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PI4KA-Related Disorder

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Summary

Clinical characteristics

PI4KA-related disorder is a clinically variable disorder characterized primarily by neurologic dysfunction (limb spasticity, developmental delay, intellectual disability, seizures, ataxia, nystagmus), gastrointestinal manifestations (multiple intestinal atresia, inflammatory bowel disease), and combined immunodeficiency (leukopenia, variable immunoglobulin defects). Age of onset is typically antenatal or in early childhood; individuals can present with any combination of these features. Rare individuals present with later-onset hereditary spastic paraplegia. Brain MRI findings can include hypomyelinating leukodystrophy, cerebellar hypoplasia/atrophy, thin or dysplastic corpus callosum, and/or perisylvian polymicrogyria.

Diagnosis/testing

The diagnosis of *PI4KA*-related disorder is established in a proband with characteristic features and biallelic *PI4KA* pathogenic variants identified by molecular genetic testing.

Management

Treatment: Individualized care by a multidisciplinary team; physical therapy, occupational therapy, mobility aids, and medical management as needed for limb spasticity and motor issues; speech-language therapy for speech impairment and/or dysphagia; communication aids as needed; educational support for intellectual disability; anti-seizure medication as needed for seizures; gastrostomy as needed for feeding issues; treatments for multiple intestinal atresia and inflammatory bowel disease per surgeon and gastroenterologist; treatment of immunodeficiency per immunologist; standard treatment for hearing and vision issues.

Surveillance: Neurologic, developmental, and gastrointestinal assessments annually or as needed; consider complete blood count and inflammatory markers annually or as indicated by symptomatology; endoscopy as

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needed; monitor for increased susceptibility to infection; annual audiology and ophthalmology evaluations throughout childhood.

Genetic counseling

PI4KA-related disorder is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *PI4KA* 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 inheriting neither of the familial pathogenic variants. Once the *PI4KA* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and prenatal and preimplantation genetic testing are possible.

GeneReview Scope

PI4KA-Related Disorder: Phenotypic Spectrum
• Hypomyelinating leukodystrophy with pyramidal features, developmental delay, and intellectual disability ± inflammatory bowel disease • Severe antenatal-onset neurologic disorder with arthrogryposis and structural brain anomalies • Multiple intestinal atresia ± immunodeficiency • Later-onset pure hereditary spastic paraplegia (SPG84)

Diagnosis

Suggestive Findings

PI4KA-related disorder is a clinically variable disorder characterized by neurologic dysfunction, gastrointestinal manifestations (bowel atresia, inflammatory bowel disease), and immunodeficiency. *PI4KA*-related disorder **should be suspected** in individuals with the following clinical, laboratory, and imaging features.

Clinical features

- **Neurologic**
  - Peripheral spasticity, often more marked in lower than upper limbs
  - Truncal hypotonia
  - Global developmental delay
  - Intellectual disability (mild to severe)
  - Seizures
  - Ataxia
  - Nystagmus
  - Intention tremor
  - Dysmetria
  - Dystonia
  - Arthrogryposis/contractures
  - Kyphosis or scoliosis
- **Gastrointestinal**
  - Multiple intestinal atresia
  - Very early onset or treatment-refractory inflammatory bowel disease
  - Nonspecific gastrointestinal symptoms (vomiting, diarrhea, constipation, gastroesophageal reflux disease)
- **Combined immunodeficiency.** Recurrent otitis media; upper and lower respiratory tract infections

Laboratory features

- Increased fecal calprotectin
- Iron-deficient anemia
- Increased C-reactive protein
- Hypogammaglobulinemia: variable immunoglobulin defects
- Leukopenia: cellular defects ranging from severe T-cell lymphopenia (affecting CD8+ T cells more than CD4+ T cells), moderate B- and NK-cell lymphopenia, to normal lymphocyte counts

Imaging features

- **Brain MRI.** Hypomyelinating leukodystrophy characterized by abnormal white matter signal (diffuse T_2-weighted elevation of white matter signal typically involving the entire supratentorial white matter), often associated with a thin corpus callosum, cerebellar hypoplasia or atrophy, progressive supratentorial atrophy, brain stem atrophy (pons and medulla oblongata), and/or polymicrogyria

  Note: Perisylvian polymicrogyria has to date been reported only in individuals with the *PI4KA* variant p.Asp1854Asn [Pagnamenta et al 2015, Verdura et al 2021].

