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NLM Citation: Dafsari HS, Ebrahimi-Fakhari D, Saffari A, et al. *EPG5*-Related Disorder. 2022 Oct 13. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

EPG5-Related Disorder

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Created: October 13, 2022.

Summary

Clinical characteristics

With the current widespread use of multigene panels and comprehensive genomic testing, it has become apparent that the phenotypic spectrum of *EPG5*-related disorder represents a continuum. At the most severe end of the spectrum is classic Vici syndrome (defined as a neurodevelopmental disorder with multisystem involvement characterized by the combination of agenesis of the corpus callosum, cataracts, hypopigmentation, cardiomyopathy, combined immunodeficiency, microcephaly, and failure to thrive); at the milder end of the spectrum are attenuated neurodevelopmental phenotypes with variable multisystem involvement. Median survival in classic Vici syndrome appears to be 24 months, with only 10% of children surviving longer than age five years; the most common causes of death are respiratory infections as a result of primary immunodeficiency and/or cardiac insufficiency resulting from progressive cardiac failure. No data are available on life span in individuals at the milder end of the spectrum.

Diagnosis/testing

The diagnosis of *EPG5*-related disorder is established in a proband with suggestive clinical findings and confirmed by identification of biallelic pathogenic (or likely pathogenic) variants in *EPG5* on molecular testing.

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Management

Treatment of manifestations: There is no cure for *EPG5*-related disorder. Supportive multidisciplinary care to improve quality of life, optimize function, and reduce complications may include specialists in clinical genetics and pediatrics as well as allied health professionals in neurology, audiology, ophthalmology, development, feeding, cardiology, pulmonology, gastroenterology, immunology, endocrinology, and nephrology. Given the complexities of medical problems in affected individuals, input from experts in palliative care and medical ethics may be beneficial, particularly when invasive procedures are under consideration.

Of particular note, rigorous and early antibacterial and antifungal treatment (potentially in an intensive care unit setting) should be considered for chest infections to prevent episodes of life-threatening sepsis and organ failure due to the consequences of primary immunodeficiency.

Surveillance: To monitor disease progression, optimize functional abilities and communication skills, and address emerging disease manifestations, regular evaluations by the treating multidisciplinary specialists as well as assessments of developmental and educational needs are recommended.

Genetic counseling

EPG5-related disorder is inherited in an autosomal recessive manner. Many individuals with *EPG5*-related disorder are born to consanguineous couples. If both parents are known to be heterozygous for an *EPG5* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being heterozygous, and a 25% chance of inheriting neither of the familial pathogenic variants. Once the *EPG5* pathogenic variants have been identified in an affected family member, carrier testing for at risk relatives and prenatal/preimplantation genetic testing are possible.

GeneReview Scope

With the current widespread use of multigene panels and comprehensive genomic testing based on an unbiased (i.e., not phenotype-driven) approach, it has become apparent that the phenotypic spectrum associated with biallelic *EPG5* pathogenic variants is a continuum that encompasses clinically defined classic Vici syndrome as well as less specific neurodevelopmental phenotypes of more moderate severity. The term "*EPG5*-related disorder" refers to this entire phenotypic spectrum and emphasizes the need to both: (1) evaluate an individual with biallelic *EPG5* pathogenic variants for medically actionable manifestations within the *EPG5*-associated phenotypic spectrum (regardless of the clinical findings that prompted molecular genetic testing); and (2) counsel families that the finding of biallelic pathogenic variants in *EPG5* is not equivalent to a diagnosis of classic Vici syndrome.

Diagnosis

Suggestive Findings

At the more severe end of the spectrum of *EPG5*-related disorder, clinically defined classic Vici syndrome commonly involves the common combined presence of agenesis of corpus callosum, cataract, cardiomyopathy, hypopigmentation, primary immunodeficiency, failure to gain weight, and microcephaly. The milder end of the spectrum involves primarily neurodevelopmental and/or neurologic features with variable but (in general) less pronounced multisystem involvement [Kane et al 2019].

EPG5-related disorder **should be suspected** in individuals with the following suggestive findings across the phenotypic spectrum and family history.

Clinical Findings

Neurodevelopmental manifestations

- **Developmental delay,** typically with significant motor delay, absence of speech, and later severe intellectual disability
- **Agenesis or dysgenesis of corpus callosum.** Variable other central nervous system abnormalities include pontine hypoplasia and less frequently cerebellar hypoplasia, mild prominence of the cisterna magna, simplified sulcation pattern and neuronal migration abnormalities, reduced operculization, reduced white matter bulk, and delayed myelination [Byrne et al 2016a, Byrne et al 2016b].

