & in most cases monotherapy is effective for complete seizure control. [1] • Education of parents/caregivers [2]
Psychiatric issues	Standardized treatment by psychiatrist	
Family/Community	Ensure appropriate social work involvement to connect families w/local resources& support.	Ongoing assessment of need for support

ASM = anti-seizure medication
1. Traditionally sodium channel blockers such as carbamazepine have been more frequently used with clear benefit. However, no clinical trials of different anti-seizure medications have been carried out, therefore definite therapeutic guidelines have not been published to date. Total remission might be lower than expected and treatment withdrawal might lead to relapses in some individuals.
2. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 6 are recommended.

Table 6. Autosomal Dominant Epilepsy with Auditory Features: Recommended Surveillance

System/Concern	Evaluation	Frequency
Neurologic	Monitor those w/seizures as clinically indicated.	At each visit
Neurocognitive	Monitor those w/memory/attention deficits &/or other neurocognitive issues.	
Psychiatric	Eval by psychiatrist for any psychiatric comorbidities	If applicable
Family/Community	Assess family need for social work support (e.g., other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	At each visit
Transition to Adult Care	Develop realistic plans for adult life (see American Epilepsy Society Transitions from Pediatric Epilepsy to Adult Epilepsy Care).	Starting by age ~10 yrs

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 ADEAF-related 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 sensory symptoms (visual, olfactory, vertiginous, or cephalic) and/or motor, psychic, and autonomic symptoms possibly related to seizures.

Note:

- Approximately one third of individuals with an ADEAF-related pathogenic variant will remain unaffected due to reduced penetrance.
- Seizures are treatable in most affected individuals.
- No interventions have been identified to prevent the development or occurrence of seizures in individuals with an ADEAF-related pathogenic.

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 ASMs may increase the risk for adverse fetal outcome (depending on the drug used, the dose, and the stage of pregnancy at which the 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 ASMs 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

By definition, 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.
- Some individuals diagnosed with ADEAF may have the disorder as the result of a *de novo* pathogenic variant; the proportion of individuals with ADEAF caused by a *de novo* pathogenic variant is believed to be low (~1%). *De novo* pathogenic variants have been reported in individuals with *LGI1*-related ADEAF [Bisulli et al 2004b, Michelucci et al 2007, Kesim et al 2016] and with *MICAL1*-related ADEAF [Bonanni et al 2024].
- If the proband appears to be the only affected family member (i.e., a simplex case), recommendations for the evaluation of the parents of the proband include a medical history to ascertain a history of seizures and – if a molecular diagnosis has been established in the proband – genetic testing for the pathogenic variant identified in the proband.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicismand will not detect a pathogenic variant that is present in the germ (gonadal) cells only.
- 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 (approximately one third of individuals with an ADEAF-related pathogenic variant will remain unaffected due to reduced penetrance). Therefore, an apparently negative family history cannot be confirmed unless a molecular diagnosis has been established in the proband and molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant identified in 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).
- Note: 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].

- 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 possibility of parental germline mosaicism [Rahbari et al 2016]. To date, parental germline mosaicism has not been reported in ADEAF.
- If the parents are clinically unaffected but their genetic status is unknown, sibs are presumed to be at increased risk for ADEAF because of the possibility of reduced penetrance in a heterozygous parent or 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 (see 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

Predictive testing (i.e., testing of asymptomatic at-risk individuals)

- Predictive testing for at-risk relatives is possible if the ADEAF-related pathogenic variant has been identified in an affected family member.
- Potential consequences of such testing as well as the capabilities and limitations of predictive testing should be discussed in the context of formal genetic counseling prior to testing.

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives to identify 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).

Family planning

- Discussion of the risks and benefits of using a given anti-seizure medication during pregnancy should ideally take place prior to conception (see Pregnancy Management).
- 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 ADEAF-related 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**
  aesnet.org
- **Canadian Epilepsy Alliance**
  Canada
  Phone: 1-866-EPILEPSY (1-866-374-5377)
  canadianepilepsyalliance.org
- **Citizens United for Research in Epilepsy (CURE)**
  www.cureepilepsy.org
- **Epilepsy Canada**
  Canada
  Phone: 877-734-0873
  Email: epilepsy@epilepsy.ca
  epilepsy.ca
- **Epilepsy Foundation**
  Phone: 800-332-1000; 866-748-8008
  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 @ LOVD	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

Despite its clinical homogeneity, autosomal dominant epilepsy with auditory features (ADEAF) is genetically heterogeneous. To date, three causative genes have been identified, *LGI1*, *MICAL1*, and *RELN*.

