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DEPDC5-Related Epilepsy

Stéphanie Baulac, PhD[1] and Sara Baldassari, PhD[1]

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Summary

Clinical characteristics

DEPDC5-related epilepsy encompasses a range of epilepsy syndromes, almost all of which are characterized by focal seizures, with seizure onset in a discrete area of the brain. While most individuals with *DEPDC5*-related epilepsy have a normal brain MRI, some have epilepsy associated with a cortical malformation, usually focal cortical dysplasia or hemimegalencephaly. Seizure syndromes include familial focal epilepsy with variable foci (FFEVF), autosomal dominant sleep-related hypermotor epilepsy (ADSHE), familial mesial temporal lobe epilepsies (FMTLE), autosomal dominant epilepsy with auditory features (ADEAF), infantile spasms, and severe developmental encephalopathy. Although psychomotor development is usually normal, developmental delays, intellectual disability, or autism spectrum disorder have been reported in some individuals.

Diagnosis/testing

The diagnosis of *DEPDC5*-related epilepsy is established in a proband with suggestive findings and at least one heterozygous pathogenic variant in *DEPDC5* identified by molecular genetic testing. Some affected individuals have biallelic variants in *DEPDC5*, and some have a second mosaic (or postzygotic) *DEPDC5* variant within the brain.

Management

Treatment of manifestations: The response to anti-seizure medication (ASM) is variable. While some individuals respond well to first-line ASMs, others are more refractory to treatment. There is currently no evidence that seizures respond better to one specific ASM. In individuals with hemimegalencephaly or focal cortical dysplasia and refractory epilepsy, resective epilepsy surgery should be explored early in the disease course. Standard treatment for developmental delay / intellectual disability and autism spectrum disorders.

Surveillance: Assess for new or ongoing neurologic manifestations (such as new-onset seizures or changes in seizure symptoms), predictive factors for sudden unexpected death in epilepsy, and developmental progress at each visit. Repeat EEG as appropriate when seizure frequency increases or when seizures of new

Author Affiliation: 1 Institut du Cerveau (ICM), Paris Brain Institute, Paris, France; Email: stephanie.baulac@icm-institute.org; Email: sara.baldassari@icm-institute.org.

symptomatology occur. Repeat brain MRI with a higher-resolution technique in individuals with treatment-resistant seizures whose first brain MRI was normal to rule out subtle cortical dysplasia.

Evaluation of relatives at risk: It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify those who are at risk for developing seizures as early as possible. This typically entails targeted molecular genetic testing for the known pathogenic variant(s) in the family.

Pregnancy management: Pregnant women should receive counseling regarding the risks and benefits of using ASM during pregnancy; the advantages and disadvantages of increasing maternal periconceptional folic acid supplementation to 4,000 µg daily; the effects of pregnancy on ASM metabolism; and the effect of pregnancy on maternal seizure control.

Genetic counseling

DEPDC5-related epilepsy is an autosomal dominant disorder; however, affected individuals with germline biallelic missense variants have been rarely reported. All probands reported to date with biallelic *DEPDC5* variants inherited variants from their heterozygous parents. In these families, heterozygous parents may or may not have manifestations of *DEPDC5*-related epilepsy. The risk to the sibs of the proband depends on the genetic status of the proband's parents. If one parent of the proband has a *DEPDC5* pathogenic variant, the risk to the sibs of inheriting the pathogenic variant is 50%. If both parents of a proband have a *DEPDC5* pathogenic variant, sibs have a 75% chance of inheriting one or two pathogenic variants and a 25% chance of inheriting neither pathogenic variant and not being affected. Once the *DEPDC5* pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

GeneReview Scope

***DEPDC5*-Related Epilepsy: Phenotypic Spectrum** [1]

Phenotypes [1]	Disorders
Epilepsy phenotypes	• Familial focal epilepsy with variable foci (FFEVF) • Autosomal dominant sleep-related hypermotor epilepsy (ADSHE) (previously termed autosomal dominant nocturnal frontal lobe epilepsy [ADNFLE]) • Familial mesial temporal lobe epilepsy (FMTLE) • Autosomal dominant epilepsy with auditory features (ADEAF) • Infantile spasms • Developmental encephalopathy with macrocephaly and polymicrogyria
Brain malformation phenotypes	• Focal cortical dysplasia • Hemimegalencephaly

For synonyms and outdated names, see Nomenclature.
1. For other genetic causes of these phenotypes, see Differential Diagnosis.

Diagnosis

No consensus clinical diagnostic criteria for *DEPDC5*-related epilepsy have been published to date.

Suggestive Findings

DEPDC5-related epilepsy **should be suspected** in individuals with the following clinical, neuroimaging, EEG, and family history findings.