Variably present highly suggestive multisystem findings

- **Immunodeficiency** manifesting as:
  - Thymic aplasia or hypoplasia [Byrne et al 2016b];
  - Severe combined immunodeficiency with prominent B cell involvement, characterized by lack of memory B cells, reduced IgG2, deficient humoral response, and T4+ cell depletion [Piano Mortari et al 2018];
  - Increased susceptibility to infections (i.e., recurrent pulmonary and/or mucocutaneous infections) [Finocchi et al 2012].
- **Failure to gain weight,** common after the first year of life despite adequate caloric intake [Byrne et al 2016b]
- **(Oculo-)cutaneous hypopigmentation** that is relative to familial and ethnic background; typically not complete albinism (Figure 1) [Byrne et al 2016b] (full text). Abnormal visual evoked potentials and retinal abnormalities on optical coherence tomography are consistent with ocular albinism [Filloux et al 2014].
- **Progressive microcephaly,** both congenital and (more commonly) acquired
- **Early-onset epilepsy,** in some cases refractory to pharmacologic treatment with progression to an epileptic encephalopathy
- **Neuromuscular findings**
  - Congenital myopathy with generalized hypotonia, contractures, mild-to-moderate creatine kinase elevation, and variable histologic features (fiber type disproportion, increased central nuclei, vacuoles, and/or mitochondrial abnormalities) on diagnostic muscle biopsy [Al-Owain et al 2010, McClelland et al 2010]. Note that a muscle biopsy is not required to confirm the diagnosis of *EPG5*-related disorder.
  - Peripheral neuropathy with absent reflexes [Byrne et al 2016b]
  - Pyramidal and extrapyramidal movement disorders (including spastic paraplegia, dystonia, choreoathetosis, and akinetic-rigid disorders)
- **Sensorineural hearing loss.** Congenital hearing loss is likely to be detected on newborn hearing screening; hearing loss with later onset is likely to be detected when prompted by specific concerns.
- **Ophthalmologic findings.** Cataracts (congenital or acquired), optic nerve atrophy, retinopathy
- **Cardiac involvement**
  - Congenital structural cardiac abnormalities
  - Acquired cardiomyopathies. Dilated cardiomyopathy is more common than hypertrophic cardiomyopathy [Byrne et al 2016a, Byrne et al 2016b].

Classic Vici Syndrome: Clinical Definition

No consensus clinical diagnostic criteria for Vici syndrome have been published; however, based on the original criteria suggested by Dionisi Vici et al [1988] (see asterisked * features) and subsequent refinement of the phenotype by Byrne et al [2016b], the presence of at least five of the following seven criteria is conventionally considered diagnostic:

