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KPTN-Related Disorder

Synonym: Macrocephaly, Autistic Features, Seizures, Developmental Delay (MASD) Syndrome

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Summary

Clinical characteristics

KPTN-related disorder is characterized by mild-to-profound intellectual disability, global developmental delay, neurobehavioral/psychiatric manifestations (anxiety, stereotypies, hyperactivity, repetitive speech, and impaired social communication), hypotonia, postnatal and progressive macrocephaly, and seizures. Generalized megalencephaly is often present on brain imaging. Some individuals have recurrent infections, conductive hearing impairment, strabismus, nystagmus, ketotic hypoglycemia, thyroid dysfunction, and/or mild skeletal manifestations.

Diagnosis/testing

The diagnosis of *KPTN*-related disorder is established in a proband with suggestive findings and biallelic pathogenic variants in *KPTN* identified by molecular genetic testing.

Management

Treatment of manifestations: Developmental and educational support; standard management for behavioral and psychiatric manifestations; standard treatment with anti-seizure medications by an experienced neurologist; pressure-equalizing tubes and/or tonsillectomy and/or adenoidectomy as needed for recurrent upper respiratory tract infections; standard treatment for ophthalmologic involvement; standard treatment for endocrine manifestations; treatment of skeletal manifestations per orthopedist; social work support and care coordination as needed.

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Surveillance: At each visit (at least annually), assess developmental progress, educational needs, mobility and self-help skills, head circumference, seizures, balance problems, oral apraxia, frequency and type of infections, musculoskeletal manifestations, and family needs; annual behavioral assessment; annual audiology evaluation; annual assessment for strabismus and vision deficits; assess for hypoglycemia in neonates and then at each visit or with intercurrent illness; educate parents and caregivers on symptoms of hypoglycemia; annual assessment of thyroid function.

Genetic counseling

KPTN-related disorder is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *KPTN* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Once the *KPTN* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and prenatal/preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

KPTN-related disorder **should be considered** in probands with the following clinical, laboratory, neuroimaging, and family history findings.

Clinical findings

- Mild-to-profound intellectual disability
- Developmental delay
- Postnatal and progressive macrocephaly (onset usually within the first year of life)
- Neurobehavioral/psychiatric manifestations associated with autism spectrum disorder (anxiety, stereotypies, hyperactivity, repetitive speech, impaired social communication)
- Neonatal/childhood hypotonia
- Seizures (generalized tonic-clonic, absence, focal, tonic seizures)
- Recurrent infections (lower respiratory tract infections, otitis media)
- Characteristic facial features in some individuals (frontal bossing, short downslanted palpebral fissures, hypertelorism, depressed nasal bridge, broad nasal tip, tall, broad chin, thick vermilion of the lower lip; see Figure 1)

Laboratory findings. Ketotic hypoglycemia, hypo- or hyperthyroidism

Neuroimaging. MRI/CT typically shows generalized megalencephaly.

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 *KPTN*-related disorder **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *KPTN* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of biallelic *KPTN* variants of uncertain

Figure 1. Photographs of individuals with *KPTN*-related disorder. Characteristic facial features include frontal bossing, downslanted palpebral fissures, hypertelorism, depressed nasal bridge, broad nasal tip, thick vermilion of the lower lip, and tall, broad chin.

Reprinted with permission from Baple et al [2014]

significance (or of one known *KPTN* pathogenic variant and one *KPTN* variant of uncertain significance) does not establish or rule out the diagnosis.

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

Note: Targeted analysis for the *KPTN* founder variants p.Ser259Ter and p.Met241_Gln246dup can be performed first in individuals of Amish and Mennonite ancestry (see Table 7).

Single-gene testing (sequence analysis of *KPTN*, followed by gene-targeted deletion/duplication analysis) is otherwise rarely useful and typically NOT recommended.

Option 1

An **intellectual disability, syndromic epilepsy, or macrocephaly multigene panel** that includes *KPTN* and other genes of interest (see Differential Diagnosis) may be considered 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 genes are likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. To date, the majority of *KPTN* pathogenic variants reported (e.g., missense, nonsense) are within the coding region or consensus splice sites and are likely to be identified on exome sequencing.

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

Table 1. Molecular Genetic Testing Used in *KPTN*-Related Disorder

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
KPTN	Sequence analysis [3]	100% [4]
	Gene-targeted deletion/duplication analysis [5]	None reported to date [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 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. 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. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.
6. To date, no large intragenic deletions/duplications have been reported in individuals with *KPTN*-related disorder.