Clinical findings

- Epilepsy (familial or sporadic), which may include:

- Focal epilepsy (emerging from any cortical region but predominantly from the frontal lobe), variable epilepsy foci (temporal, parietal), or hypermotor seizures
- Nocturnal or sleep-related seizures
- Drug-resistant epilepsy
- Infantile spasms

- Otherwise normal neurologic examination
- Normal psychomotor development and cognition in most, although developmental delay, intellectual disability, and/or neuropsychiatric features (autism spectrum disorder, attention-deficit/hyperactivity disorder) have been described rarely.
- Sudden unexpected death in epilepsy

Neuroimaging/EEG findings

- Brain MRI may demonstrate focal cortical dysplasia, hemimegalencephaly, or rarely other malformations (polymicrogyria, pachygyria, heterotopia, hypoplasia of corpus callosum)

  Note: A normal brain MRI does not preclude the diagnosis.

- Interictal EEG may show focal (frontal, temporal, parietal, or occipital) epileptiform abnormalities that remain constant over time, typically with a background EEG that is normal.

Family history is typically consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations), although a few affected individuals have biallelic missense variants [Ververi et al 2023]. Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of *DEPDC5*-related epilepsy is established in a proband with suggestive findings and at least one heterozygous pathogenic (or likely pathogenic) variant in *DEPDC5* identified by molecular genetic testing (see Table 1). Some rare affected individuals have biallelic missense variants in *DEPDC5*.

Notes: (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 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 *DEPDC5* variant of uncertain significance does not establish or rule out the diagnosis of the disorder. (3) While most individuals with *DEPDC5*-related epilepsy have only a heterozygous germline (i.e., constitutional) pathogenic variant, some individuals with cortical malformations (most frequently focal cortical dysplasia or hemimegalencephaly) have been reported to have a brain-specific postzygotic (or mosaic) pathogenic variant in *DEPDC5* on the non-mutated allele (i.e., a second pathogenic variant or "second hit") in addition to a heterozygous constitutional pathogenic variant (see Molecular Genetics).

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. As the differential diagnosis for genetic causes of epilepsy and brain malformations is broad, single-gene testing (sequence analysis of *DEPDC5*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

Molecular genetic testing approaches typically include a **multigene panel** or **comprehensive genomic testing** (exome sequencing, genome sequencing).

Note: As some *DEDPC5* pathogenic variants are postzygotic (or mosaic), deep sequencing of surgical resected brain tissue (from epilepsy surgery) could be considered in the diagnostic evaluation of an affected individual if there is a high suspicion for this condition and a surgical brain tissue resection is either planned or a brain tissue sample is available.

- **A multigene panel** that includes genes associated with epilepsy with or without brain malformations (e.g., *AKT3*, *CHRNA2*, *CHRNA4*, *CHRNB2*, *DEPDC5*, *KCNT1*, *MTOR*, *NPRL2*, *NPRL3*, *PIK3CA*, *PTEN*, *RHEB*) may be considered. Notes: (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*; thus, clinicians need to determine which multigene panel 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. (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. (5) As brain-specific mosaic pathogenic variants of *DEPDC5* have been identified in some individuals, the depth of sequencing of a multigene panel and sample type may determine the yield of molecular diagnostic testing using these panels.

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

- **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. If no germline pathogenic variant is found in *DEPDC5*, sequence analysis with methods to detect somatic mosaicism could be considered (see above).

  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 *DEPDC5*-Related Epilepsy

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
DEPDC5	Sequence analysis [3]	~96% [4]
	Gene-targeted deletion/duplication analysis [5]	~4% [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. 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.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020] as well as the following references: Dibbens et al [2013], Ishida et al [2013], Lal et al [2014], Martin et al [2014], Picard et al [2014], Scheffer et al [2014], Baulac et al [2015], Carvill et al [2015], D'Gama et al [2015], Nascimento et al [2015], Pippucci et al [2015], Scerri et al [2015], Striano et al [2015], Bagnall et al [2016], Ricos et al [2016], Weckhuysen et al [2016], Baldassari et al [2019b], Sim et al [2019], Krenn et al [2020], Liu et al [2020], Benova et al [2021], Wang et al [2021], Zhang et al [2021], Arenas-Cabrera et al [2022], Bacq et al [2022], Ververi et al [2023]
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.

Clinical Characteristics

Clinical Description

DEPDC5-related epilepsy encompasses a range of epilepsy syndromes, almost all of which are characterized by focal seizures, with seizure onset in a discrete area of the brain. While about 60% of individuals with *DEPDC5*-related epilepsy have a normal brain MRI [Baldassari et al 2019a], some have epilepsy associated with a cortical

malformation, usually focal cortical dysplasia type II or hemimegalencephaly. Most affected individuals have a family history of focal epilepsy.