LGI1 encodes leucine-rich glioma inactivated protein 1 (LGI1), a secreted protein [Sirerol-Piquer et al 2006] expressed mainly in glutamatergic neurons, particularly in the neocortex and limbic regions [Kalachikov et al 2002].

Most pathogenic variants of *LGI1* cause defective secretion, whereas a few pathogenic variants are secretion competent. Both classes of variants have loss-of-function effects, but secretion-competent pathogenic variants appear to exert their effect extracellularly by decreasing molecular affinity for both ADAM22 and ADAM23 [Sirerol-Piquer et al 2006, Dazzo et al 2016]. Furthermore, one study suggested that LGI1 may influence the risk for epilepsy through a glutamatergic mechanism through its interaction with ADAM22 controlling the synaptic content of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors, and thereby modulating synaptic transmission as well as regulating the maturation of excitatory synapses [Lovero et al 2015].

MICAL1 encodes [F-actin]-monooxygenase MICAL1 (MICAL1), a protein that contains an enzymatically active oxidoreductase activity that induces disassembly of actin filaments, thereby regulating the organization of the actin cytoskeleton in developing and adult neurons as well as other cell types [Vanoni 2017]. Pathogenic variants in *MICAL1* reported to date have been 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. Therefore, this gain-of-function effect that induces dysregulation of the actin cytoskeleton dynamics in neurons is a likely mechanism underlying *MICAL1*-related ADEAF [Dazzo et al 2018].

RELN encodes reelin, a large protein secreted by Cajal-Retzius cells during embryonic development and by GABAergic neurons in the postnatal brain [D'Arcangelo 2014]. Pathogenic variants in *RELN* are 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, which have apparently normal brains but display functional and molecular defects at the synapse [Smalheiser et al 2000, Ventruti et al 2011]. Similar synaptic defects may also be associated with the heterozygous pathogenic variants in *RELN* in ADEAF giving rise to epilepsy. One study showed that pathogenic *RELN* variants abolish or significantly reduce secretion of mutated proteins in vitro; the loss-of-function effect results from impaired trafficking of mutated reelin along the secretory pathway; and mutated proteins are degraded by the autophagy system [Dazzo & Nobile 2022].

Most pathogenic variants reported in *RELN* affected structurally important amino acids or likely protein folding [Dazzo et al 2015a, Michelucci et al 2020].

Mechanism of disease causation

- *LGI1*. Loss of function (defective secretion or reduced binding to receptors)
- *MICAL1*. Gain of function
- *RELN*. Loss of function (defective secretion)

Chapter Notes

Author Notes

Project Coordinator, Epilepsy Family Study of Columbia University
Columbia University

Tel: 212-305-9188
Email: efscu@columbia.edu

Acknowledgements

We are grateful for the research support of the Telethon Foundation, the Genetics Commission of the Italian League Against Epilepsy, and the Fondo di Beneficenza Intesa San Paolo.

Author History

Emanuela Dazzo, PhD (2024-present)
Roberto Michelucci, MD, PhD (2019-present)
Carlo Nobile, PhD; CNR Institute of Neuroscience (2019-2024)
Ruth Ottman, PhD; Columbia University (2007-2019)
Elena Pasini, MD (2024-present)

Revision History

- 9 May 2024 (gm) Comprehensive update posted live
- 10 January 2019 (bp) Comprehensive update posted live
- 27 August 2015 (me) Comprehensive update posted live
- 31 January 2013 (me) Comprehensive update posted live
- 13 July 2010 (me) Comprehensive update posted live
- 20 April 2007 (me) Review posted live
- 1 February 2007 (ro) Original submission

References

Literature Cited

Andermann F, Kobayashi E, Andermann E. Genetic focal epilepsies: state of the art and paths to the future. Epilepsia. 2005;46 Suppl 10 :61-7. PubMed PMID: 16359475.