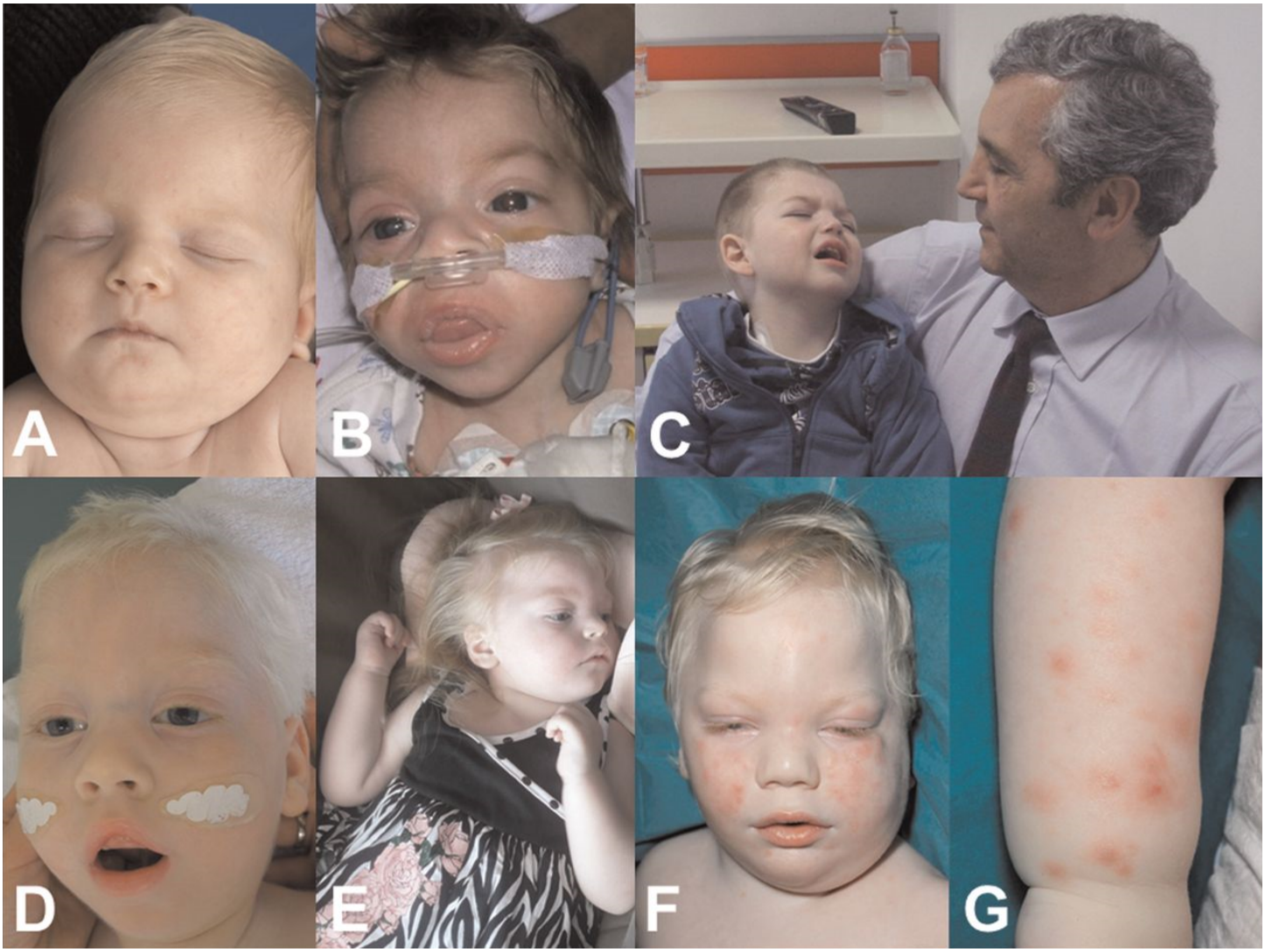

Figure 1. Distinctive facial features in *EPG5*-related disorder. Note hypopigmentation in relation to ethnic and familial background. Some individuals present with myopathic facial features. In some individuals a recurrent, often confluent maculopapular rash is present.

Reproduced from Byrne et al [2016b] with permission

- Agenesis of corpus callosum *
- (Progressive) microcephaly
- Cataracts *
- Cardiomyopathy *
- (Severe combined) primary immunodeficiency *
- (Oculo-)cutaneous hypopigmentation *
- Failure to gain weight despite adequate caloric intake

Family History

Family history is consistent with autosomal recessive inheritance (e.g., parental consanguinity and/or affected sibs). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of *EPG5*-related disorder **is established** in a proband with suggestive clinical findings and confirmed by identification of biallelic pathogenic (or likely pathogenic) variants in *EPG5* on molecular testing (Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic *EPG5* variants of uncertain significance (or of one known *EPG5* pathogenic variant and one *EPG5* variant of uncertain significance) does not establish or rule out a diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing).

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. The diagnosis of *EPG5*-related disorder in individuals meeting the clinical definition of classic Vici syndrome is likely to be established using gene-targeted testing. At the other end of the spectrum, individuals with less distinctive findings are likely to be diagnosed through more comprehensive and less targeted genomic testing.

- **Single-gene testing.** This highly selective testing may be an option when the phenotypic findings suggest the diagnosis of classic Vici syndrome.

  This approach involves performing sequence analysis of *EPG5* to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

- **Multigene panels.***EPG5* and other genes of interest may be included in multigene panels for developmental delay, microcephaly, developmental brain malformations, early-onset epileptic encephalopathies, mitochondrial disorders, and/or primary immunodeficiencies (see Differential Diagnosis). These panels are 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.

- **Comprehensivegenomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

  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 *EPG5*-Related Disorder

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
EPG5	Sequence analysis [3]	98%-99% [4]
	Gene-targeted deletion/duplication analysis [5]	1%-2% [4, 6]

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. Cullup et al [2013], Byrne et al [2016b], and data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
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.
6. Shimada et al [2018]

Clinical Characteristics

Clinical Description

With the current widespread use of multigene panels and comprehensive genomic testing, it has become apparent that the phenotypic spectrum of biallelic *EPG5* pathogenic variants causing *EPG5*-related disorder represents a continuum of variable severity. Vici syndrome (defined as a neurodevelopmental disorder with multisystem involvement characterized by the combination of agenesis of the corpus callosum, cataracts, hypopigmentation, cardiomyopathy, combined immunodeficiency, microcephaly, and failure to thrive; see Suggestive Findings, Classic Vici Syndrome) is at the most severe end of the spectrum; however, milder, attenuated neurodevelopmental phenotypes with a variable degree of multisystem involvement are increasingly recognized.

To date, around 90 individuals have been identified with biallelic *EPG5* pathogenic variants. These reports have mostly shown individuals toward the more severe end of the phenotypic spectrum, while reports of individuals with only neurologic disease but no more extensive multisystem involvement are scarce [Kane et al 2019]. Several sub-phenotypes (e.g., those presenting with predominantly immunologic features) remain very likely underdiagnosed and should be carefully evaluated in future genotype-phenotype correlation studies.

The description of the phenotypic spectrum associated with *EPG5*-related disorders is based on clinical reports published to date (see Table 2).

Table 2. *EPG5*-Related Disorder: Frequency of Select Features

Feature		% of Persons w/Feature
Most common findings		
Brain malformations	Corpus callosum agenesis or thinning	100%
	Thalamic abnormalities	20%
	Neuronal migration abnormalities or polymicrogyria	20%

Table 2. continued from previous page.

Feature		% of Persons w/Feature
Neurologic	Developmental delay / Intellectual disability	100%
	Neonatal muscular hypotonia	70%
	Seizures	70%
	Movement disorders	65%
Immunodeficiency		95%
Failure to gain weight [1]		90%
(Oculo-)cutaneous hypopigmentation		90%
Microcephaly		90%
Cardiac involvement	Cardiomyopathy	60%-68%
	Congenital heart defects	8%-15%
Ophthalmologic involvement [2]	Cataract	70%
	Retinal abnormalities	35%
	Optic nerve atrophy	30%
Sensorineural hearing loss		65%
Anemia, leucopenia, thrombocytopenia		50%
Less common findings		
Thyroid agenesis or dysplasia		10%
Thymic aplasia		10%
Pulmonary hypoplasia		10%
Renal tubular dysfunction		10%

Adapted from Byrne et al [2016a] and Byrne et al [2016b], based on 90 persons with *EPG5*-related disorder reported to date
1. Either due to or irrespective of gastrointestinal features
2. Note that multiple ophthalmologic features may present in a given person (e.g., cataract with retinal abnormalities).