To date, nearly 200 symptomatic individuals have been identified with a pathogenic variant in *DEPDC5* [Dibbens et al 2013, Ishida et al 2013, Lal et al 2014, Martin et al 2014, Picard et al 2014, Scheffer et al 2014, Baulac et al 2015, Carvill et al 2015, D'Gama et al 2015, Nascimento et al 2015, Pippucci et al 2015, Scerri et al 2015, Striano et al 2015, Bagnall et al 2016, Ricos et al 2016, Weckhuysen et al 2016, Baldassari et al 2019b, Sim et al 2019, Krenn et al 2020, Liu et al 2020, Benova et al 2021, Wang et al 2021, Zhang et al 2021, Arenas-Cabrera et al 2022, Bacq et al 2022, Ververi et al 2023]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. *DEPDC5*-Related Epilepsy: Frequency of Select Features in Symptomatic Individuals [1]

Feature	Feature Subtype (if applicable)	% of Persons w/ Feature [2]	Comment
Epilepsy & related complications	All types	100% [3]	Most commonly frontal lobe seizures / sleep-related hypermotor epilepsy (30%)
	Infantile spasms	6%	
	SUDEP	10%	
Brain malformations	All types	20%	
	Focal cortical dysplasia	17%	Mostly type II
	Hemimegalencephaly	2%	
	Polymicrogyria	<1%	One person was reported w/ bilateral polymicrogyria. [4]
Developmental/learning issues	Developmental delays (language, motor)	8%	
	Intellectual disability	12%	Most reported persons w/ID have FCD/focal epilepsy or drug-resistant epilepsy.
	Developmental delay	7%	
	Autism spectrum disorder	5%	

FCD = focal cortical dysplasia; SUDEP = sudden unexpected death in epilepsy

1. Asymptomatic heterozygotes are common in families with *DEPDC5*-related epilepsy. Penetrance is therefore reduced and may be as low as 60% [Dibbens et al 2013, Ishida et al 2013].

2. Percentages are based on nearly 200 reported symptomatic individuals with heterozygous pathogenic (or likely pathogenic) variants only and do not include individuals with biallelic pathogenic variants in *DEPDC5*.

3. Most symptomatic individuals are diagnosed because they have epilepsy, so this percentage is biased toward those individuals who have epilepsy as a feature.

4. Ricos et al [2016]

Epilepsy. In general, the age of seizure onset can range from infancy to adulthood. However, not every person with a heterozygous pathogenic variant in *DEPDC5* will develop epilepsy (see Penetrance). A variety of epilepsy phenotypes have been described in affected individuals/families.

- **Familial focal epilepsy with variable foci (FFEVF)** is characterized by focal seizures that arise from different cortical regions of the brain in members of the same family. However, each affected individual in the family has one specific focal seizure type.
  - Average age of seizure onset is 4.5 years, and seizure symptomatology depend on the focal region of the brain in which the seizures originate.

- Frontal lobe and temporal lobe seizures are most common; parietal and occipital lobe seizures are also seen.
- Age of onset, seizure frequency, and drug response may vary considerably within a family.
- EEGs may show focal interictal abnormalities that typically stay constant in a given individual.

- **Autosomal dominant sleep-related hypermotor epilepsy (ADSHE)** is characterized by clusters of nocturnal motor seizures, which are often stereotyped and brief (lasting from a few seconds to a few minutes). They vary from simple arousals from sleep to dramatic, often bizarre, hyperkinetic events with tonic or dystonic features. Affected individuals may experience an aura. Retained awareness during seizures is common. A minority of individuals experience daytime seizures.
  - About 80% of individuals develop ADSHE within the first two decades of life, with a mean age of onset of about 5 years.
  - Clinical neurologic examination is usually normal and intellect preserved, but intellectual disability, cognitive deficits, or psychiatric comorbidity may occur.
  - Within a family, the manifestations of the disorder may vary considerably; however, seizures have a consistent onset within the frontal region.
  - ADSHE is lifelong but not progressive. As an individual reaches middle age, seizures may become milder and less frequent.

- **Familial temporal lobe epilepsy** has rarely been described [Ishida et al 2013, Krenn et al 2020] and includes two subtypes.

  - Familial mesial temporal lobe epilepsy (FMTLE) is characterized by focal seizures with ictal mesial temporal lobe symptomatology, including psychic symptoms such as déjà vu and fear or autonomic symptoms such as nausea. Hippocampal sclerosis is commonly observed, as are febrile seizures preceding focal seizures.