Berkovic SF, Serratosa JM, Phillips HA, Xiong L, Andermann E, Díaz-Otero F, Gómez-Garre P, Martín M, Fernández-Bullido Y, Andermann F, Lopes-Cendes I, Dubeau F, Desbiens R, Scheffer IE, Wallace RH, Mulley JC, Pandolfo M. Familial partial epilepsy with variable foci: clinical features and linkage to chromosome 22q12. Epilepsia. 2004;45:1054-60. PubMed PMID: 15329069.

Bisulli F, Naldi I, Baldassari S, Magini P, Licchetta L, Castegnaro G, Fabbri M, Stipa C, Ferrari S, Seri M, Goncalves Silva GE, Tinuper P, Pippucci T. Autosomal dominant partial epilepsy with auditory features: a new locus on chromosome 19q13.11-q13.31. Epilepsia 2014;55:841-8. PubMed PMID: 24579982.

Bisulli F, Tinuper P, Avoni P, Striano P, Striano S, d'Orsi G, Vignatelli L, Bagattin A, Scudellaro E, Florindo I, Nobile C, Tassinari CA, Baruzzi A, Michelucci R. Idiopathic partial epilepsy with auditory features (IPEAF): a clinical and genetic study of 53 sporadic cases. Brain. 2004a;127:1343-52. PubMed PMID: 15090473.

Bisulli F, Tinuper P, Scudellaro E, Naldi I, Bagattin A, Avoni P, Michelucci R, Nobile C. A de novo LGI1 mutation in sporadic partial epilepsy with auditory features. Ann Neurol. 2004b;56:455-6. PubMed PMID: 15349881.

Bisulli F, Menghi V,Vignatelli L, et al. Epilepsy with auditory features: long-term outcome and predictors of terminal remission. Epilepsia. 2018;59:834. PubMed PMID: 29464704.

Bonanni P, Giorda R, Michelucci R, Nobile C, Dazzo E. A de novo pathogenic variant in MICAL-1 causes epilepsy with auditory features. Epilepsia Open. 2024. Epub ahead of print, PubMed PMID: 38654463.

Brodtkorb E, Gu W, Nakken KO, Fischer C, Steinlein OK. Familial temporal lobe epilepsy with aphasic seizures and linkage to chromosome 10q22-q24. Epilepsia. 2002;43:228-35. PubMed PMID: 11906506.

Brodtkorb E, Michler RP, Gu W, Steinlein OK. Speech-induced aphasic seizures in epilepsy caused by LGI1 mutation. Epilepsia. 2005a;46:963-6. PubMed PMID: 15946341.

Brodtkorb E, Steinlein OK, Sand T. Asymmetry of long-latency auditory evoked potentials in LGI1-related autosomal dominant lateral temporal lobe epilepsy. Epilepsia. 2005b;46:1692-4. PubMed PMID: 16190946.

Callenbach PM, van den Maagdenberg AM, Hottenga JJ, van den Boogerd EH, de Coo RF, Lindhout D, Frants RR, Sandkuijl LA, Brouwer OF. Familial partial epilepsy with variable foci in a Dutch family: clinical characteristics and confirmation of linkage to chromosome 22q. Epilepsia. 2003;44:1298-305. PubMed PMID: 14510823.

Chabrol E, Popescu C, Gourfinkel-An I, Trouillard O, Depienne C, Senechal K, Baulac M, LeGuern E, Baulac S. Two novel epilepsy-linked mutations leading to a loss of function of LGI1. Arch Neurol. 2007;64:217-22. PubMed PMID: 17296837.

Coppola A, Cellini E, Stamberger H, Saarentaus E, Cetica V, Lal D, Djémié T, Bartnik-Glaska M, Ceulemans B, Helen Cross J, Deconinck T, Masi S, Dorn T, Guerrini R, Hoffman-Zacharska D, Kooy F, Lagae L, Lench N, Lemke JR, Lucenteforte E, Madia F, Mefford HC, Morrogh D, Nuernberg P, Palotie A, Schoonjans AS, Striano P, Szczepanik E, Tostevin A, Vermeesch JR, Van Esch H, Van Paesschen W, Waters JJ, Weckhuysen S, Zara F, De Jonghe P, Sisodiya SM, Marini C; EuroEPINOMICS-RES Consortium; EpiCNV Consortium. Diagnostic implications of genetic copy number variation in epilepsy plus. Epilepsia. 2019;60:689-706. PubMed PMID: 30866059.

