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CASK Disorders

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Summary

Clinical characteristics

CASK disorders include a spectrum of phenotypes in both females and males. Two main types of clinical presentation are seen:

- Microcephaly with pontine and cerebellar hypoplasia (MICPCH), generally associated with pathogenic loss-of-function variants in *CASK*
- X-linked intellectual disability (XLID) with or without nystagmus, generally associated with hypomorphic *CASK* pathogenic variants

MICPCH is typically seen in females with moderate-to-severe intellectual disability, progressive microcephaly with or without ophthalmologic anomalies, and sensorineural hearing loss. Most are able to sit independently; 20%-25% attain the ability to walk; language is nearly absent in most. Neurologic features may include axial hypotonia, hypertonia/spasticity of the extremities, and dystonia or other movement disorders. Nearly 40% have seizures by age ten years. Behaviors may include sleep disturbances, hand stereotypies, and self biting.

MICPCH in males may occur with or without severe epileptic encephalopathy in addition to severe-to-profound developmental delay. When seizures are present they occur early and may be intractable.

In individuals and families with milder (i.e., hypomorphic) pathogenic variants, the clinical phenotype is usually that of XLID with or without nystagmus and additional clinical features. Males have mild-to-severe intellectual disability, with or without nystagmus and other ocular features. Females typically have normal intelligence with some displaying mild-to-severe intellectual disability with or without ocular features.

Diagnosis/testing

The diagnosis of a CASK disorder is established in a female who is heterozygous for a CASK pathogenic variant and in a male who is hemizygous for a CASK pathogenic variant on molecular genetic testing. Rarely, affected males have a mosaic pathogenic variant.

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Management

Treatment of manifestations: Treatment is symptomatic and includes standard management of developmental delay and intellectual disability issues; medication for seizures; nutritional support; use of physiotherapy; and treatment of abnormal vision or hearing loss.

Genetic counseling

CASK disorders are inherited in an X-linked manner. Risk to the family members of a proband with a *CASK* disorder depends on the phenotype (i.e., MICPCH or XLID ± nystagmus) in the proband.

- **MICPCH.** Most affected females and males represent simplex cases (i.e., the only affected family member) and have the disorder as the result of a *de novo CASK* pathogenic variant. Because heterozygous females manifest the phenotype, an asymptomatic mother is unlikely to be heterozygous for the *CASK* pathogenic variant. If a proband represents a simplex case, the recurrence risk to sibs appears to be low but greater than that of the general population because of the possibility of parental germline mosaicism.
- **XLID ± nystagmus.** The father of a male with a *CASK* disorder will not have the disorder nor will he be hemizygous for the *CASK* pathogenic variant. If a male is the only affected family member, the mother may be a heterozygote or the affected male may have a *de novo* pathogenic variant. In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote. If the mother of the proband has a *CASK* pathogenic variant, the chance of transmitting it in each pregnancy is 50%: males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will typically be asymptomatic but may have a range of manifestations. If the *CASK* pathogenic variant cannot be detected in maternal leukocyte DNA, the risk to sibs is greater than that of the general population because of the possibility of parental germline mosaicism.

Once the *CASK* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for a *CASK* disorder are possible.

GeneReview Scope

CASK Disorders: Included Phenotypes [1]
• Intellectual disability and microcephaly with pontine and cerebellar hypoplasia (MICPCH) • X-linked intellectual disability (XLID) with or without nystagmus

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

Diagnosis

CASK disorders are associated with a wide phenotypic spectrum ranging from mild-to-severe intellectual disability with or without nystagmus to moderate-to-profound intellectual disability and progressive microcephaly with pontine and cerebellar hypoplasia (MICPCH), often associated with seizures. *CASK* disorders are X-linked and more commonly reported in females than in males. MICPCH in females is the most common phenotype to date.

Suggestive Findings

CASK disorders **should be considered** in individuals with intellectual disability of any degree and any of the following additional findings:

- Progressive microcephaly up to -10 SD
- Pontine and cerebellar hypoplasia

- Hypotonia, hypertonia, or a combination of both (central hypotonia and hypertonia of extremities)
- Seizures (including early and intractable seizures comprising Ohtahara syndrome, West syndrome, or myoclonic epilepsy)
- Nystagmus, strabismus, optic nerve hypoplasia, and/or retinopathy
- Sensorineural hearing loss
- Short stature

Establishing the Diagnosis

The diagnosis of a *CASK* disorder **is established** in a female who is heterozygous for a *CASK* pathogenic variant and in a male who is hemizygous for a *CASK* pathogenic (or likely pathogenic) variant (see Table 1).