Antenatal presentation in the second trimester with agenesis of the corpus callosum, underdevelopment of the temporal lobes [Touraine et al 2017], and focal cortical microdysgenesis has been reported [Aggarwal et al 2018].

At the more severe end of the disorder spectrum, presentation is typically in the neonatal period or early infancy with callosal agenesis and (relative) hypopigmentation. (Severe) combined immunodeficiency, cardiomyopathy, and/or cataracts may or may not be present at birth but usually develop during the first year of life [Byrne et al 2016b].

At the less severe end of the disorder spectrum, presentations ranging from hypotonia and microcephaly in infancy to nonspecific global neurodevelopmental delay with associated movement disorders (but no other signs of multisystem involvement) during early childhood have been reported [Kane et al 2019].

Brain malformations. The most common brain malformation is agenesis of the corpus callosum, followed by pontine hypoplasia, enlargement of the cisterna magna, thalamic signal changes, and neuronal migration abnormalities [Byrne et al 2016b, Hori et al 2017].

Dysgenesis (rather than agenesis) of the corpus callosum has also been reported and may be more prominent in individuals with milder neurodevelopmental features [Kane et al 2019].

Neurologic

- **Developmental delay.** The severe end of the spectrum involves neurodevelopmental delay with failure to achieve ambulation, intellectual disability, and lack of speech in nearly all individuals [Byrne et al 2016a, Byrne et al 2016b]. The mildest presentation reported to date was delay in the attainment of motor and language skills at the age of 3.5 years, with speech and language development limited to a few words [Kane et al 2019].
- **Neonatal muscular hypotonia.** Presentation at birth may include profound generalized hypotonia with the combination of both central and peripheral hypotonia and associated respiratory and bulbar involvement [Byrne et al 2016b]. In some individuals at the severe end of the disorder spectrum, reduced fetal movements in utero and/or contractures of antenatal onset have been reported, potentially with an underlying myopathy and/or neuropathy. Currently there is only limited understanding of the pathogenesis and/or progression of neuromuscular features resulting from the lack of muscle or nerve biopsies in affected individuals.
- **Seizures**, mostly generalized tonic-clonic seizures, occur in the first two years of life in more than 60% of individuals, ranging from infrequent seizures to severe epileptic encephalopathy with burst-suppression patterns or hypsarrhythmia on EEG [Byrne et al 2016b]. Status epilepticus may occur in individuals at the more severe end of the spectrum.

  About 50% of affected individuals have seizures in response to fever, while individuals at the milder end of the spectrum may show transient loss of acquired skills with febrile seizures without long-term developmental regression [Kane et al 2019].

  Although seizures may be well-controlled with standard anti-seizure medications, the response varies.
- **Movement disorders** include spastic paraplegia and extrapyramidal movement disorders, particularly dystonia, choreoathetosis, and akinetic-rigid disorders.
- **Neuromuscular features** include variable myopathic features (including fiber size disproportion, type 1 predominance, increased central nuclei, vacuoles, and mitochondrial abnormalities) on muscle biopsy and features of an axonal neuropathy on nerve biopsy [McClelland et al 2010, Byrne et al 2016b].

Primary immunodeficiency. A combined immunodeficiency of variable severity as a result of defects in both T and B cells is common and may present with recurrent and unusual infections from the neonatal period or infancy onward. Immunologic studies may reveal prominent B cell involvement, characterized by lack of memory B cells, reduced immunoglobulin G2, deficient humoral response, and T4+ cell depletion. Bacterial and fungal agents (including *Streptococcus viridans*, *Staphylococcus hominis*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Candida albicans*) may cause pneumonias, skin abscesses, oral mucocutaneous candidiasis, enterocolitis, and intractable diarrhea. Infections may quickly progress to septic shock and should be managed urgently and proactively (see Management, Treatment of Manifestations).

Recurrent episodes of otherwise unexplained fever without identification of a pathogenic organism also require proactive and immediate management (see Management, Treatment of Manifestations).

Thymus aplasia or hypoplasia has been reported in around one fifth of affected individuals.

Failure to gain weight. Poor weight gain despite adequate caloric intake is common, and profound failure to thrive is seen in a substantial proportion of affected individuals. Poor weight gain may be due to the principal underlying anabolic defect as a consequence of the primary autophagy defect; other potential causes may include gastrointestinal involvement with feeding difficulties, gastroesophageal reflux disease with risk for aspiration pneumonias, intractable diarrhea, and other features mimicking inflammatory bowel syndrome [Shimada et al 2018].

(Oculo-)cutaneous hypopigmentation. Cutaneous hypopigmentation is common but never complete and always relative to ethnic and familial background [Byrne et al 2016a, Byrne et al 2016b]. For ocular manifestations of hypopigmentation, see **Ophthalmologic features** in this section.

Cardiac involvement includes both structural congenital heart defects and acquired cardiomyopathies.