Dazzo E, Fanciulli M, Serioli E, Minervini G, Pulitano P, Binelli S, Di Bonaventura C, Luisi C, Pasini E, Striano S, Striano P, Coppola G, Chiavegato A, Radovic S, Spadotto A, Uzzau S, La Neve A, Giallonardo AT, Mecarelli O, Tosatto SC, Ottman R, Michelucci R, Nobile C. Heterozygousreelinmutations cause autosomal-dominantlateraltemporalepilepsy. Am J Hum Genet. 2015a;96:992-1000. PubMed PMID: 26046367.

Dazzo E, Leonardi E, Belluzzi E, Malacrida S, Vitiello L, Greggio E, Tosatto SC, Nobile C. Secretion-positive LGI1 mutations linked to lateral temporal epilepsy impair binding to ADAM22 and ADAM23 receptors. PLoS Genet. 2016;12:e1006376. PubMed PMID: 27760137.

Dazzo E, Nobile C. Epilepsy-causing Reelin mutations result in impaired secretion and intracellular degradation of mutant proteins. Hum Mol Genet. 2022;31:665-73. PubMed PMID: 34508592.

Dazzo E, Rehberg K, Michelucci R, Passarelli D, Boniver C, Vianello Dri V, Striano P, Striano S, Pasterkamp RJ, Nobile C. Mutations in MICAL-1cause autosomal-dominant lateral temporal epilepsy. Ann Neurol. 2018;83:483-93. PubMed PMID: 29394500.

Dazzo E, Santulli L, Posar A, Fattouch J, Conti S, Loden-van Straaten M, Mijalkovic J, De Bortoli M, Rosa M, Millino C, Pacchioni B, Di Bonaventura C, Giallonardo AT, Striano S, Striano P, Parmeggiani A, Nobile C. Autosomal dominant lateral temporal epilepsy (ADLTE): novel structural and single-nucleotide LGI1 mutations in families with predominant visual auras. Epilepsy Res. 2015b;110:132-8. PubMed PMID: 25616465.

Deprez L, Peeters K, Van Paesschen W, Claeys KG, Claes LR, Suls A, Audenaert D, Van Dyck T, Goossens D, Del-Favero J, De Jonghe P. Familial occipitotemporal lobe epilepsy and migraine with visual aura – linkage to chromosome 9q. Neurology. 2007;68:1995-2002. PubMed PMID: 17460155.

Di Bonaventura C, Carni M, Diani E, Fattouch J, Vaudano EA, Egeo G, Pantano P, Maraviglia B, Bozzao L, Manfredi M, Prencipe M, Giallonardo TA, Nobile C. Drug resistant ADLTE and recurrent partial status epilepticus with dysphasic features in a family with a novel LGI1mutation: electroclinical, genetic, and EEG/fMRI findings. Epilepsia. 2009;50:2481-6. PubMed PMID: 19552651.

Di Donato N, Guerrini R, Billington CJ, Barkovich AJ, Dinkel P, Freri E, Heide M, Gershon ES, Gertler TS, Hopkin RJ, Jacob S, Keedy SK, Kooshavar D, Lockhart PJ, Lohmann DR, Mahmoud IG, Parrini E, Schrock E,

Severi G, Timms AE, Webster RI, Willis MJH, Zaki MS, Gleeson JG, Leventer RJ, Dobyns WB. Monoallelic and biallelic mutations in RELN underlie a graded series of neurodevelopmental disorders. Brain. 2022;145:3274-87. PubMed PMID: 35769015.

Fanciulli M, Pasini E, Malacrida S, Striano P, Striano S, Michelucci R, Ottman R, Nobile C. Copy number variations and susceptibility to lateral temporal epilepsy: a study of 21 pedigrees. Epilepsia. 2014;55:1651-8. PubMed PMID: 25243798.