- **Gastrointestinal imaging.** Intestinal atresia of the small bowel and/or colon may be extensive, affecting the gastrointestinal tract from the pylorus to the anus.

- **Gastrointestinal endoscopic and histopathologic features.** Multiple abnormalities are noted including multiple distinct small lumens, lined by mucosa and surrounding muscularis mucosa, dilatated and narrowed lumen, with areas of mucosal atrophy and foci of acute neutrophilic mucosal inflammation. Endoscopic and histologic findings in individuals with inflammatory bowel disease include lymphoid mucosal infiltration; epithelial damage, ileal/general colonic inflammation; and histologic features of Crohn disease, ulcerative colitis, or unspecified inflammatory bowel disease.

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

Establishing the Diagnosis

The diagnosis of *PI4KA*-related disorder **is established** in a proband with suggestive clinical features, brain MRI features, and/or intestinal histology, and biallelic pathogenic (or likely pathogenic) variants in *PI4KA* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include any likely pathogenic variants. (2) Identification of biallelic *PI4KA* variants of uncertain significance (or of one known *PI4KA* pathogenic variant and one *PI4KA* variant of uncertain significance) does not establish or rule out the diagnosis. (3) Genetic analysis of *PI4KA* is complicated by the presence of two non-processed pseudogene partial copies, *PI4KAP1* and *PI4KAP2*, each located <1 Mb from *PI4KA*.

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) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other neurodevelopmental disorders are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic findings suggest the diagnosis of *PI4KA*-related disorder, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**.

- **Single-gene testing.** Sequence analysis of *PI4KA* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Typically, 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; however, to date, no deletions or duplications of *PI4KA* have been identified as a cause of this disorder.

  Note: Targeted analysis for the known founder variant c.4867T>G (p.Tyr1623Asp) can be performed first in individuals of Amish ancestry who present at birth with multiple intestinal atresia with or without immunodeficiency.

- **A multigene panel** that includes *PI4KA* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

Option 2

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.

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 *PI4KA*-Related Disorder

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
PI4KA	Sequence analysis [3]	100% [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [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 missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Pagnamenta et al [2015], Salter et al [2021], Verdura et al [2021], 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.

Clinical Characteristics

Clinical Description

PI4KA-related disorder is a clinically variable disorder characterized by neurologic dysfunction, gastrointestinal manifestations (intestinal atresia, inflammatory bowel disease), and immunodeficiency. Onset is typically antenatal or in early childhood. Four overlapping clinical phenotypes have been described:

- Hypomyelinating leukodystrophy with pyramidal features including lower limb spasticity, developmental delay, and intellectual disability, with or without inflammatory bowel disease. The most common presentation; neurologic features typically present in infancy or early childhood.
- Severe antenatal-onset neurologic disorder with arthrogryposis and structural brain anomalies (e.g., perisylvian polymicrogyria, cerebellar hypoplasia)
- Multiple intestinal atresia presenting shortly after birth, with or without immunodeficiency
- Rarely, later-onset pure hereditary spastic paraplegia

To date, 24 individuals have been identified with *PI4KA* pathogenic variants [Pagnamenta et al 2015, Salter et al 2021, Verdura et al 2021]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. *PI4KA*-Related Disorder: Frequency of Select Features

Feature		Proportion of Persons w/Feature [1]	Comment
Neurologic manifestations	Limb spasticity	16/16	6/16 w/lower limb spasticity; 10/16 w/upper & lower limb spasticity
	Developmental delay	14/16	
	Intellectual disability	15/16	
	Seizures	10/16	
	Ataxia	10/16	
	Nystagmus	8/16	
Brain MRI findings	Hypomyelinating leukodystrophy / delayed myelination	12/16	Includes only those who survived beyond neonatal period & underwent neuroimaging
	Cerebellar hypoplasia / atrophy	12/19	
	Dysplastic/thin corpus callosum	11/19	
	Perisylvian polymicrogyria	4/19	
Multiple intestinal atresia		5/24	
Inflammatory bowel disease		4/24	
Immunodeficiency		6/21	