Clinical Characteristics

Clinical Description

KPTN-related disorder is characterized by mild-to-profound intellectual disability, developmental delay, neurobehavioral/psychiatric manifestations (including anxiety and findings associated with autism spectrum disorder such as stereotypies, hyperactivity, repetitive speech, and impaired social communication), postnatal progressive macrocephaly, and seizures. To date, 54 individuals from 32 families have been identified with biallelic pathogenic variants in *KPTN* [Baple et al 2014, Pajusalu et al 2015, Lucena et al 2020, Pacio Miguez et al 2020, Thiffault et al 2020, Horn et al 2023, Levitin et al 2023, Liaqat et al 2023]. The following description of the phenotypic features associated with this condition is based on these reports.

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

Feature	% of Persons w/Feature	Comment
Intellectual disability	100%	Mild to profound
Developmental delay	93%	
Neurobehavioral/ psychiatric manifestations	84%	Anxiety, stereotypies, impaired social interactions, hyperactivity, repetitive speech
Hypotonia	55%	
Macrocephaly	49%	Postnatal & progressive w/onset in 1st year of life

Table 2. continued from previous page.

Feature	% of Persons w/Feature	Comment
Seizures	44%	Generalized tonic-clinic, absence, focal/complex partial
Characteristic craniofacial features	84%	84% of affected persons have frontal bossing & ≥1 additional feature (short downslanted palpebral fissures, hypertelorism, depressed nasal bridge, broad nasal tip, tall, broad chin, thick vermilion of lower lip).
Recurrent infections	27%	
Strabismus/nystagmus	12%	
Ketotic hypoglycemia	8%	

Baple et al [2014]; Pajusalu et al [2015]; Lucena et al [2020]; Pacio Miguez et al [2020]; Thiffault et al [2020]; Horn et al [2023]; Levitin et al [2023]; Liaqat et al [2023]; E Baple, unpublished data

Developmental delay is a variable feature. Early motor development is characterized by hypotonia in 55% of affected individuals (21/38), with delayed motor milestones in 60% (30/50). The average age at walking was two years (range: 1-5 years). Language development is highly variable and ranges from normal speech development to nonverbal (8/54 individuals were nonverbal); speech delay is observed in 93% (50/54).

Movement coordination abnormalities include balance problems and oral apraxia, which may lead to infant feeding difficulties.

Intellectual disability (ID) is seen in all affected individuals to date, although severity is highly variable, from mild to profound. Overall severity of ID, as reported by treating clinicians, is as follows: mild ID in approximately 30% (14/47) of affected individuals, moderate ID in 53% (25/47), severe ID in 15% (7/47), and profound ID in 2% (1/47). Generally, the severity of ID is related to the presence and control of seizures. Detailed psychometric tests were carried out in six Amish individuals and identified a moderate level of ID with impairment in all cognitive domains, except relative sparing of narrative memory function [Levitin et al 2023]. Dyslexia and dysgraphia have been reported in affected individuals.

Neurobehavioral/psychiatric manifestations are a common but variable feature. Anxiety was reported in 57% (25/44) of affected individuals, including panic attacks and phobias. Stereotypies were reported in 52% (24/46) of individuals, including hand flapping/clapping/rubbing, picking, head banging, and rocking. Impaired social interactions were reported in 50% (24/48) of individuals, hyperactivity in 31% (14/45), repetitive speech in 28% (11/39), and a single individual had a tic disorder.

Macrocephaly. An occipitofrontal circumference (OFC) more than two standard deviations (SD) above the mean was identified in 49% (23/47) of individuals with *KPTN*-related disorder, although 96% (45/47) had a larger-than-average OFC. OFC range is between 0.44 SD below the mean and 6.11 SD above the mean. Macrocephaly develops postnatally, within the first year of life. Data on birth OFC was available for 22/54 individuals; of these, only one individual was macrocephalic at birth, and 45% (10/22) had an OFC below average at birth. A single individual had macrocephaly associated with raised intracranial pressure requiring shunt insertion. The proportion of individuals with macrocephaly increases with age: 31% (5/16) between birth and age 6 years, and 53% (9/17) in adulthood. Delayed anterior fontanelle closure has been observed in four individuals. Wide metopic suture was reported in a single individual. Note: A single affected Amish individual was reported to have sagittal craniosynostosis [Baple et al 2014], but it has subsequently been shown that this was caused by a separate unrelated inherited condition in this family.