Cardiomyopathy is seen in 80%-90% of individuals with cardiac involvement in *EPG5*-related disorders and has a significant effect on morbidity and mortality. Both dilated and hypertrophic cardiomyopathy can be seen and usually develop in early childhood. Acute decompensation of cardiac function during infections / intercurrent illness is possible.

Congenital heart defects including patent foramen ovale, ventricular or atrial septal defects, hypoplastic aortic arch, and mitral valve insufficiency are seen in about 10%-20% of individuals with cardiac involvement.

Ophthalmologic features mainly include bilateral nuclear and anterior polar cataracts (70%), retinal abnormalities (35%; e.g., retinopathy), and bilateral optic nerve atrophy (30%). Other reported ocular abnormalities are mild fundus hypoplasia, evidence of misrouting of optic pathways in evoked potentials recorded across the mid-occipital scalp, and a poorly defined fovea demonstrating a lesser degree of foveal depression in optical coherence tomography [Filloux et al 2014]. This observation is similar to other congenital disorders of autophagy with ocular hypopigmentation, as noted in Table 3.

Sensorineural hearing loss (SNHL) may be detected after birth through brain auditory evoked responses in individuals at the severe end of the spectrum. To date, there have been no reports of hearing loss in individuals at the milder end of spectrum or in those with a progressive disease course; however, in individuals with severe disability, SHNL may not have been suspected and/or proactively investigated.

Hematologic abnormalities with anemia, low platelet counts, and idiopathic thrombocytopenic purpura can be triggered by infections without apparent bone marrow suppression. Onset, severity, and course are variable.

Other multisystem involvement (in <20% of affected individuals but probably underreported) [Byrne et al 2016a, Byrne et al 2016b] include the following:

- **Thyroid abnormalities**, including thyroid aplasia/hypoplasia or thyroid dysfunction in the presence of a normally formed thyroid gland [Byrne et al 2016a]
- **Pulmonary hypoplasia**
- **Hepatomegaly and/or splenomegaly** [Byrne et al 2016a]
- **Kidney abnormalities** with features suggestive of renal tubular acidosis or electrolyte imbalances (in particular hypokalemia)
- **Morbilliform maculopapular rashes** [Byrne et al 2016a, Huenerberg et al 2016, Hızal et al 2020]

Prognosis. Natural history data for individuals with classic Vici syndrome on the severe end of the *EPG5*-related disorder spectrum suggest a median survival time of 24 months, with only 10% of affected individuals surviving longer than age five years [Byrne et al 2016b]. The most common causes of death at the most severe end of the spectrum are respiratory infections as a result of primary immunodeficiency and/or cardiac insufficiency resulting from progressive cardiac failure.

While it may be expected that the disease course in individuals with phenotypes on the less severe end of the *EPG5*-related disorder spectrum may be milder and associated with a longer life span (in particular if cardiorespiratory and/or immunologic features are absent), to date no comprehensive follow-up data are available.

Genotype-Phenotype Correlations

Precise genotype-phenotype correlations are difficult to establish because of the relatively limited number of affected individuals and the lack of long-term natural history data.

Homozygosity for c.1007A>G (p.Gln336Arg), a likely founder variant in individuals of Ashkenazi Jewish background, is associated with a longer life expectancy and a less severe phenotype with apparently reduced cardiac and immunologic involvement, possibly due to a variable effect on *EPG5* splicing with some residual expression of normal EPG5 protein [Byrne et al 2016b, Kane et al 2016]. Genotype-phenotype correlations for individuals compound heterozygous for the c.1007A>G (p.Gln336Arg) variant and a second (truncating) variant are less clear but probably are characterized by intermediate severity.

Other possible correlations. Emerging data suggest a correlation between severity of the phenotype and residual EPG5 protein expression. Median survival was nine months for infants with homozygous truncating *EPG5* variants in comparison to 48 months for children with compound heterozygous variants, often involving at least one missense change [Byrne et al 2016b].

Bulk autophagy is at least partially impaired in fibroblasts from individuals with phenotypes on the severe end of the *EPG5*-related disorder spectrum who have *EPG5* loss-of-function variants with decreased EPG5 protein expression [Cullup et al 2013, Byrne et al 2016a].

A milder decrease in mRNA and protein expression has been associated with a primarily neurologic phenotype without major multisystem involvement [Kane et al 2019].

Nomenclature

Classic Vici syndrome, a phenotype on the more severe end of the *EPG5*-related disorder spectrum, may also be referred to as *EPG5*-related Vici syndrome or immunodeficiency with cleft lip/palate, cataract, hypopigmentation, and absent corpus callosum.

Prevalence

The birth prevalence for *EPG5*-related disorder is unknown but is expected to be low, at least for phenotypes on the severe end of the phenotypic spectrum. While it is possible that less severe phenotypes with fewer specific features are more common, no reliable epidemiologic data are available to date.

The variant c.1007A>G (p.Gln336Arg) is a likely founder variant in individuals with Ashkenazi Jewish ancestry [Byrne et al 2016b, Kane et al 2016].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *EPG5*.

Differential Diagnosis

The differential diagnosis of *EPG5*-related disorder depends on the presenting features and severity on the phenotypic spectrum. Differential diagnoses with features overlapping those of individuals with phenotypes on the more severe end of the disorder spectrum are summarized in Table 3.