1. Affected persons who died before a specific clinical sign would become apparent are not included in the table.

Neurologic Manifestations

Limb spasticity. All individuals with molecularly confirmed *PI4KA*-related disorder reported to date who survived beyond age one month developed or presented with limb spasticity. In all but two individuals this was most likely secondary to hypomyelinating leukodystrophy. The hypertonia and brisk reflexes are more marked in the lower than upper limbs, with six individuals having normal tone in the upper extremities at the time of examination. The limb spasticity is generally progressive, resulting in affected individuals requiring mobility aids for ambulation (if walking is achieved).

Two individuals with a pure hereditary spastic paraplegia phenotype and later onset of disease (age 2 years and 17 years) have been described [Verdura et al 2021].

Developmental delay has been reported in 14 individuals to date. One additional individual had delayed gross motor skills but normal language development. Of the 16 reported individuals who survived the neonatal period, nine achieved ambulation with or without support. Five had no expressive language at the time of examination (age range at examination: 3-13 years), four spoke several words (age range: 5-24 years) and four had delayed language development but were able to communicate in sentences of variable length (age range: 10-13 years).

Intellectual disability (ID). Of those who survived the neonatal period, ID has been reported in all except one individual. Of these 15 individuals, three had mild ID, five had moderate ID, and seven had severe ID.

Seizures are commonly reported; multiple seizure types are described (e.g., infantile spasms, tonic seizures, myoclonic, atypical absences). Seizure severity and response to treatment have been variable.

Additional neurologic features include ataxia, nystagmus, tremor, dysmetria, dystonia, and dysphagia. Six affected individuals displayed a tremor of the upper extremities, in three individuals this was described as an intention tremor. Dysmetria was present in three individuals. Dystonia was present in four individuals and most often affected the hands. Four individuals were reported to have dysphagia, two being mild and two requiring gastrostomy insertion.

Musculoskeletal complications include arthrogryposis (reported in 3 severely affected individuals), contractures, and kyphosis or scoliosis, reported in four individuals.

Gastrointestinal Disease

Intestinal atresia was the presenting feature in 13 Amish neonates (5 had molecular confirmation of the *PI4KA* variant p.Tyr1623Asp). The atresia was extensive and affected the gastrointestinal tract from pylorus to anus. Only one individual had sufficient patent bowel length to attempt resection at initial surgery, but ongoing inflammation, subsequent restenosis, and novel antral atresia prevented enteral feeding. The severity of the atresia was fatal in all affected neonates in the first month of life. Histologic evaluation from affected bowel sections revealed bowel inflammation and excessive luminal cell detritus, sections of "cord-like" bowel with no central lumen, and sections of "sieve-like" bowel with multiple, small interconnecting lumina. The surrounding muscular wall and ganglion cells appeared normal. Postmortem histologic findings described in an affected fetus were suggestive of an abnormality of epithelial organogenesis [Salter et al 2021].

Inflammatory bowel disease (IBD). The IBD phenotype includes IBD unclassified, ulcerative colitis, Crohn disease, variable pancolitis, and ileocolonic inflammation. The age of onset varies from infancy to young adulthood. To date, IBD has been reported in three individuals, one with very early-onset colitis diagnosed at age six weeks, one with severe treatment-refractory ulcerative colitis with onset at age 19 years, and one with steroid-dependent, stenosing-pattern Crohn disease diagnosed at age 21 years. An additional individual had long-standing iron deficiency anemia and markedly elevated fecal calprotectin, highly suggestive of undiagnosed inflammatory bowel disease. A further four individuals are reported to have bowel dysfunction, without any additional clinical details [Salter et al 2021, Verdura et al 2021].