Epilepsy is reported in 44% (24/54) of individuals with *KPTN*-related disorder. Age of onset of seizures varies between ages three months and 32 years, with a mean age of seizure onset of 7.4 years. Seizure types include generalized tonic-clonic seizures (100%, 24 individuals), with additional absence (33%, 8 individuals), focal / impaired awareness (29%, 7 individuals), and tonic seizures (1 individual). Development of seizures and seizure

frequency appear to increase with age and correlate with severity of ID, with seizures often becoming refractory to multiple anti-seizure medications (ASMs). In four individuals generalized tonic-clonic seizures resolved in childhood or early adulthood, following optimization of ASMs (with ongoing absence seizures in one individual). No ASM has been identified as having greater or specific efficacy for seizure treatment in individuals with *KPTN*-related disorder. EEG findings in six individuals show similar features of mild generalized slowing indicative of diffuse cerebral dysfunction, with multifocal epileptiform discharges and frequent bifrontal spike and slow wave.

Neuroimaging (MRI/CT) is normal in more than 80% of individuals with *KPTN*-related disorder, aside from generalized megalencephaly, which was reported in 20/34 individuals with no structural brain abnormalities. Other subtle neuroanatomic changes in 14 individuals included: mild ventriculomegaly (5 individuals) associated with findings of generalized megalencephaly; pineal cyst (3 individuals); cavum of the septum pellucidum (2 individuals, 1 of whom also had a pineal cyst); nonspecific white matter hyperintensities (2 individuals); raised intracranial pressure (1 individual) requiring treatment with a shunt; calvarial thickening (1 individual) likely related to ASMs; optic nerve tortuosity (1 individual); calcified sylvian artery aneurysm (1 individual).

Additional craniofacial features reported in some individuals with *KPTN*-related disorder are subtle and include frontal bossing (84%, 38/45), scaphocephaly (15%, 6/39), short downslanted palpebral fissures (37%, 15/41), hypertelorism (33%, 14/42), depressed nasal bridge (17%, 8/48), broad nasal tip, thick vermilion of the lower lip, high-arched palate (8%, 4/48), tall, broad chin (40%, 17/43), and mild retrognathia (see Figure 1).

Recurrent infections, reported in 13/49 individuals, have included lower respiratory tract infections and otitis media. One individual was neutropenic, and another had immunoglobulin A deficiency.

Hearing loss. Conductive hearing loss has been reported in several individuals associated with otitis media.

Ophthalmic abnormalities. Strabismus and/or horizontal nystagmus were reported in 6/49 individuals. Esotropia, amblyopia, and severe astigmatism have also been reported.

Endocrine abnormalities. Ketotic hypoglycemia (often with intercurrent illness) was reported in 4/49 individuals. Additional endocrine abnormalities include hypo- or hyperthyroidism and hyperprolactinemia. Precocious puberty has been reported in three individuals (male and female).

Skeletal abnormalities include joint hypermobility, scoliosis, pectus excavatum/carinatum, short metacarpals, and fifth finger clinodactyly.

Other

- Hepatosplenomegaly (2 individuals)
- Hepatomegaly (1 individual)
- Splenomegaly (1 individual)

Prognosis. Based on current data, life span is not limited by this condition, as several adults have been reported; the oldest individual diagnosed with *KPTN*-related disorder was age 57 years at last assessment. Data on possible progression of behavior abnormalities or neurologic findings are still limited. It is notable that four of the 54 identified individuals are deceased, one at age nine years from status epilepticus and three individuals in their 3rd or 4th decade from accidental causes or infection. Since many adults with disabilities have not undergone advanced genetic testing, it is likely that adults with this condition are underrecognized and underreported.

Genotype-Phenotype Correlations

Although no specific genotype-phenotype correlations have been conclusively identified, biallelic predicted loss-of-function variants (e.g., frameshift, nonsense) appear to have a greater degree of severity of ID and increased frequency of seizures when compared with biallelic protein-altering variants (e.g., missense, inframe indels).

Prevalence

KPTN-related disorder is rare, and the prevalence is unknown. To date, 54 individuals from 32 families with *KPTN*-related disorder have been identified [Baple et al 2014, Pajusalu et al 2015, Lucena et al 2020, Pacio Miguez et al 2020, Thiffault et al 2020, Horn et al 2023, Levitin et al 2023, Liaqat et al 2023].