Note: For more information on the immunologic abnormalities in *EPG5*-related disorder and related differential diagnoses, see Piano Mortari et al [2018] and Deneubourg et al [2022].

Table 3. Multisystem Disorders in the Differential Diagnosis of *EPG5*-Related Disorder

Gene(s)	Differential Disorder	MOI	Phenotype
AP3B1 *AP3D1*	Hermansky-Pudlak syndrome types 2 (*AP3B1*) & 10 (*AP3D1*)	AR	• Primary immunodeficiency w/(oculo-)cutaneous hypopigmentation, DD, seizures, & failure to gain weight • Not assoc w/ACC or cardiomyopathy
CTDP1	Congenital cataracts, facial dysmorphism, & neuropathy	AR	• Cataracts, myopathy, neuropathy, DD, brain malformation • Not assoc w/cardiomyopathy, immunodeficiency, or hypopigmentation
LAMTOR2	*LAMTOR2*-associated primary immunodeficiency (OMIM 610798)	AR	• Primary immunodeficiency w/↓ of memory B cells, cutaneous hypopigmentation, coarse facies, short stature • Not assoc w/neurologic features (DD, mvmt disorders) or brain malformations
LYST	Chediak-Higashi syndrome	AR	• Primary immunodeficiency w/hemophagocytic lymphohistiocytosis, oculocutaneous albinism, failure to gain weight, delayed myelination, cortical atrophy, mvmt disorder, myopathy • Not assoc w/ACC or cardiomyopathy
PI4K2A [1] *PI4KA* [2]	PI4 kinase deficiency (See *PI4KA*-Related Disorder.)	AR	Neurodevelopmental disabilities, dysplastic corpus callosum, immunodeficiency
RAB27A	Griscelli syndrome type 2 (OMIM 607624)	AR	• Primary immunodeficiency w/hemophagocytic lymphohistiocytosis, cutaneous albinism, mvmt disorder • Not assoc w/ACC or cardiomyopathy
RAB3GAP1 *RAB3GAP2* *RAB18* *TBC1D20*	Warburg micro syndrome (See RAB18 Deficiency.)	AR	• Dysgenesis of corpus callosum, DD, mvmt disorder, microcephaly • Not assoc w/immunodeficiency or hypopigmentation
SIL1	Marinesco-Sjögren syndrome	AR	• DD, cataracts, myopathy, neuropathy, mvmt disorder, skeletal deformities • Not assoc w/cardiomyopathy, immunodeficiency, or hypopigmentation
SNAP29	*SNAP29*-associated cerebral dysgenesis (OMIM 609528)	AR	• Dysgenesis of corpus callosum, neuronal migration abnormalities, progressive microcephaly, DD, ichthyosis, palmoplantar keratoderma • Not assoc w/immunodeficiency or cardiomyopathy
VPS45	*VPS45*-associated immunodeficiency (OMIM 615285)	AR	• Primary immunodeficiency w/failure to gain weight & DD • Not assoc w/hypopigmentation or brain malformations

Adapted from Byrne et al [2016a], Table 3
ACC = agenesis of the corpus callosum; AR = autosomal recessive; DD = developmental delay; MOI = mode of inheritance
1. Dafsari et al [2022]
2. Verdura et al [2021]

Management

No comprehensive clinical practice guidelines for *EPG5*-related disorder have been published; however, a number of investigations for the diagnosis and surveillance of individuals with clinically defined classic Vici syndrome have been recommended [Byrne et al 2016a, Table 2] (full text). These evaluations are presented in more detail below.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *EPG5*-related disorder, the evaluations summarized in Table 4 (if not performed as part of initial diagnostic process) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with *EPG5*-Related Disorder

System/Concern	Evaluation	Comment
Central nervous system involvement	By pediatric neurologist / developmental pediatrician	• To evaluate development of motor, speech, & language abilities • Brain MRI for agenesis/dysgenesis of corpus callosum & other brain malformations • Consider EEG & ASM if seizures are a concern. • Consider specific treatment for mvmt disorders (e.g., PT, botulinum toxin or baclofen for spasticity, &/or trihexyphenidyl for dystonia).
Musculoskeletal	By orthopedics	To assess for contractures, scoliosis, & foot deformities
	By PT	To incl PT eval & assessment for mobility, ADL
Feeding difficulties & failure to gain weight	By pediatric gastroenterologist / speech-language pathologist / dietician	• To incl eval of aspiration risk & nutritional status • Consider eval for gastric tube placement in those w/dysphagia &/or ↑ risk of aspiration, or poor weight gain.
Ophthalmologic involvement	By pediatric ophthalmologist	To assess visual acuity, refractive error, strabismus, & more complex findings (e.g., cataracts, fundus changes consistent w/ocular albinism) that may require referral for subspecialty care &/or low vision services
Sensorineural hearing loss	By audiologist	To evaluate degree of hearing loss as indicated
Cardiac involvement	By pediatric cardiologist	To assess for cardiac malformations &/or degree/type of cardiomyopathy
Immuno-deficiency	By pediatric immunologist	• To evaluate for symptoms of primary immunodeficiency • To arrange specific testing (i.e., immunoglobulins, T, B, & NK cell numbers & function) • To assess for thymus aplasia/hypoplasia on chest x-ray
Pulmonary function	By pediatric pulmonologist	• To evaluate for aspiration risk & secretion mgmt • Consider antibiotic prophylaxis.
Hepatic function	By pediatrician; referral to hepatologist as needed	To assess liver function; liver ultrasound as indicated
Renal function	By pediatrician; referral to nephrologist as needed	To assess kidney function as indicated
Thyroid function	By pediatrician; referral to endocrinologist as needed	• To check for thyroid aplasia/hypoplasia • To assess thyroid function as clinically indicated
Ethics consultation	Clinical ethics services	To assess health care decisions in context of best interest of child & values & preferences of family
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *EPG5*-related disorder to facilitate medical & personal decision making