  - Autosomal dominant epilepsy with auditory features (ADEAF) is characterized by focal seizures with auditory auras and symptoms suggesting lateral temporal onset. It is considered a mild syndrome, with onset in adolescence or adulthood, low seizure frequency, and only rare secondarily generalized seizures.

    It is unclear if ADEAF is part of *DEPDC5*-related epilepsy. While a heterozygous *DEPDC5* pathogenic variant can be found in individuals with seizures with auditory features, to date heterozygous *DEPDC5* pathogenic variants have not been identified in larger families with the classic ADEAF phenotype [Bisulli et al 2016].

- **Infantile spasms** have been reported as the initial seizure type in 10 unrelated individuals with *DEPDC5* pathogenic variants [Carvill et al 2015, Tsang et al 2018, Baldassari et al 2019a, Lee et al 2019, Sim et al 2019], all but one of whom had some degree of developmental delay [Carvill et al 2015].
  - Focal seizures occurred later in most affected individuals; four had focal cortical dysplasia.
  - In individuals with infantile spasms, hypsarrhythmia can be seen.

- **Sudden unexpected death in epilepsy (SUDEP)** has been described in about 10% of families with pathogenic germline heterozygous *DEPDC5* variants in one study and has been reported in several individuals with *DEPDC5*-related epilepsy in case reports or small case series [Nascimento et al 2015, Bagnall et al 2016, Baldassari et al 2019a]. SUDEP may occur in heterozygous individuals without cognitive or developmental issue and without exposure to polytherapy. Therefore, affected individuals should be monitored regularly for known predictive factors of SUDEP, such as frequency of generalized tonic-clonic seizures (see Management) [Bacq et al 2022, Samanta 2022]. Further evidence from larger studies is needed to confirm to what extent individuals with *DEPDC5*-related epilepsy have an increased risk for SUDEP.

Neurodevelopment and behavior is usually normal, although a minority of affected individuals have been reported to have intellectual disability (ID) or autism spectrum disorder [Dibbens et al 2013, Ricos et al 2016, Baldassari et al 2019a], particularly if they have a history of infantile spasms or brain malformations. Individuals with ID who do not have infantile spasms typically have mild ID, while those with a history of infantile spasms have severe-to-profound ID.

Neuroimaging/histopathology. Brain MRI is normal in most individuals; however, about 20% of individuals have a cortical malformation detected on MRI and/or histopathologic examination [Scheffer et al 2014, Baulac et al 2015, D'Gama et al 2015, Mirzaa et al 2016, Ricos et al 2016, Weckhuysen et al 2016, Baldassari et al 2019a].

- Most reported individuals had focal cortical dysplasia type IIa (characterized by cortical dyslamination frequently associated with the presence of dysmorphic neurons) associated with early-onset drug-resistant seizures.
- Hemimegalencephaly (characterized typically by enlargement and dysplasia of one cerebral hemisphere) has been reported in several affected individuals.
- Other reported findings seen in a few individuals include the following:
  - Bilateral symmetric perisylvian polymicrogyria
  - Pachygyria
  - Subtle band heterotopia
  - Hypoplasia of the corpus callosum in addition to focal cortical dysplasia

Biallelic pathogenic variants in *DEPDC5*. A more severe phenotype has been described in nine individuals with biallelic constitutional (non-mosaic) missense variants in *DEPDC5* [Ververi et al 2023]. The phenotype consisted of progressive developmental encephalopathy, early-onset refractory epilepsy with multifocal seizures, bilateral polymicrogyria, and congenital macrocephaly. The presence of multisystemic features involving eye and cardiac defects has also been reported in these individuals.

Genotype-Phenotype Correlations

No definitive genotype-phenotype correlations have been identified.

- In general, individuals with a heterozygous nonsense or frameshift pathogenic variant leading to a premature stop codon are more likely to have brain malformations (focal cortical dysplasia or hemimegalencephaly) [Scheffer et al 2014, Baulac et al 2015, D'Gama et al 2015, Scerri et al 2015, Ricos et al 2016, Weckhuysen et al 2016, Baldassari et al 2019b, Sim et al 2019].
- Individuals with germline biallelic pathogenic variants and a severe multisystemic phenotype are very rare (only a few individuals have been reported), and therefore no definite genotype-phenotype associations can be defined (see Clinical Description).

Penetrance

Asymptomatic heterozygotes are common in families with *DEPDC5*-related epilepsy. Penetrance is therefore reduced and may be as low as 60% [Dibbens et al 2013, Ishida et al 2013].

Nomenclature

Familial focal epilepsy with variable foci (FFEVF) [Dibbens et al 2013, Ishida et al 2013] was previously referred to as familial partial epilepsy with variable foci.