Immunodeficiency. The immunologic phenotype of *PI4KA*-related disorder remains to be fully elucidated but appears to be a combined variable immunodeficiency comprising hypogammaglobulinemia or agammaglobulinemia and/or leukopenia [Salter et al 2021, Verdura et al 2021]. Cellular defects range from severe T-cell lymphopenia (affecting CD8+ T cells more than CD4+ T cells), to moderate B- and NK-cell lymphopenia, to normal lymphocyte counts. Immunoglobulin defects range from agammaglobulinemia to combined variable immunodeficiency affecting IgG and IgM (with normal IgA and IgE levels). Comprehensive immunophenotyping has only been undertaken in one infant with multiple intestinal atresia, with findings

consistent with a combined immunodeficiency reminiscent of that seen in *TTC7A*-related disease. Several other affected individuals have hypogammaglobulinemia with or without lymphopenia and/or a history of recurrent infections. One Amish neonate with multiple intestinal atresia had lymphopenia; full immunophenotyping was not performed and the child died before manifesting any symptoms of immunodeficiency.

One of the most severely affected living individuals with neurologic disease had combined immunodeficiency and at age ten years developed a lymphoma with adult-onset characteristics: grade 3A follicular non-Hodgkin lymphoma with bcl6-translocation and without a *MAP2K1* pathogenic variant. This individual was homozygous for *PI4KA* variant p.Asp1854Asn [Salter et al 2021].

Autoimmune neutropenia has been described in one individual [Verdura et al 2021].

Other

- Genitourinary anomalies (e.g., renal cysts, rectovaginal fistula, cryptorchidism, duplication of the collecting system)
- Nonspecific mild dysmorphic features
- Hearing loss described in two individuals; confirmed to be sensorineural in one
- Reduced visual acuity, optic nerve atrophy, strabismus, and/or ocular motor apraxia
- Juvenile idiopathic arthritis described in one individual (onset age: 9 years 8 months) [Verdura et al 2021]

Genotype-Phenotype Correlations

To date, the limited number of individuals described with *PI4KA*-related disorder prevents identification of conclusive phenotype-genotype correlations. However, some patterns have emerged:

- Currently, homozygosity for the **p.Tyr1623Asp** variant has only been described in individuals of Amish ancestry and results in a consistent phenotype of extensive multiple intestinal atresia. The families primarily chose palliative care and all affected neonates died within the first month of life. Comprehensive immunophenotyping was only carried out in one Amish infant, in whom findings were consistent with a combined immunodeficiency reminiscent of that seen in *TTC7A*-related disease.
- The **p.Asp1854Asn** variant, located within the PI4KA catalytic domain, was identified in three fetuses in *trans* with nonsense variant p.Arg796Ter. The phenotype included bilateral perisylvian polymicrogyria, cerebellar hypoplasia, arthrogryposis, and gastrointestinal histology consistent with an abnormality of epithelial organogenesis. Two Turkish individuals homozygous for *PI4KA* variant p.Asp1854Asn have subsequently been identified; both presented with severe neurologic disease and cortical gyral abnormalities. Functional studies suggest that this variant reduces the catalytic function of PI4KA to near-undetectable levels [Pagnamenta et al 2015, Salter et al 2021].

Prevalence

To date, 24 individuals with *PI4KA*-related disorder have been identified.

Within the Amish community, founder variant p.Tyr1623Asp is present at an allele frequency of 0.0006. To date, all identified carriers of Amish ancestry are from Ohio.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *PI4KA*.

Differential Diagnosis

The differential diagnosis of *PI4KA*-related disorder includes hypomyelinating leukodystrophies with early childhood onset (see Table 3 for a nonexhaustive list of hypomyelinating leukodystrophies) and *TTC7A*-related gastrointestinal defects and immunodeficiency syndrome.