Two founder *KPTN* variants have been identified in the Ohio Amish community; p.Ser259Ter accounts for 82.1% of pathogenic variants and p.Met241_Gln246dup accounts for 17.9% of pathogenic variants in the Ohio Amish community, based on studies of >10,000 exomes and genomes from North American Amish and Mennonite individuals [Baple et al 2014]. To date, there have been 14 individuals with *KPTN*-related disorder identified within the Amish community (population size: approximately 340,000).

Pathogenic variant p.Met241_Gln246dup has been identified in several affected individuals from Europe and the United States and likely represents a European founder variant.

Pathogenic variant p.Ser200IlefsTer55 has been identified in affected individuals from Brazil, Spain, France, Germany, Ireland, and the United Kingdom.

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

Table 3. Disorders Associated with Macrocephaly and Intellectual Disability / Developmental Delay in the Differential Diagnosis of *KPTN*-Related Disorder

Gene	Disorder	MOI	Selected Features of Disorder	
			Overlapping w/*KPTN*-related disorder (in addition to macrocephaly [1] & ID/DD)	Distinguishing from *KPTN*-related disorder
CHD8	*CHD8*-related neurodevelopmental disorder w/overgrowth	AD	• ASD • Downslanted palpebral fissures • Seizures	• GI issues (e.g., recurrent constipation ± periods of diarrhea) • Developmental regression of social, speech, &/or motor skills in infancy & early childhood
FMR1	Fragile X syndrome [1] (See *FMR1* Disorders.)	XL	• ASD • Behavioral issues (e.g., hyperactivity) • Frontal bossing • Prominent jaw • Seizures	• Macroorchidism • Mitral valve prolapse

Table 3. continued from previous page.

Gene	Disorder	MOI	Selected Features of Disorder	
			Overlapping w/*KPTN*-related disorder (in addition to macrocephaly [1] & ID/DD)	Distinguishing from *KPTN*-related disorder
MTOR	Smith-Kingsmore syndrome (OMIM 616638)	AD	• Facial features (frontal bossing, hypertelorism, downslanted palpebral fissures) • Hypotonia • Seizures • Behavioral issues	Skin pigmentary abnormalities
NSD1	Sotos syndrome	AD	• Facial features (frontal bossing, pointed chin, downslanted palpebral fissures) • Hypotonia • Seizures • Ocular issues (incl strabismus & nystagmus) • Behavioral issues • Ventriculomegaly	• Generalized overgrowth • Additional syndromic features incl congenital heart disease, renal anomalies, & scoliosis
NFIX	*NFIX*-related Malan syndrome (OMIM 614753)	AD	• Behavioral issues (incl a specific anxious profile & ADHD) • Downslanted palpebral fissures • Hypotonia • Ocular issues (incl strabismus & nystagmus) • Ventriculomegaly	
PPP2R5D	*PPP2R5D*-related neurodevelopmental disorder	AD	• ASD • Hypertelorism • Seizures • Tone abnormalities	Hypotonic facies
PTEN	*PTEN* hamartoma tumor syndrome	AD	• ASD • Scoliosis • Pectus excavatum	• Cancer predisposition • Dermatologic features incl skin tags/papules • Hamartomatous tumors
	Autism/pervasive developmental disorder & macrocephaly (OMIM 605309)	AD	• ASD • Depressed nasal bridge • Frontal bossing • Hepatomegaly/splenomegaly • Recurrent infections	Hypogammaglobulinemia
SETD2	*SETD2*-related neurodevelopmental disorder ± macrocephaly/overgrowth (See *SETD2*-Related Neurodevelopmental Disorders.)	AD	• Anxiety • ASD • Downslanted palpebral fissures • Hypotonia • Seizures • Ventriculomegaly	• Chiari I malformation & syringomyelia • Polycystic ovarian syndrome
STRADA	Polyhydramnios megalencephaly & symptomatic epilepsy (OMIM 611087)	AR	• Facial features: frontal bossing, prominent chin, hypertelorism • Hypotonia • Seizures • Strabismus • Ventriculomegaly	

Table 3. continued from previous page.