Prevalence

The prevalence of *DEPDC5*-related epilepsy is unknown. Nearly 200 unrelated probands with *DEPDC5*-related epilepsy have been reported to date.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *DEPDC5*.

Differential Diagnosis

The differential diagnosis for *DEPDC5*-related epilepsy includes other focal epilepsy syndromes as well as other genetic causes of (familial) focal epilepsy and focal cortical dysplasia (see Table 3). Of note, *DEPDC5* is the most frequently involved gene among genetic focal epilepsies.

Table 3. Genes of Interest in the Differential Diagnosis of *DEPDC5*-Related Epilepsy

Gene(s)	Disorder	MOI	Clinical Features of Differential Diagnosis Disorder	
			Overlapping w/*DEPDC5*-related epilepsy	Distinguishing from *DEPDC5*-related epilepsy
CHRNA2 *CHRNA4* *CHRNB2* *CRH*	*CHRNA2*-, *CHRNA4*, *CHRNB2*-, & *CRH*-related ADSHE	AD	Frontal lobe seizures [1]	Frontal lobe seizures in *DEPDC5*-related ADSHE occur more frequently during wakefulness & less frequently in clusters; no cortical malformations in *CHRNA2*-, *CHRNA4*, *CHRNB2*-, & *CRH*-related ADSHE to date. [2]
KCNT1	*KCNT1*-related epilepsy	AD	EIMFS & ADSHE	Persons w/*KCNT1*-related ADSHE are more likely to develop seizures at a younger age, have cognitive comorbidity, & display psychiatric & behavioral issues than those w/ADSHE from other causes.
LGI1 *RELN*	*LGI1*- & *RELN*-related ADEAF [3]	AD	Focal epilepsy syndrome in which auditory symptoms &/or receptive aphasia are prominent ictal manifestations. Affected persons have focal seizures ± altered consciousness; most typical features are auras consisting of humming or buzzing, or more complex auditory hallucinations. Most affected persons also have secondarily generalized seizures, but these are rare.	ADEAF is more commonly assoc w/ pathogenic variants in *LGI1* & *RELN* than w/pathogenic variants in *DEPDC5*.
NPRL2 *NPRL3* [4]	*NPRL2*- & *NPRL3*-related focal epilepsy (OMIM 617116 & 617118)	AD	Familial focal epilepsies incl families w/ADSHE or FFEVF, of which some family members can have FCD type II [5]	*NPRL2*- & *NPRL3*-related epilepsies are similar to *DEPDC5*-related epilepsies. *DEPDC5* & *NPRL2/3* are part of the same complex, GATOR1, [4] a repressor of the amino acid-sensing branch of the mTOR pathway. To date, 35 persons have been reported w/*NPRL2* or *NPRL3* pathogenic variants.

Table 3. continued from previous page.

Gene(s)	Disorder	MOI	Clinical Features of Differential Diagnosis Disorder	
			Overlapping w/*DEPDC5*-related epilepsy	Distinguishing from *DEPDC5*-related epilepsy
MTOR	FCD (OMIM 607341) & Smith-Kingsmore syndrome (OMIM 616638)	AD or somatic	Focal epilepsy, FCD type II, hemimegalencephaly, polymicrogyria	Hyperpigmented macules, macrocephaly. Germline pathogenic *MTOR* variants cause Smith-Kingsmore syndrome. Persons w/germline *MTOR* pathogenic variants typically represent simplex cases (i.e., only affected family member). Somatic *MTOR* variants cause hemimegalencephaly & FCD.
AKT3	FCD, hemimegalencephaly, & *AKT3*-related megalencephaly-polydactyly-polymicrogyria-hydrocephalus syndrome [6]	AD or somatic	Focal epilepsy, FCD type II, hemimegalencephaly, polymicrogyria	Macrocephaly, vascular malformations. Persons w/*AKT3* pathogenic variants typically represent simplex cases (i.e., only affected family member).
PIK3CA	*PIK3CA*-related overgrowth spectrum	Somatic	Focal epilepsy, FCD type II, hemimegalencephaly, polymicrogyria	Macrocephaly, somatic overgrowth, polydactyly, syndactyly, vascular/lymphatic malformations
RHEB	FCD & hemimegalencephaly [7]	Somatic	Focal epilepsy, FCD type II, hemimegalencephaly	Somatic mutations
PIK3C2B	Focal epilepsy [8]	AD	Focal epilepsy	To date, all persons w/*PIK3C2B* pathogenic variants have represented simplex cases (i.e., only affected family member).
PTEN [9]	Megalencephaly, hemimegalencephaly	Somatic	Focal epilepsy, FCD type II, hemimegalencephaly	Macrocephaly, overgrowth, hamartomas, familial cancer