Table 3. Genes of Interest in the Differential Diagnosis of *PI4KA*-Related Disorder

Gene	DiffDx Disorder	MOI	Key Features of DiffDx Disorder	
			Overlapping w/*PI4KA*-related disorder	Distinguishing from *PI4KA*-related disorder
HYCC1 (*FAM126A*)	Hypomyelination & congenital cataract	AR	Hypomyelinating leukodystrophy. Cerebellar signs are variably present.	Congenital cataracts variably present & psychomotor regression; peripheral neuropathy present in majority of affected persons. Polymicrogyria, IBD, & immunodeficiency have not been described.
PLP1	*PLP1* disorders incl Pelizaeus-Merzbacher disease & spastic paraplegia 2 (SPG2)	XL	Hypomyelinating leukodystrophy. Prominent cerebellar features. Variable age of onset w/spastic paraparesis described as SPG2 in those w/later onset.	Polymicrogyria, IBD, & immunodeficiency have not been described.
RARS1	*RARS1*-related hypomyelinating leukodystrophy (OMIM 616140)	AR	Hypomyelinating leukodystrophy. Severe refractory epilepsy / epileptic encephalopathy has been described.	Polymicrogyria, IBD & immunodeficiency have not been described.
TTC7A	Gastrointestinal defects & immunodeficiency syndrome (OMIM 243150)	AR	Heterogeneous intestinal & immunologic disease manifestations incl but not limited to multiple intestinal atresia, very early-onset IBD, & combined immunodeficiency	Neurologic anomalies have not been described.

AR = autosomal recessive; DiffDx = differential diagnosis; IBD = inflammatory bowel disease; MOI = mode of inheritance; XL = X-linked

Management

No clinical practice guidelines for *PI4KA*-related disorder have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *PI4KA*-related disorder, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with *PI4KA*-Related Disorder

System/Concern	Evaluation	Comment
Neurologic	• Neurologic eval for spasticity, cerebellar signs, & dystonia • Brain MRI • EEG (Seizures may be subclinical.)	To evaluate for hypomyelinating leukodystrophy, cerebellar hypoplasia/atrophy, thin or dysplastic corpus callosum, &/or perisylvian polymicrogyria

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Neurocognitive development	• Assessment by developmental pediatrician of developmental milestones, cognitive function, speech (communication) & feeding (swallowing) • Assessment by PT of functional disability & equipment needs	
Multiple intestinal atresia	• Pediatric gastroenterology assessment • Abdominal radiographs • Further abdominal imaging as needed	Plain abdominal radiographs may reveal dilatated loops, & MRI may identify multiple strictures. Exploratory laparoscopy or laparotomy will ultimately be required if clinical signs suggest severe obstruction.
Inflammatory bowel disease	• Eval by gastroenterologist • CBC ± inflammatory markers (CRP) • Fecal calprotectin • Endoscopic investigations as indicated by symptomatology	There should be a lower threshold for IBD investigation in persons w/moderate-to-severe DD/ID in whom clinical findings could be consistent w/IBD & communication of abdominal symptomology may be challenging.
Immunodeficiency	• Immunology assessment • Immunophenotyping incl lymphocyte subsets & immunoglobulins • Thymic ultrasound	• Recommended in all persons w/*PI4KA*-related disorder as signs & symptoms may be subtle or subclinical • Lymphopenia w/disruption of epithelial barrier results in ↑ risk for pathogenic proliferation & sepsis.
Genitourinary anomalies	Consider renal (& pelvic) imaging.	Assess for structural anomalies.
Hearing	Audiologic assessment	Assess for hearing loss.
Vision	Ophthalmologic assessment	Assess for nystagmus, ↓ visual acuity, optic nerve atrophy, strabismus, & ocular motor dyspraxia.
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *PI4KA*-related disorder 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; • Home nursing referral.	

CBC = complete blood count; CRP = C-reactive protein; DD = developmental delay; IBD = inflammatory bowel disease; ID = intellectual disability; MOI = mode of inheritance; PT = physical therapist
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Individualized care by a multidisciplinary team including a pediatrician, neurologist, gastroenterologist, clinical geneticist, physical therapist, occupational therapist, speech-language therapist, ophthalmologist, audiologist, and primary care physician is recommended.