Gene	Disorder	MOI	Selected Features of Disorder	
			Overlapping w/*KPTN*-related disorder (in addition to macrocephaly [1] & ID/DD)	Distinguishing from *KPTN*-related disorder
SZT2	Early infantile epileptic encephalopathy 18 (OMIM 615476)	AR	• Facial features: frontal bossing, hypertelorism, downslanted palpebral fissures, high-arched palate • Hypotonia • Persistent cavum septum pellucidum • Seizures • Ventriculomegaly	
TRIO	*TRIO*-related neurodevelopmental disorder	AD	• ASD • Downslanted palpebral fissures • Frontal bossing • Seizures • Stereotypies	Poor growth

AD = autosomal dominant; ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; DD = developmental delay; ID = intellectual disability; GI = gastrointestinal; MOI = mode of inheritance; XL = X-linked
1. Fragile X syndrome is associated with a large occipitofrontal head circumference (>50th percentile).

Management

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

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *KPTN*-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. *KPTN*-Related Disorder: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • To incl assessment for balance problems & oral apraxia • Eval for early intervention / special education
Neurobehavioral/ Psychiatric	Neuropsychiatric eval	For persons age >12 months: screening for neurobehavioral/psychiatric manifestations incl anxiety, stereotypies, impaired social interaction, & hyperactivity
Neurologic	Assessment of head circumference	
	Neurologic eval	Low threshold for EEG if seizures are a concern.
Immunology	Assessment for recurrent infections incl otitis media & respiratory tract infections	
Hearing	Audiology eval	Assessment for recurrent otitis & conductive hearing impairment
Ophthalmologic	Eval by ophthalmologist	Assessment for strabismus, nystagmus, & amblyopia

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Endocrine	• Assessment for hypoglycemia in neonatal period, in infancy, & w/ intercurrent illness • Assessment for hypo- & hyperthyroidism & hyperprolactinemia	
Skeletal manifestations	Assessment for joint hypermobility, scoliosis, & chest wall deformity	
Genetic counseling	By genetics professionals [1]	To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of *KPTN*-related disorder to facilitate medical & personal decision making
Family support & resources	By clinicians, wider care team, & family support organizations	Assessment of family & social structure to determine need for: • Community or online resources such as Parent to Parent • Social work involvement for parental support • Home nursing referral

MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is currently no cure for *KPTN*-related disorder. Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 5).

Table 5. *KPTN*-Related Disorder: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability / Neurobehavioral issues	See Developmental Delay / Intellectual Disability Management Issues.	
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [1]
Chronic otitis media / Recurrent infections	Referral to otolaryngologist for consideration of pressure-equalizing tubes &/or tonsillectomy/ adenoidectomy	
Ophthalmologic involvement	Standard treatment per pediatric ophthalmologist	
Endocrine manifestations	Standard treatment of hypoglycemia, hypo- or hyperthyroidism, & hyperprolactinemia	
Skeletal manifestations	Treatment per orthopedist	

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
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 • Consider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication

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.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Neurobehavioral/Psychiatric Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Concerns about destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

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

Table 6. *KPTN*-Related Disorder: Recommended Surveillance

System/Concern	Evaluation	Frequency
Development	• Monitoring of developmental progress & educational needs • Physical medicine, OT/PT assessment of mobility, self-help skills	At each visit (annually or as needed)
Neurobehavioral/ Psychiatric	Assessment for anxiety, stereotypies, impaired social interaction, hyperactivity, & repetitive speech	Annually or as needed

Table 6. continued from previous page.

System/Concern	Evaluation	Frequency
Neurologic	Assess head circumference.	At each visit throughout childhood & adolescence
	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations such as seizures, balance problems, & oral apraxia.	At each visit (annually or as needed)
Immunology	Assess frequency & type of infections.	
Hearing	Audiology eval	Annually or as needed
Ophthalmologic	Assessment for strabismus & vision deficits	Annually
Endocrine	Monitor for hypoglycemia.	• Monitor in neonatal period & then at each visit & during intercurrent illness. • Education on symptoms of hypoglycemia for parents/caregivers
	Assess thyroid function w/thyroxine & TSH.	Annually
Musculoskeletal	Assess for joint hypermobility, chest wall deformity, & scoliosis.	At each visit (annually or as needed)
Family/Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	At each visit

OT = occupational therapy; PT = physical therapy; TSH = thyroid-stimulating hormone

Evaluation of Relatives at Risk

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

Therapies Under Investigation

Current studies of the efficacy of mTOR inhibitors are under way in *KPTN*-related disorder mouse models. Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

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

Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for a *KPTN* pathogenic variant.