Note: (1) Rarely, affected males have a mosaic pathogenic variant. (2) Per ACMG 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. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants.

Because the phenotype of *CASK* disorders is often indistinguishable from many other inherited disorders with intellectual disability, microcephaly, and/or pontine and cerebellar hypoplasia, recommended molecular genetic testing approaches include use of a **multigene panel** or **comprehensive genomic testing**.

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

- **A multigene panel** for intellectual disability or brain malformation or specialized for pontocerebellar hypoplasia that includes *CASK* 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 this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

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

- **Comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is another good option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

  Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/ duplication analysis (which may include **exome array** or **chromosomal microarray analysis** to detect exon and whole-gene deletions or duplications).

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

Note: (1) In a few males, *CASK* rearrangements in the hemizygous state as well as *CASK* rearrangements and a deletion-insertion variant in the mosaic state have been reported [Saitsu et al 2012, Moog et al 2015, Hayashi et

al 2017]. (2) Karyotype analysis may be appropriate when sequence analysis and deletion/duplication analysis do not identify a pathogenic variant and the suspicion of a *CASK* disorder is high. Two females with a balanced Xp inversion disrupting *CASK* have been observed [Najm et al 2008; K Kutsche, unpublished].

Table 1. Molecular Genetic Testing Used in *CASK* Disorders

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
CASK	Sequence analysis [3]	~70% [4, 5]
	Gene-targeted deletion/duplication analysis [6]	~30% [4, 5, 6]
	CMA [7]	~28% [4, 7]
	Karyotype	Rare [8]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Percentages are based on female probands. Surviving male probands are more likely to have a variant detected by sequence analysis (see Genotype-Phenotype Correlations).
6. 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. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole gene; however, breakpoints of large deletions and/or deletion of adjacent genes (e.g., those described by Moog et al [2011], Burglen et al [2012], Hayashi et al [2012], Hayashi et al [2017]) may not be detected by these methods.
7. Chromosomal microarray analysis (CMA) uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *CASK*) that cannot be detected by sequence analysis. Most reported deletions/duplications in *CASK* are large enough to be detected by CMA. The ability to determine the size of the deletion/duplication depends on the type of microarray used and the density of probes in the Xp11.4 region. CMA designs in current clinical use target the Xp11.4 region.
8. Two females with a balanced Xp inversion disrupting *CASK* have been observed [Najm et al 2008; K Kutsche, unpublished].

Clinical Characteristics

Clinical Description

CASK disorders are more commonly reported in females and include a spectrum of phenotypes that differs in females and males:

- Females typically have moderate-to-severe intellectual disability and in most individuals, progressive microcephaly with pontine and cerebellar hypoplasia (MICPCH). Possible findings are ophthalmologic anomalies and sensorineural hearing loss. Females who are relatives of males with the X-linked intellectual disability (XLID) ± nystagmus phenotype may rarely present with a mild-to-severe intellectual disability phenotype.
- In males the spectrum is broad, ranging from severe (intellectual disability and MICPCH, or early-infantile epileptic encephalopathy [Ohtahara syndrome, West syndrome, or early myoclonic epilepsy]) to mild (XLID ± nystagmus and additional clinical features) [Moog et al 2015].

To date, 130 individuals (45 males and 85 females) have been identified with a pathogenic variant in *CASK* [Moog et al 2011, Burglen et al 2012, Hayashi et al 2012, Takanashi et al 2012, Moog et al 2015, Dunn et al 2017, Hayashi et al 2017, Muthusamy et al 2017, Cristofoli et al 2018, Rama Devi et al 2019]. The following description of the phenotypic features associated with this condition is based on these reports.

Females

A total of 85 females with MICPCH have been reported to date, the eldest of whom is age 25 years. The following information about the natural history is based on the recent reviews of Moog et al [2011], Burglen et al [2012], Hayashi et al [2012], and Takanashi et al [2012] unless otherwise noted.

Microcephaly with Pontine and Cerebellar Hypoplasia (MICPCH)

Head circumference. At birth the occipital frontal circumference (OFC) is in the normal or low-normal range in approximately two thirds of affected females; the others show microcephaly (OFC < -2 SD). Microcephaly invariably becomes severe (OFC -3.5 to -10 SD) during the first year, and usually during the first four months of life.

Developmental delay / intellectual disability (DD/ID). Affected females acquire head control and make eye contact in the range of two to 24 months. Most affected females are able to sit independently between seven and 36 months; only 20%-25% attain the ability to walk (between 18 and 72 months).

Language is nearly absent in most; some utter words. One individual could say two-word sentences. Intellectual development is severely impaired in nearly all affected females, with a few showing moderate ID.

The behavioral phenotype may include sleep disturbances, hand stereotypies, and self biting.