Fanciulli M, Santulli L, Errichiello L, Barozzi C, Tomasi L, Rigon L, Cubeddu T, de Falco A, Rampazzo A, Michelucci R, Uzzau S, Striano S, de Falco FA, Striano P, Nobile C. LGI1 microdeletion in autosomaldominantlateraltemporalepilepsy. Neurology. 2012;78:1299-303. PubMed PMID: 22496201.

Fertig E, Lincoln A, Martinuzzi A, Mattson RH, Hisama FM. Novel LGI1 mutation in a family with autosomal dominant partial epilepsy with auditory features. Neurology. 2003;60:1687-90. PubMed PMID: 12771268.

Flex E, Pizzuti A, Di Bonaventura C, Douzgou S, Egeo G, Fattouch J, Manfredi M, Dallapiccola B, Giallonardo AT. LGI1 gene mutation screening in sporadic partial epilepsy with auditory features. J Neurol. 2005;252:62-6. PubMed PMID: 15654555.

Furia A, Licchetta L, Muccioli L, Ferri L, Mostacci B, Mazzoni S, Menghi V, Minardi R, Tinuper P, Bisulli F. Epilepsy with auditory features: from etiology to treatment. Front Neurol. 2022;12:807939. PubMed PMID: 35153984.

Hedera P, Abou-Khalil B, Crunk AE, Taylor KA, Haines JL, Sutcliffe JS. Autosomal dominant lateral temporal epilepsy: two families with novel mutations in the LGI1 gene. Epilepsia. 2004;45:218-22. PubMed PMID: 15009222.

Heiman GA, Kamberakis K, Gill R, Kalachikov S, Pedley TA, Hauser WA, Ottman R. Evaluation of depression risk in LGI1 mutation carriers. Epilepsia. 2010; 51:1685-90. PubMed PMID: 20659151.

Ho YY, Ionita-Laza I, Ottman R. Domain-dependent clustering and genotype-phenotype analysis of LGI1 mutations in ADPEAF. Neurology. 2012;78:563-8. PubMed PMID: 22323750.

Hong SE, Shugart YY, Huang DT, Shahwan SA, Grant PE, Hourihane JO, Martin ND, Walsh CA. Autosomal recessive lissencephaly with cerebellar hypoplasia is associated with human RELN mutations. Nat Genet. 2000;26:93-6. PubMed PMID: 10973257.

Huang SJ, Amendola LM, Sternen DL. Variation among DNA banking consent forms: points for clinicians to bank on. J Community Genet. 2022;13:389-97. PubMed PMID: 35834113.

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 AH, Pedley TA, Hauser WA, Ottman R, Gilliam TC. Mutations in LGI1 cause autosomal-dominant partial epilepsy with auditory features. Nat Genet. 2002;30:335-41. PubMed PMID: 11810107.

Kanemoto K, Kawasaki J. Familial aphasic episodes: another variant of partial epilepsy with simple inheritance? Epilepsia. 2000;41:1036-8. PubMed PMID: 10961632.

Kawamata J, Ikeda A, Fujita Y, Usui K, Shimohama S, Takahashi R. Mutations in LGI1 gene in Japanese families with autosomal dominant lateral temporal lobe epilepsy: the first report from Asian families. Epilepsia. 2010;51:690-3. PubMed PMID: 19780791.

Kesim YF, Uzun GA, Yucesan E, Tuncer FN, Ozdemir O, Bebek N, Ozbek U, Iseri SA, Baykan B. Screening LGI1 in a cohort of 26 lateral temporal lobe epilepsy patients with auditory aura from Turkey detects a novel de novo mutation. Epilepsy Res. 2016;120:73-8. PubMed PMID: 26773249.

Kobayashi E, Santos NF, Torres FR, Secolin R, Sardinha LA, Lopez-Cendes I, Cendes F. Magnetic resonance imaging abnormalities in familial temporal lobe epilepsy with auditory auras. Arch Neurol. 2003;60:1546–51. PubMed PMID: 14623726.

Lovero KL, Fukata Y, Granger AJ, Fukata M, Nicoll RA. The LGI1-ADAM22 protein complex directs synapse maturation through regulation of PSD-95 function. Proc Natl Acad Sci U S A. 2015;112:E4129-37. PubMed PMID: 26178195.