AD = autosomal dominant; ADEAF = autosomal dominant epilepsy with auditory features; ADSHE = autosomal dominant sleep-related epilepsy; AR = autosomal recessive; EIMFS = epilepsy of infancy with migrating focal seizures; FCD = focal cortical dysplasia; FFEVF = familial focal epilepsy with variable foci; MOI = mode of inheritance

1. Picard et al [2014]
2. Scheffer et al [2014], Baulac et al [2015], Baldassari et al [2019a]
3. Previously referred to as autosomal dominant partial epilepsy with auditory features (ADPEAF) or autosomal dominant lateral temporal lobe epilepsy (ADTLE) [Bisulli et al 2021]
4. NPRL2 and NPRL3, together with DEPDC5, form a complex called GATOR1 (*G*AP *a*ctivity *to*wards *R*ags) complex.
5. Korenke et al [2016], Ricos et al [2016], Sim et al [2016], Weckhuysen et al [2016]
6. Poduri et al [2012]
7. Baldassari et al [2019b], Lee et al [2021]
8. Gozzelino et al [2022]
9. Macken et al [2019]

Management

No clinical practice guidelines for *DEPDC5*-related epilepsy have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *DEPDC5*-related epilepsy, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with *DEPDC5*-Related Epilepsy

System/Concern	Evaluation	Comment
Neurologic	Assessment by neurologist for eval of suspected seizures, as indicated	To incl EEG & high-resolution brain MRI to evaluate for focal cortical dysplasia or other brain malformations
	Assessment for predictive factors for SUDEP [1]	
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Genetic counseling	By genetics professionals [2]	To inform affected persons & their families re nature, MOI, & implications of *DEPDC5*-related disorders to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support.	

MOI = mode of inheritance; SUDEP = sudden unexpected death in epilepsy
1. Predictive factors may include frequent generalized clonic-tonic seizures.
2. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no specific cure for *DEPDC5*-related epilepsy.

Supportive care to improve quality of life, maximize function, and reduce complications is recommended (see Table 5).

Table 5. Treatment of Manifestations in Individuals with *DEPDC5*-Related Epilepsy

Manifestation/Concern	Treatment	Considerations/Other
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [1]
Brain malformations	Resective epilepsy surgery may be considered in persons w/focal epilepsy that is refractory to medical therapy.	• In those w/FCD or hemimegalencephaly, epilepsy surgery should be explored early in disease course. • Surgical outcomes have been variable. [2]
Developmental delay / Intellectual disability	Standard treatment, which may incl supportive developmental therapies (OT, PT, ST) to address specific delayed areas	Consultation w/neurodevelopmental specialist may be considered.
Autism spectrum disorder	Standard treatment, which may incl ABA therapy	

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Family/Community	Ensure appropriate social work involvement to connect families w/local resources & support.	

ABA = applied behavior analysis; ASM = anti-seizure medication; FCD = focal cortical dysplasia; OT = occupational therapy; PT = physical therapy; ST = speech therapy
1. 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.
2. In one study, four of five unrelated individuals who underwent epilepsy surgery with resection of the focal cortical dysplasia had a favorable postoperative outcome [Baulac et al 2015]. In contrast, another study reported a poor surgical outcome in four individuals [Benova et al 2021].

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. Recommended Surveillance for Individuals with *DEPDC5*-Related Epilepsy

System/Concern	Evaluation	Frequency/Indication
Neurologic	Assess for new or ongoing manifestations, such as new-onset seizures &/or changes in seizures or tone.	At each visit
	Assess for predictive factors for SUDEP. [1]	
	Repeat brain MRI (incl higher-resolution brain MRI).	For those w/treatment-resistant seizures whose first brain MRI was normal
	Repeat EEG.	To address any ↑ in seizure frequency or new seizure symptomatology
Development	Monitor developmental progress.	At each visit
Family/Community	Assess family need for social work support, care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	

SUDEP = sudden unexpected death in epilepsy
1. Predictive factors may include frequent generalized clonic-tonic seizures.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify those who are at risk for the development of seizures as early as possible. This typically entails targeted molecular genetic testing for the known pathogenic variant(s) in the family.