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	Referral to palliative care when deemed appropriate by family & health care providers

Adapted from Byrne et al [2016a], Table 2
ADL = activities of daily living; ASM = anti-seizure medication; MOI = mode of inheritance; PT = physical therapy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for *EPG5*-related disorder.

Supportive care recommendations to improve quality of life, optimize function, and reduce complications are summarized in Table 5. This may include multidisciplinary care by specialists in clinical genetics and pediatric specialists and allied health professionals in neurology, audiology, ophthalmology, development, feeding, cardiology, pulmonology, gastroenterology, immunology, endocrinology, and nephrology. Considering the complexities of medical problems in some affected individuals, input from palliative care and medical ethics may also be beneficial, particularly when decisions about invasive procedures are made.

Consider rigorous and early antibacterial and antifungal treatment (potentially in an intensive care unit setting) for chest infections to prevent episodes of life-threatening sepsis and organ failure due to the consequences of primary immunodeficiency.

Table 5. Treatment of Manifestations in Individuals with *EPG5*-Related Disorder

Manifestation/Concern	Treatment	Considerations/Other
Central nervous system involvement	Treatment w/ASM	Most persons respond to standard ASM, but response may vary.
	Treatment for mvmt disorders	
	Referral for early intervention & developmental support	See Developmental Delay / Intellectual Disability Management Issues.
	Antispasticity medications (i.e., oral baclofen or botulinum toxin injections), surgical tendon release	
Musculoskeletal	PT/OT	Referral to orthopedic surgeon as indicated
Feeding difficulties & failure to gain weight	• Nutritional supplementation as directed by dietitian • Consider gastrostomy placement.	Gastrostomy tube feeding ↓ aspiration risk, provides a reliable route for medication, & may improve somatic growth.
Ophthalmologic involvement	Cataract surgery	
	Low vision services	Through early intervention programs
Sensorineural hearing loss	Per treating pediatric ENT/audiologist	Use of hearing aids may be indicated.
Cardiac involvement	Per treating cardiologist	

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Dermatologic involvement	Per primary care physician	Avoid excessive sun exposure; use protective clothing & sunscreen when appropriate.
Immunodeficiency	• Per treating immunologist • Immunoglobulin infusions, vitamin D supplementation, antimicrobial prophylaxis [1]	Consider lack of specific antibody response due to defect of memory B cells to certain immunizations (e.g., tetanus or pneumococcal vaccine). [2]
Pulmonary function	• During chest infections, rigorous antibiotic therapy, chest physiotherapy, potentially ICU treatment & ventilation • Antibiotic prophylaxis	Consider both central & obstructive apnea; polysomnographic monitoring as indicated; & noninvasive ventilatory support.
Thyroid function	Thyroid hormone replacement	As clinically indicated
Liver function		Consider coagulation abnormalities if liver function is disturbed.
Renal function	Per treating nephrologist	Consider hypokalemia in particular.
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	Ongoing assessment of need for palliative care involvement &/or home nursing

Adapted from Byrne et al [2016a], Table 2
ASM = anti-seizure medication; OT = occupational therapy; PT = physical therapy
1. Finocchi et al [2012]
2. No data are available on use of live viral vaccines in individuals with this disorder.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.

    - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
    - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
    - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
    - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Surveillance

To identify the multidisciplinary evaluations (and their frequency) for assessing disease progression, optimizing functional abilities and communication skills, and addressing other disease manifestations, see Table 6.

Table 6. Recommended Surveillance for Individuals with *EPG5*-Related Disorder

System/Concern	Evaluation	Frequency
Central nervous system involvement	• Assess for mvmt disorders & seizure activity. • Perform EEG if clinically indicated.	Every 6 mos
Development	Monitor developmental progress & educational needs.	
Musculoskeletal	• PT/OT eval • Assess for contractures, scoliosis, &/or foot deformities. • Hip/spine x-rays as indicated	
Ophthalmologic involvement	• Ophthalmologic eval for cataracts, visual acuity • Assess need for support services for visually impaired.	Every 12 mos
Sensorineural hearing loss	Brain stem evoked responses in case of suspected hearing impairment	As clinically indicated
Cardiac involvement	Echocardiography per treating cardiologist	Every 6 mos
Pulmonary function	• Monitor for aspiration & pulmonary complications. • Polysomnography as indicated	
Immunodeficiency	Regular full blood counts & specific immunologic investigations per treating immunologist.	
Thyroid function	Monitor for hypothyroidism.	As clinically indicated
Renal function	Monitor kidney function & anticipate electrolyte imbalances.	