Magini P, Bisulli F, Baldassari S, Stipa C, Naldi I, Licchetta L, Menghi V, Tinuper P, Seri M, Pippucci T. LGI1 microdeletions are not a frequent cause of partial epilepsy with auditory features (PEAF). Epilepsy Res. 2014;108:972-7. PubMed PMID: 24721199.

Manna I, Mumoli L, Labate A, Citrigno L, Ferlazzo E, Aguglia U, Quattrone A, Gambardella A. Autosomal dominant lateral temporal epilepsy (ADLTE): absence of chromosomal rearrangements in LGI1 gene. Epilepsy Res 2014;108:597-9. PubMed PMID: 24315022.

Martinez-Granero F, Blanco-Kelly F, Sanchez-Jimeno C, Avila-Fernandez A, Arteche A, Bustamante-Aragones A, Rodilla C, Rodríguez-Pinilla E, Riveiro-Alvarez R, Tahsin-Swafiri S, Trujillo-Tiebas MJ, Ayuso C, Rodríguez de Alba M, Lorda-Sanchez I, Almoguera B. Comparison of the diagnostic yield of aCGH and genome-wide sequencing across different neurodevelopmental disorders. NPJ Genom Med. 2021;6:25. PubMed PMID: 33767182.

Michelucci R, Dazzo E, Volpi L, Pasini E, Riguzzi P, Minardi R, Marliani AF, Tappatà M, Bisulli F, Tassinari CA, Nobile C. Autosomal dominant lateral temporal lobe epilepsy associated with a novel reelin mutation. Epileptic Disord. 2020;22:443-8. PubMed PMID: 32723706.

Michelucci R, Gardella E, de Haan GJ, Bisulli F, Zaniboni A, Cantalupo G, Alberto Tassinari C, Tinuper P, Nobile C, Nichelli P, Kasteleijn-NolstTrenité DG. Telephone-induced seizures: a new type of reflex epilepsy. Epilepsia. 2004;45:280-3. PubMed PMID: 15009231.

Michelucci R, Mecarelli O, Bovo G, Bisulli F, Testoni S, Striano P, Striano S, Tinuper P, Nobile C. A de novo LGI1 mutation causing idiopathic partial epilepsy with telephone-induced seizures. Neurology. 2007;68:2150-1. PubMed PMID: 17562837.

Michelucci R, Pasini E, Malacrida S, Striano P, Bonaventura CD, Pulitano P, Bisulli F, Egeo G, Santulli L, Sofia V, Gambardella A, Elia M, de Falco A, Neve A, Banfi P, Coppola G, Avoni P, Binelli S, Boniver C, Pisano T, Marchini M, Dazzo E, Fanciulli M, Bartolini Y, Riguzzi P, Volpi L, de Falco FA, Giallonardo AT, Mecarelli O, Striano S, Tinuper P, Nobile C. Low penetrance of autosomal dominant lateral temporal epilepsy in Italian families without LGI1 mutations. Epilepsia. 2013;54:1288-97. PubMed PMID: 23621105.

Michelucci R, Pasini E, Nobile C. Lateral temporal lobe epilepsies: clinical and genetic features. Epilepsia. 2009;50 Suppl 5 :52-4. PubMed PMID: 19469848.

Michelucci R, Poza JJ, Sofia V, de Feo MR, 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 VF, Stephani U, Tassinari CA, Moschonas NK, Siebert R, Lopez de Munain A, Perez-Tur J, Nobile C. Autosomal dominant lateral temporal epilepsy: clinical spectrum, new epitempin mutations, and genetic heterogeneity in seven European families. Epilepsia. 2003;44:1289-97. PubMed PMID: 14510822.

Michelucci R, Pulitano P, Di Bonaventura C, Binelli S, Luisi C, Pasini E, Striano S, Striano P, Coppola G, La Neve A, Giallonardo AT, Mecarelli O, Serioli E, Dazzo E, Fanciulli M, Nobile C. The clinical phenotype of autosomaldominant lateral temporal lobe epilepsy related to reelin mutations. Epilepsy Behav. 2017;68:103-7. PubMed PMID: 28142128.