- Molecular genetic testing is recommended for the parents of the proband to confirm that both parents are heterozygous for a *KPTN* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder, although increased head circumference (above the mean for age and sex) is commonly observed.

Sibs of a proband

- If both parents are known to be heterozygous for a *KPTN* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder, although increased head circumference (above the mean for age and sex) is commonly observed.

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

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

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *KPTN* 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.
- Carrier testing should be considered for the reproductive partners of known carriers, particularly if both partners are of the same ancestry. Founder variants have been identified in the Ohio Amish community (see Table 7).

Prenatal Testing and Preimplantation Genetic Testing

Once the *KPTN* 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.

- **KPTN Alliance**
  Email: KPTNalliance@gmail.com
  kptnalliance.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. KPTN-Related Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
KPTN	19q13.32	KICSTOR complex protein kaptin	KPTN	KPTN

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 KPTN-Related Disorder (View All in OMIM)

615620	KAPTIN; KPTN
615637	INTELLECTUAL DEVELOPMENTAL DISORDER, AUTOSOMAL RECESSIVE 41; MRT41

Molecular Pathogenesis

KPTN encodes KICSTOR complex protein kaptin (kaptin), a core component of the KICSTOR complex alongside three other proteins, ITFG2 (KICSTOR complex protein ITFG2; also called integrin-alpha FG-GAP repeat-containing protein 2), C12orf66 (KICSTOR subunit 2; also called KICSTOR complex protein C12orf66 or chromosome 12 open reading frame 66), and SZT2 (KICSTOR complex protein SZT2; also called seizure threshold 2 protein homolog) [Wolfson et al 2017]. Kaptin was identified as a key regulator of the mTORC1 (the mechanistic target of rapamycin complex 1) pathway. The KICSTOR complex recruits GATOR1 (GAP activity toward Rags 1) to the lysosomal membrane, which modulates downstream mTORC1 signaling in response to cellular amino acid levels. The serine/threonine protein kinase mTORC1 is within the canonical phosphoinositide 3-kinase (PI3K)-AKT-mTOR signaling cascade. Importantly, loss of KICSTOR components has been shown to inhibit GATOR1 recruitment and increase mTORC1 signaling even under unfavorable metabolic conditions (i.e., when cellular amino acid and nutrient levels are low). Several neurodevelopmental disorders have been associated with hyperactivation of mTORC1, termed "mTORopathies" (e.g., *PTEN* hamartoma tumor syndrome, tuberous sclerosis complex, and *STRADA*-related disorders).

Further studies of *Kptn*$^{-/-}$ mice and human induced pluripotent stem cell (iPSC) models support the pathogenic mechanism of *KPTN*-related disorder as likely resulting from hyperactivated mTOR signaling. Levels of phosphorylation of ribosomal protein S6, a downstream target of mTORC1 strongly linked to mTOR pathway activation, were significantly increased in *Kptn*$^{-/-}$ mice, and treatment with the mTOR inhibitor rapamycin significantly reduced this increase in phosphorylation of S6 and levels of mTOR activation [Levitin et al 2023]. Transcriptomic studies of both *Kptn*$^{-/-}$ mouse and human iPSC models also identified significant dysregulation of gene expression of mTOR pathway regulators [Levitin et al 2023]. These findings are consistent with the

proposed role of kaptin as a negative regulator of mTORC1 activity and confirm *KPTN*-related disorder as an mTORopathy.

Mechanism of disease causation. Loss of function

Table 7. *KPTN* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_007059.3 NP_008990.2	c.714_731dup18	p.Met241_Gln246dup	Founder variant in Ohio Amish community [Baple et al 2014]; recurrent variant in persons of European ancestry (See Prevalence.)
	c.776C>A	p.Ser259Ter	Founder variant in Ohio Amish community [Baple et al 2014] (See Prevalence.)
	c.597_598dup	p.Ser200IlefsTer55	Recurrent variant in persons from Brazil, Spain, France, Germany, Ireland, & the UK (See Prevalence.)

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 and Mennonite communities can be found at Windows of Hope Project.

Prof Emma Baple and Dr Lettie Rawlins continue to be involved in clinical studies of *KPTN*-related disorder and in supporting the work of the KPTN Alliance.

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