Table 5. Treatment of Manifestations in Individuals with *PI4KA*-Related Disorder

Manifestation/Concern	Treatment	Considerations/Other
Limb spasticity & motor delays	• PT, OT, use of appropriate mobility aids • Medical mgmt may incl baclofen (incl intrathecal baclofen), diazepam, & intramuscular botulinum toxin.	Spasticity may → joint contractures & scoliosis.
Speech impairment	Speech-language therapy; use of communication aids (e.g., talker)	
Intellectual disability	Educational support	
Seizures	Use of standard anti-seizure medications; dependent on specific seizure type	
Dysphagia	• Speech-language therapy • Gastrostomy as needed	
Multiple intestinal atresia (MIA)	• There is no known treatment for MIA. • Parenteral nutrition • Intestinal transplant may be considered but is assoc w/ high mortality rate. • Since there is no established cure, quality of life is an important consideration. In children w/poor prognosis due to MIA, palliative approaches may be considered.	In one infant w/*PI4KA*-related MIA, IBD & small bowel stenosis recurred following surgical resection. [1, 2]
Inflammatory bowel disease (IBD)	• Standard anti-inflammatory medications & dietary mgmt established for treatment of IBD incl: immunosuppressants, steroids, & antibody therapies • Surgery may be required for treatment-resistant disease & to remove obstructions.	Note: Traditional IBD therapies do little to treat intestinal disease in *TTC7A*-related MIA or very early-onset IBD. [2]
Immunodeficiency	• Identification of the nature of immune dysfunction should inform clinical mgmt. • HSCT may correct immune defects & ↑ survival in persons w/severe immunodeficiency.	• Note: HSCT does not appear to improve phenotypes related to intestinal epithelial defects in *TTC7A*-related disease; graft-vs-host disease & sepsis are potential complications that may exacerbate intestinal disease. [2] • Decision making should also incl burden of treatment in children w/ID.
Hearing	Standard treatment for hearing issues	
Vision	Treatment per ophthalmologist	

ID = intellectual disability; HSCT = hematopoietic stem cell transplantation; OT = occupational therapy; PT = physical therapy
1. Note: Surgical bowel resections in individuals w/*TTC7A*-related MIA do not prevent the formation of new atresias.
2. Due to the phenotypic and mechanistic overlap between *TTC7A*- and *PI4KA*-related bowel disease, this information may be applicable to *PI4KA*-related disorder.

Surveillance

To date, no general surveillance guidelines have been developed; monitoring should be individualized.

Table 6. Recommended Surveillance for Individuals with *PI4KA*-Related Disorder

System/Concern	Evaluation	Frequency
Neurologic	Neurologic assessment to monitor for progression of limb spasticity, dysphagia, cerebellar signs, dystonia, & seizures	Annually & as indicated by symptomatology
Developmental delay / Intellectual disability	Assessment of developmental milestones by pediatrician	As indicated by clinical presentation

Table 6. continued from previous page.

System/Concern	Evaluation	Frequency
Inflammatory bowel disease	• Assessment by gastroenterologist for clinical signs of IBD, which may develop at any age. • Consider CBC & inflammatory markers, incl fecal calprotectin, CRP. • ± endoscopic investigations if clinical concerns or limited communication due to neurologic manifestations	Annually & as indicated by symptomatology
Immunology	Monitor for clinical signs of infection susceptibility & have a low threshold for repeating immunologic investigations, as immunodeficiency may be difficult to recognize at very early ages & may develop in later in life.	
Hearing	Audiology eval	Annually throughout childhood
Vision	Ophthalmology eval	

CBC = complete blood count; CRP = C-reactive protein; IBD = inflammatory bowel disease

Evaluation of Relatives at Risk

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

Therapies Under Investigation

Recent investigation of anti-apoptotic medications in laboratory and animal models of *TTC7A*-related gastrointestinal defects and immunodeficiency syndrome (OMIM 243150) suggest that leflunomide may be a potential treatment for bowel inflammation and stenosis in this condition [Jardine et al 2020]. Due to the phenotypic and mechanistic overlap between *TTC7A*- and *PI4KA*-related bowel disease, this treatment may be applicable to *PI4KA*-related disorder. To date, however, no data exist to support the efficacy of leflunomide in treating *PI4KA*-related bowel disease.