Table 6. continued from previous page.

System/Concern	Evaluation	Frequency
Failure to gain weight &/or gastrointestinal involvement	• Assess for aspiration risk. • Assess nutritional status. • Monitor for constipation & bowel dysfunction. • Assess plasma amino acid levels if clinically indicated.	Every 6 mos
Liver function	Monitor liver function.	As clinically indicated
Family support & resources	Monitor educational/family needs.	Every 12 mos

Adapted from Byrne et al [2016a], Table 2

Evaluation of Relatives at Risk

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

Therapies Under Investigation

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. 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

EPG5-related disorder is inherited in an autosomal recessive manner.

Many individuals with *EPG5*-related disorder are born to consanguineous couples [Byrne et al 2016b].

Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for an *EPG5* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *EPG5* 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 *EPG5* 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 are not at risk of developing *EPG5*-related disorder. In one study, subtle clinical manifestations (including early-onset cataracts, vitiligo, and an increased incidence of certain tumor disorders) were described in families of individuals with *EPG5* pathogenic variants [Byrne et al 2016a]. These preliminary observations require confirmation in larger series.

Sibs of a proband

- If both parents are known to be heterozygous for an *EPG5* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being heterozygous, and a 25% chance of inheriting neither of the familial pathogenic variants.
- Heterozygotes are not at risk of developing *EPG5*-related disorder. In one study, subtle clinical manifestations (including early-onset cataracts, vitiligo, and an increased incidence of certain tumor disorders) were described in families of individuals with *EPG5* pathogenic variants [Byrne et al 2016a]. These preliminary observations require confirmation in larger series.

Offspring of a proband. To date, individuals with *EPG5*-related disorder are not known to reproduce.

Other family members. Each sib of the proband's parents is at a 50% risk of being heterozygous for an *EPG5* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *EPG5* pathogenic variants in the family.

Related Genetic Counseling Issues

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 the parents of affected children and young adults who are carriers or are at risk of being carriers.
- Carrier testing for reproductive partners of known carriers should be considered, particularly if consanguinity is likely and/or if the reproductive partner is of the same ethnic background. An *EPG5* founder variant has been identified in individuals of Ashkenazi Jewish heritage (see Genotype-Phenotype Correlations and Prevalence).

Prenatal Testing and Preimplantation Genetic Testing

Once the *EPG5* pathogenic variants have 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.

- **MedlinePlus**
  Vici syndrome
- **Vici Syndrome Organization**
  www.vicisyndrome.org

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. EPG5-Related Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
EPG5	18q12.3-q21.1	Ectopic P granules protein 5 homolog	EPG5	EPG5

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 EPG5-Related Disorder (View All in OMIM)

242840	VICI SYNDROME; VICIS
615068	ECTOPIC P-GRANULES AUTOPHAGY PROTEIN 5 HOMOLOG; EPG5

Molecular Pathogenesis

Macroautophagy (hereafter referred to as autophagy), a cellular degradation process, is pivotal for the recycling of proteins and organelles, specifically within post-mitotic cells such as neurons [Ebrahimi-Fakhari et al 2016]. The process of autophagy involves sequestration of cytoplasmic material into the double-membraned autophagosome and targeting to the lysosome for degradation. Ectopic P granules protein 5 homolog (EPG5), in concert with RAB7, serves as a tethering factor to facilitate autophagosome-lysosome fusion [Tian et al 2010], and probably also other intracellular fusion processes. *EPG5*-related disorder is thought to result from a defect in the late stages of the autophagy pathway, namely, autophagosome-lysosome fusion. Global reduction in autophagic flux leads to impaired development and function in a multitude of tissues and, thus, to a multisystem disease.

Mechanism of disease causation. Loss of function

Table 7. Notable *EPG5* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_020964.3 NP_066015.2	c.1007A>G	p.Gln336Arg [1]	Possible founder variant in persons of Ashkenazi Jewish ancestry [Byrne et al 2016b, Kane et al 2016]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Nucleotide substitution is predicted to affect splicing between exon 2 and 5, resulting in several different isoforms [Kane et al 2016].

Chapter Notes

Author Notes

Heinz Jungbluth, Darius Ebrahimi-Fakhari, Afshin Saffari, and Hormos Dafsari are actively involved in clinical and basic research regarding individuals with *EPG5*-related disorder. They would be happy to communicate with persons who have any questions regarding the diagnosis of *EPG5*-related disorder, other congenital disorders of autophagy, or similar considerations.

Contact Heinz Jungbluth and Hormos Dafsari to inquire about review of *EPG5* variants of uncertain significance.

Heinz Jungbluth, Manolis Fanto, Celine Deneubourg, and Hormos Dafsari are interested in and work on the molecular biological research in *EPG5*-related disorder.

Acknowledgments

HSD was supported by the Cologne Clinician Scientist Program / Medical Faculty / University of Cologne and German Research Foundation (CCSP, DFG project no. 413543196).

HJ was supported by Action Medical Research, United Kingdom, the GOSH Charity / Sparks, and a European Commission H2020-MSCA-ITN-2017 grant.

Revision History

- 13 October 2022 (bp) Review posted live
- 19 April 2022 (def) Original submission

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