Monlong J, Girard SL, Meloche C, Cadieux-Dion M, Andrade DM, Lafreniere RG, Gravel M, Spiegelman D, Dionne-Laporte A, Boelman C, Hamdan FF, Michaud JL, Rouleau G, Minassian BA, Bourque G, Cossette P. Global characterization of copy number variants in epilepsy patients from whole genome sequencing. PLoS Genet. 2018;14:e1007285. PubMed PMID: 29649218.

Ottman R, Risch N, Hauser WA, Pedley TA, Lee JH, Barker-Cummings C, Lustenberger A, Nagle KJ, Lee KS, Scheuer ML, Neystat M, Susser M, Wilhelmsen K. Localization of a gene for partial epilepsy to chromosome 10q. Nat Genet. 1995;10:56-60. PubMed PMID: 7647791.

Ottman R, Rosenberger L, Bagic A, Kamberakis K, Ritzl EK, Wohlschlager AM, Shamim S, Sato S, Liew C, Gaillard WD, Wiggs E, Berl MM, Reeves-Tyer P, Baker EH, Butman JA, Theodore WH. Altered language processing in autosomal dominant partial epilepsy with auditory features. Neurology. 2008;71:1973-80. PubMed PMID: 19064878.

Ottman R, Winawer MR, Kalachikov S, Barker-Cummings C, Gilliam TC, Pedley TA, Hauser WA. LGI1 mutations in autosomal dominant partial epilepsy with auditory features. Neurology. 2004;62:1120-6. PubMed PMID: 15079011.

Pisano T, Marini C, Brovedani P, Brizzolara D, Pruna D, Mei D, Moro F, Cianchetti C, Guerrini R. Abnormal phonologic processing in familial lateral temporal lobe epilepsy due to a new LGI1 mutation. Epilepsia. 2005;46:118-23. PubMed PMID: 15660777.

Pizzuti A, Flex E, Di Bonaventura C, Dottorini T, Egeo G, Manfredi M, Dallapiccola B, Giallonardo AT. Epilepsy with auditory features: a LGI1 gene mutation suggests a loss-of-function mechanism. Ann Neurol. 2003;53:396-9. PubMed PMID: 12601709.

Poza JJ, Sáenz A, Martínez-Gil A, Cheron N, Cobo AM, Urtasun M, Martí-Massó JF, Grid D, Beckmann JS, Prud'homme JF, López de Munain A. Autosomal dominant lateral temporal epilepsy: clinical and genetic study of a large Basque pedigree linked to chromosome 10q. Ann Neurol. 1999;45:182-8. PubMed PMID: 9989620.

Rahbari R, Wuster A, Lindsay SJ, Hardwick RJ, Alexandrov LB, Turki SA, Dominiczak A, Morris A, Porteous D, Smith B, Stratton MR, Hurles ME, et al. Timing, rates and spectra of human germline mutation. Nat Genet. 2016;48:126-33. PubMed PMID: 26656846.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405-24. PubMed PMID: 25741868.

Riney K, Bogacz A, Somerville E, Hirsch E, Nabbout R, Scheffer IE, Zuberi SM, Alsaadi T, Jain S, French J, Specchio N, Trinka E, Wiebe S, Auvin S, Cabral-Lim L, Naidoo A, Perucca E, Moshé SL, Wirrell EC, Tinuper P. International League Against Epilepsy classification and definition of epilepsy syndromes with onset at a variable age: position statement by the ILAE Task Force on Nosology and Definitions. Epilepsia. 2022;63:1443-74. PubMed PMID: 35503725.

Rosanoff MJ, Ottman R. Penetrance of LGI1 mutations in autosomal dominant partial epilepsy with auditory features. Neurology. 2008;71:567-71. PubMed PMID: 18711109.

Sarma AK, Khandker N, Kurczewski L, Brophy GM. Medical management of epileptic seizures: challenges and solutions. Neuropsychiatr Dis Treat. 2016;12:467-85 PubMed PMID: 26966367.

Scheffer IE, Phillips HA, O'Brien CE, Saling MM, Wrennall JA, Wallace RH, Mulley JC, Berkovic SF. Familial partial epilepsy with variable foci: a new partial epilepsy syndrome with suggestion of linkage to chromosome 2. Ann Neurol. 1998;44:890-9. PubMed PMID: 9851433.