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

PI4KA-related disorder is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are presumed to be heterozygous for a *PI4KA* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *PI4KA* 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, the following possibilities should be considered:
  - 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].
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a *PI4KA* 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 inheriting neither of the familial pathogenic variants.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. Unless an affected individual's reproductive partner also has *PI4KA*-related disorder or is a carrier, offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *PI4KA*. (Note: Within the Amish community, the founder variant p.Tyr1623Asp is present at an allele frequency of 0.0006.)

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *PI4KA* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *PI4KA* 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 young adults who are carriers or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the *PI4KA* 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.

- **American Association on Intellectual and Developmental Disabilities (AAIDD)**
  Phone: 202-387-1968
  Fax: 202-387-2193
  www.aaidd.org

- **Medical Home Portal**
  Leukodystrophies
- **MedlinePlus**
  Intellectual Disability
- **National Institute of Neurological Disorders and Stroke (NINDS)**
  Phone: 800-352-9424
  Hereditary Spastic Paraplegia 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. PI4KA-Related Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
PI4KA	22q11.21	Phosphatidylinositol 4-kinase alpha	PI4KA	PI4KA

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 PI4KA-Related Disorder (View All in OMIM)

600286	PHOSPHATIDYLINOSITOL 4-KINASE, ALPHA; PI4KA
616531	NEURODEVELOPMENTAL DISORDER WITH SPASTICITY, HYPOMYELINATING LEUKODYSTROPHY, AND BRAIN ABNORMALITIES; NEDSPLB
619621	SPASTIC PARAPLEGIA 84, AUTOSOMAL RECESSIVE; SPG84
619708	GASTROINTESTINAL DEFECTS AND IMMUNODEFICIENCY SYNDROME 2; GIDID2

Molecular Pathogenesis

PI4KA encodes the kinase protein phosphatidylinositol 4-kinase alpha (PI4KIIIα), which is ubiquitously expressed and essential for the production of downstream phosphatidylinositides. Phosphatidylinositides (particularly phosphatidylinositol-4-phosphate, phosphatidylinositol-4,5-bisphosphate, and phosphatidylinositol-3,4,5-trisphosphate) undertake fundamental signaling roles in the plasma membrane and other organelles and have a key role in maintaining cell membrane integrity.

The function of PI4KIIIα depends on a functioning C-terminal catalytic domain and the ability to form a heterotrimeric complex with TTC7A or TTC7B and HYCC1 (FAM126A) to maintain PI4KIIIα stability. The complex is then localized to the cell membrane via another protein, EFR3.

The distribution of the TTC7A and TTC7B complexes varies across tissue types; TTC7A-containing complex is more prevalent in gastrointestinal tissues and TTC7B-containing complexes are more prevalent in neurologic tissues. Due to differences in binding sites between PI4KIIIα and TTC7A or TTC7B, *PI4KA* variants may affect these two complexes – and thus the corresponding tissues – differently, resulting in a predominantly gastrointestinal or neurologic phenotype.

The neurologic phenotype associated with the founder variant in the Amish community may be explained by its impact on PI4KIIIα's ability to form a complex with TTC7A and near-normal catalytic activity [Salter et al 2021].

Mechanism of disease causation. *PI4KA* pathogenic variants may cause disease by one of the following mechanisms:

- Nonsense-mediated mRNA decay and loss of functional protein
- Loss of PI4KIIIα catalytic activity due to variants that affect the catalytic domain
- Loss of protein stability due to inability to form a complex with TTC7A or TTC7B and HYCC1

To date, no affected individuals with biallelic *PI4KA* complete loss-of-function variants have been reported – indicating that complete loss of PI4KIIIα function may be incompatible with life.

***PI4KA*-specific laboratory technical considerations.** Genetic analysis of *PI4KA* is complicated by the presence of two non-processed pseudogene partial copies, *PI4KAP1* and *PI4KAP2*, each located within 1 Mb from *PI4KA*.