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 medications (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, 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

Loss-of-function pathogenic variants in *DEPDC5* lead to hyperactivation of the mTORC1 pathway (see Molecular Genetics). Therefore, mTORC1 inhibitors including rapamycin (or everolimus) have been proposed as a potential targeted treatment option. Animal model studies, notably *Depdc5* knockout rodent models, have shown that mTOR inhibitors reduce the frequency of seizures [Marsan et al 2016, Ribierre et al 2018, Yuskaitis et al 2019]. So far, the clinical use of mTORC1 inhibitors has only been studied in the more severe mTORopathy tuberous sclerosis complex [Wiegand et al 2021], and in focal cortical dysplasia type II [Kato et al 2022] with mitigated results. Further studies are needed to determine whether (subsets of) individuals with *DEPDC5* could benefit from treatment with this class of drugs.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

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

DEPDC5-related epilepsy is typically inherited in an autosomal dominant manner. In rare cases autosomal recessive inheritance of missense variants has been reported in association with a severe multisystemic phenotype (five families, including three consanguineous families) [Ververi et al 2023].

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- Many individuals diagnosed with *DEPDC5*-related epilepsy inherited a pathogenic variant from a heterozygous parent [Dibbens et al 2013, Ishida et al 2013, Baldassari et al 2019a]. Because asymptomatic heterozygotes are common in families with *DEPDC5*-related epilepsy, a heterozygous parent may or may not have manifestations of *DEPDC5*-related epilepsy.
- A proband with *DEPDC5*-related epilepsy may have the disorder as the result of a *de novo* pathogenic variant. The overall proportion of individuals with *DEPDC5*-related epilepsy caused by a *de novo* pathogenic variant is unknown [Dibbens et al 2013, Carvill et al 2015, Mirzaa et al 2016, Ricos et al 2016, Baldassari et al 2019a, Liu et al 2020].
- Some individuals with *DEPDC5*-related epilepsy and cortical malformations have a germline (i.e., constitutional) pathogenic variant and a second *DEPDC5* pathogenic variant that is mosaic and only present in brain tissue (i.e., a second mutational event).
- If the proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing for the constitutional pathogenic variant identified in the proband is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.

- If the constitutional 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 gonosomal mosaicism [Baulac et al 2015]. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.
- The family history of some individuals diagnosed with *DEPDC5*-related epilepsy may appear to be negative because of a milder phenotype, reduced penetrance, or late onset of the disorder in heterozygous family members. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the *DEPDC5* pathogenic variant identified in the proband.

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

- If a parent of the proband is affected and/or is known to have the *DEPDC5* pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%.
- Reduced penetrance and intrafamilial variable expressivity are observed in *DEPDC5*-related epilepsy. Sibs who inherit a pathogenic variant:
  - May or may not have manifestations of *DEPDC5*-related epilepsy – asymptomatic heterozygotes are common in families with *DEPDC5*-related epilepsy, and penetrance may be as low as 60% (see Penetrance);
  - May have different phenotypic manifestations of *DEPDC5*-related epilepsy than other affected family members – the age of seizure onset, seizure type, seizure severity, drug response, and presence of cortical malformations can vary between affected family members (see Genotype-Phenotype Correlations).
- If the *DEPDC5* pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism. Parental gonosomal mosaicism has been reported in one family [Baulac et al 2015].
- If the parents have not been tested for the *DEPDC5* pathogenic variant but are clinically unaffected, sibs are still presumed to be at increased risk for *DEPDC5*-related epilepsy because of the possibility of reduced penetrance in a heterozygous parent or parental germline mosaicism.

Offspring of a proband

- Each child of an individual with autosomal dominant *DEPDC5*-related epilepsy is at a 50% risk of inheriting the constitutional *DEPDC5* pathogenic variant.
- The specific phenotype, age of onset, and disease severity cannot be predicted accurately in offspring who inherit a *DEPDC5* pathogenic variant because of reduced penetrance and variable expressivity.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *DEPDC5* pathogenic variant, the parent's family members may be at risk.

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for a *DEPDC5* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *DEPDC5* pathogenic variant and to allow reliable recurrence risk assessment.

- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder. Heterozygous parents of a proband with autosomal recessive *DEPDC5*-related epilepsy may be at risk of developing epilepsy based on one report [Ververi et al 2023].

Sibs of a proband. If both parents are known to be heterozygous for a *DEPDC5* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.

Offspring of a proband. To date, it is unknown whether individuals with autosomal recessive severe *DEPDC5*-related epilepsy are able to reproduce.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *DEPDC5* pathogenic variant.

Carrier detection. Carrier testing for at-risk relatives requires prior identification of the *DEPDC5* pathogenic variants in the family.

Related Genetic Counseling Issues

Predictive testing for autosomal dominant *DEPDC5*-related epilepsy. Predictive testing for at-risk asymptomatic adult family members requires prior identification of the *DEPDC5* pathogenic variant in the family.

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.

Prenatal Testing and Preimplantation Genetic Testing

Once the *DEPDC5* pathogenic variant(s) have been identified in an affected family member, prenatal testing for a pregnancy at increased risk for *DEPDC5*-related epilepsy and preimplantation genetic testing are possible. Note, however, that the specific phenotype, age of onset, and disease severity cannot be accurately predicted on the basis of molecular genetic testing results.