Sirerol-Piquer MS, Ayerdi-Izquierdo A, Morante-Redolat JM, Herranz-Pérez V, Favell K, Barker PA, Pérez-Tur J. The epilepsy gene LGI1 encodes a secreted glycoprotein that binds to the cell surface. Hum Mol Genet. 2006;15:3436-45. PubMed PMID: 17067999.

Smalheiser NR, Costa E, Guidotti A, Impagnatiello F, Auta J, Lacor P, Kriho V, Pappas GD. Expression of reelin in adult mammalian blood, liver, pituitary pars intermedia, and adrenal chromaffin cells. Proc Natl Acad Sci U S A. 2000;97:1281-6. PubMed PMID: 10655522.

Tessa C, Michelucci R, Nobile C, Giannelli M, Della Nave R, Testoni S, Bianucci D, Tinuper P, Bisulli F, Sofia V, De Feo MR, Giallonardo AT, Tassinari CA, Mascalchi M. Structural anomaly of left lateral temporal lobe in epilepsy due to mutated LGI1. Neurology. 2007;69:1298-300. PubMed PMID: 17875918.

Truty R, Patil N, Sankar R, Sullivan J, Millichap J, Carvill G, Entezam A, Esplin ED, Fuller A, Hogue M, Johnson B, Khouzam A, Kobayashi Y, Lewis R, Nykamp K, Riethmaier D, Westbrook J, Zeman M, Nussbaum RL, Aradhya S. Possible precision medicine implications from genetic testing using combined detection of sequence and intragenic copy number variants in a large cohort with childhood epilepsy. Epilepsia Open. 2019;4:397-408. PubMed PMID: 31440721.

Usui K, Ikeda A, Nagamine T, Matsubayashi J, Matsumoto R, Hiraumi H, Kawamata J, Matsuhashi M, Takahashi R, Fukuyama H. Abnormal auditory cortex with giant N100m signal in patients with autosomal dominant lateral temporal lobe epilepsy. Clin Neurophysiol. 2009;120:1923-6. PubMed PMID: 19793676.

Vanoni MA. Structure-function studies of MICAL, the unusual multidomain flavoenzyme involved in actin cytoskeleton dynamics. Arch Biochem Biophys. 2017;632:118-41. PubMed PMID: 28602956.

Ventruti A, Kazdoba TM, Niu S, D'Arcangelo G. Reelin deficiency causes specific defects in the molecular composition of the synapses in the adult brain. Neuroscience. 2011;189:32-42. PubMed PMID: 21664258.

Wang Y, Ottman R, Rabinowitz D. A method for estimating penetrance from families sampled for linkage analysis. Biometrics. 2006;62:1081-8. PubMed PMID: 17156282.

Wei Z, Ye X, Wang C, Xu J, Zhang P, Liu Q, Zhao J. Case report: stereoelectroencephalography and stereoelectroencephalography-guided radiofrequency thermocoagulation in familial lateral temporal lobe epilepsy. Front Neurol. 2022;13:864070. PubMed PMID: 35444610.

Winawer MR, Martinelli Boneschi F, Barker-Cummings C, Lee JH, Liu J, Mekios C, Gilliam TC, Pedley TA, Hauser WA, Ottman R. Four new families with autosomal dominant partial epilepsy with auditory features: clinical description and linkage to chromosome 10q24. Epilepsia. 2002;43:60-7. PubMed PMID: 11879388.

Winawer MR, Ottman R, Hauser WA, Pedley TA. Autosomal dominant partial epilepsy with auditory features: defining the phenotype. Neurology. 2000;54:2173-6. PubMed PMID: 10851389.

Xiong L, Labuda M, Li DS, Hudson TJ, Desbiens R, Patry G, Verret S, Langevin P, Mercho S, Seni MH, Scheffer I, Dubeau F, Berkovic SF, Andermann F, Andermann E, Pandolfo M. Mapping of a gene determining familial partial epilepsy with variable foci to chromosome 22q11-q12. Am J Hum Genet. 1999;65:1698-710. PubMed PMID: 10577924.

License