Table 7. Notable *PI4KA* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_058004.3 NP_477352.3	c.4867T>G	p.Tyr1623Asp	Assoc w/MIA; Amish founder variant [Salter et al 2021]
	c.5560G>A	p.Asp1854Asn	Recurrent variant resulting in significantly ↓ PI4KA enzymatic activity. To date, persons w/this variant appear to have early onset & severe neurologic disease [Pagnamenta et al 2015, Salter et al 2021].

MIA = multiple intestinal atresia
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.

Chapter Notes

Author Notes

Further information on our work with the Amish community can be found at Windows of Hope Project.

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References

Literature Cited

Jardine S, Anderson S, Babcock S, Leung G, Pan J, Dhingani N, Warner N, Guo C, Siddiqui I, Kotlarz D, Dowling JJ, Melnyk RA, Snapper SB, Klein C, Thiagarajah JR, Muise AM. Drug screen identifies leflunomide for treatment of inflammatory bowel disease caused by TTC7A deficiency. Gastroenterology. 2020;158:1000-15. PubMed PMID: 31743734.

Jónsson H, Sulem P, Kehr B, Kristmundsdottir S, Zink F, Hjartarson E, Hardarson MT, Hjorleifsson KE, Eggertsson HP, Gudjonsson SA, Ward LD, Arnadottir GA, Helgason EA, Helgason H, Gylfason A, Jonasdottir A, Jonasdottir A, Rafnar T, Frigge M, Stacey SN, Th Magnusson O, Thorsteinsdottir U, Masson G, Kong A, Halldorsson BV, Helgason A, Gudbjartsson DF, Stefansson K. Parental influence on human germline de novo mutations in 1,548 trios from Iceland. Nature. 2017;549:519-22. PubMed PMID: 28959963.

Pagnamenta AT, Howard MF, Wisniewski E, Popitsch N, Knight SJ, Keays DA, Quaghebeur G, Cox H, Cox P, Balla T, Taylor JC, Kini U. Germline recessive mutations in PI4KA are associated with perisylvian polymicrogyria, cerebellar hypoplasia and arthrogryposis. Hum Mol Genet. 2015;24:3732-41. PubMed PMID: 25855803.

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

Salter CG, Cai Y, Lo B, Helman G, Taylor H, McCartney A, Leslie JS, Accogoli A, Zara F, Traverso M, Fasham J, Lees JA, Ferla M, Chioza BA, Wenger O, Scott E, Cross HE, Crawford J, Warshawsky I, Keisling M, Agamanolis D, Melver CW, Cox H, Elawad M, Marton T, Wakeling M, Holzinger D, Tippelt S, Munteanu M, Valcheva D, Deal C, Van Meerbeke S, Vockley CW, Butte MJ, Acar U, van der Knaap MS, Korenke GC, Kotzaeridou U, Balla T, Simons C, Uhlig HH, Crosby AH, De Camilli P, Wolf NI, Baple EL. Biallelic PI4KA variants cause neurological, intestinal and immunological disease. Brain. 2021;144:3597-610. PubMed PMID: 34415310.

Stenson PD, Mort M, Ball EV, Chapman M, Evans K, Azevedo L, Hayden M, Heywood S, Millar DS, Phillips AD, Cooper DN. The Human Gene Mutation Database (HGMD®): optimizing its use in a clinical diagnostic or research setting. Hum Genet. 2020;139:1197-207. PubMed PMID: 32596782.

Verdura E, Rodríguez-Palmero A, Vélez-Santamaria V, Planas-Serra L, de la Calle I, Raspall-Chaure M, Roubertie A, Benkirane M, Saettini F, Pavinato L, Mandrile G, O'Leary M, O'Heir E, Barredo E, Chacón A, Michaud V, Goizet C, Ruiz M, Schlüter A, Rouvet I, Sala-Coromina J, Fossati C, Iascone M, Canonico F, Marcé-Grau A, de Souza P, Adams DR, Casasnovas C, Rehm HL, Mefford HC, González Gutierrez-Solana L, Brusco A, Koenig M, Macaya A, Pujol A. Biallelic PI4KA variants cause a novel neurodevelopmental syndrome with hypomyelinating leukodystrophy. Brain. 2021;144:2659-69. PubMed PMID: 34415322.

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