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
- **Epilepsy Foundation**
  Phone: 301-459-3700
  Fax: 301-577-2684
  www.epilepsy.com
- **National Institute of Neurological Disorders and Stroke (NINDS)**
  Phone: 800-352-9424 (toll-free); 301-496-5751; 301-468-5981 (TTY)
  Epilepsy Information Page

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. DEPDC5-Related Epilepsy: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
DEPDC5	22q12.2-q12.3	GATOR1 complex protein DEPDC5	DEPDC5	DEPDC5

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 DEPDC5-Related Epilepsy (View All in OMIM)

604364	EPILEPSY, FAMILIAL FOCAL, WITH VARIABLE FOCI 1; FFEVF1
614191	DEP DOMAIN-CONTAINING PROTEIN 5; DEPDC5

Molecular Pathogenesis

DEPDC5 encodes a ubiquitously expressed protein of 1,603 amino acids, GATOR complex protein DEPDC5 (DEPDC5). The 3D structure was recently resolved and identified five domains (NTD, SABA, SHEN, DEP, and CTD) [Shen et al 2018]. DEPDC5 acts as a GTPase-activating protein for RagA/B and, together with NPRL2 and NPRL3, is part of the GATOR1 complex that inhibits the mechanistic target of the rapamycin complex 1 (mTORC1) pathway in response to low amino acid cellular levels [Bar-Peled et al 2013, Panchaud et al 2013]. A role of DEPDC5 in the signaling pathway has been confirmed in vivo in a *Depdc5* knockout rat [Marsan et al 2016]. Rapamycin complex 1 has serine-threonine kinase activity that phosphorylates several downstream proteins, regulating essential cellular functions like protein synthesis, cell growth, migration, and proliferation [Lasarge & Danzer 2014, Liu & Sabatini 2020]. Most pathogenic variants are likely to lead to a loss of function.

Several nonsense pathogenic variants have been shown to be targeted by nonsense-mediated mRNA decay [Ishida et al 2013, Picard et al 2014].

Preliminary in vitro functional studies investigated the effect on mTORC1 signaling of ten *DEPDC5* variants identified in individuals with focal epilepsy: seven missense variants, two nonsense variants, and one in-frame deletion. The two nonsense variants and the 3-bp deletion clearly disrupted the DEPDC5-dependent inhibition of mTORC1, while none of the seven missense variants had this effect [van Kranenburg et al 2015].

Some individuals with cortical malformations (most frequently focal cortical dysplasia type II or hemimegalencephaly) have been reported to have a brain-specific mosaic (or postzygotic) pathogenic variant in *DEPDC5* on the normal (or non-mutated) allele (i.e., a "second hit") in addition to a heterozygous constitutional pathogenic variant [Baulac et al 2015, D'Gama et al 2017, Ribierre et al 2018, Baldassari et al 2019b, Sim et al 2019, Lee et al 2020]. In addition, somatic copy-neutral loss of heterozygosity of the *DEPDC5* non-mutated allele may also occur [Mirzaa et al 2016, Baldassari et al 2019b], leading to brain tissues with biallelic pathogenic *DEPDC5* variants.

Mechanism of disease causation. Loss of function

***DEPDC5*-specific laboratory technical considerations – targeted testing for mosaicism.** Sequence analysis of DNA derived from affected brain tissues (whether visibly affected or not) may detect a pathogenic variant that is not present in DNA isolated from peripheral blood or other peripheral tissues (e.g., saliva). Note: Sensitivity to detect low-level mosaicism of a mosaic pathogenic variant is greatest using next-generation sequencing in tissues other than blood and has a high yield when analyzing affected (brain) tissues in particular.

Chapter Notes

Author Notes

Dr Stéphanie Baulac is a neurogeneticist, research director, and group leader at ICM (Paris Brain Institute) working on the genetics and neurobiology of focal epilepsies with brain malformations.

Dr Sara Baldassari is a neurogeneticist and principal investigator working at the ICM (Paris Brain Institute) on the genetics and physiopathology of focal epilepsies with brain malformations.

To volunteer for research contact:

Stéphanie Baulac
Institut du Cerveau (ICM)-Paris Brain Institute
Pitié-Salpêtrière Hospital
47 bd de l'Hôpital
75013 Paris, France
Email: stephanie.baulac@icm-institute.org

Author History

Sara Baldassari, PhD (2023-present)
Stéphanie Baulac, PhD (2016-2023)
Sarah Weckhuysen, MD, PhD; Vlaams Instituut voor Biotechnologie (2016-2023)

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