Neurologic features include (axial) hypotonia, hypertonia of the extremities (possibly progressing to spasticity), and dystonia or other movement disorders. Seizures of various types are observed in about 40%; onset is between birth and age ten years.

The severity of the pontocerebellar hypoplasia observed on MRI is not of prognostic value [Moog et al 2011].

MRI findings

- Pontine and cerebellar hypoplasia with diffuse mild-to-severe hypoplasia of the cerebellum affecting the hemispheres and vermis proportionally [Moog et al 2011, Burglen et al 2012, Hayashi et al 2012, Takanashi et al 2012] (Figure 1). Pons and cerebellum have been reported to have a normal appearance in two females with progressive microcephaly, ID, and a pathogenic variant in *CASK* [Cristofoli et al 2018].
  - Cerebellar hemispheres can be affected asymmetrically.
  - Pontine hypoplasia may be mild to severe with relative sparing of the pontine bulging.
- Normal- or low normal-sized corpus callosum with low cerebrum / corpus callosum ratio [Takanashi et al 2010]
- Associated MRI finding: mildly reduced number and complexity of gyri in the frontal region of the cerebral cortex and mild dilatation of the lateral ventricles [Moog et al 2011]

Other findings

- Birth length is normal. Short stature is common by age four years [Moog et al 2011, Takanashi et al 2012].
- Scoliosis is frequently observed.
- Various ophthalmologic findings can be observed, in particular optic nerve hypoplasia, retinopathy, nystagmus, and strabismus [LaConte et al 2019].
- Approximately 28% of affected females have sensorineural hearing loss [Moog et al 2011, Burglen et al 2012, Takanashi et al 2012].
- Congenital visceral anomalies (e.g., renal/urologic or cardiac anomalies) are rarely seen; no particular anomaly occurs recurrently.
- Recent reviews suggest a facial phenotype consisting of well-drawn arched eyebrows, a broad nasal bridge and tip, small or short nose, long philtrum or protruding maxilla, small chin, and large ears.

Mortality in affected females has not been reported.

X-Linked Intellectual Disability (XLID) ± Nystagmus

Clinical findings in the majority of heterozygotes (typically identified as relatives of more severely affected males):

- Normal intelligence; mild-to-severe ID in some females only
- Normal-to-mild ocular findings including congenital nystagmus and strabismus
- No additional neurologic signs besides mild tremor or absence seizures
- MRI finding: normal or mainly unknown

Males

A total of 45 males from birth to age 59 years with a pathogenic *CASK* variant have been described [Moog et al 2015, Dunn et al 2017, Hayashi et al 2017, Muthusamy et al 2017, Rama Devi et al 2019].

The phenotype in males represents a clinical continuum from the severe to the mild end of the spectrum and can be classified into three phenotypic groups [Moog et al 2015].

MICPCH with Severe Epileptic Encephalopathy

Head circumference. At birth, the OFC was (low) normal in half of the individuals. The other half had primary microcephaly (OFC <-2 SD). Mild-to-severe postnatal microcephaly evolved rapidly during the first months (OFC -2.7 to -9 SD).

DD/ID. All affected males had severe-to-profound DD or no development at all.

Neurologic features include early and intractable seizures (Ohtahara syndrome [Saitsu et al 2012], West syndrome [Takanashi et al 2012], myoclonic epilepsy [Nakamura et al 2014]), burst suppression and spasms [Moog et al 2015], and hyperkinesia [Rama Devi et al 2019].

MRI findings

- Typically severe diffuse pontocerebellar hypoplasia
- Simplified gyri, cortical atrophy, and hypomyelination may be also observed.

Other findings

- Multiple (minor) anomalies have been reported [Burglen et al 2012, Saitsu et al 2012, Moog et al 2015].
- Septal heart defects, tetralogy of Fallot and hydronephrosis can be observed [Nakamura et al 2014, Moog et al 2015].

Mortality. Males with this phenotype may have perinatal or early lethality. One affected male died at age two months [Rama Devi et al 2019], one at seven months, and another at 21 months [Moog et al 2015].

MICPCH with Severe Developmental Disorder

MICPCH in combination with a severe developmental disorder but without severe epilepsy has been reported in six males. The phenotype of male individuals in this group is comparable to MICPCH in females [Moog et al 2015, Hayashi et al 2017]:

- **Head circumference**. Postnatal microcephaly
- **DD/ID.** Severe
- **Neurologic features.** Mild ataxia reported in one male, dystonia/dyskinesia in another male. No seizures.
- **MRI findings.** Variable degree of diffuse pontocerebellar hypoplasia
- **Other findings.** Nystagmus

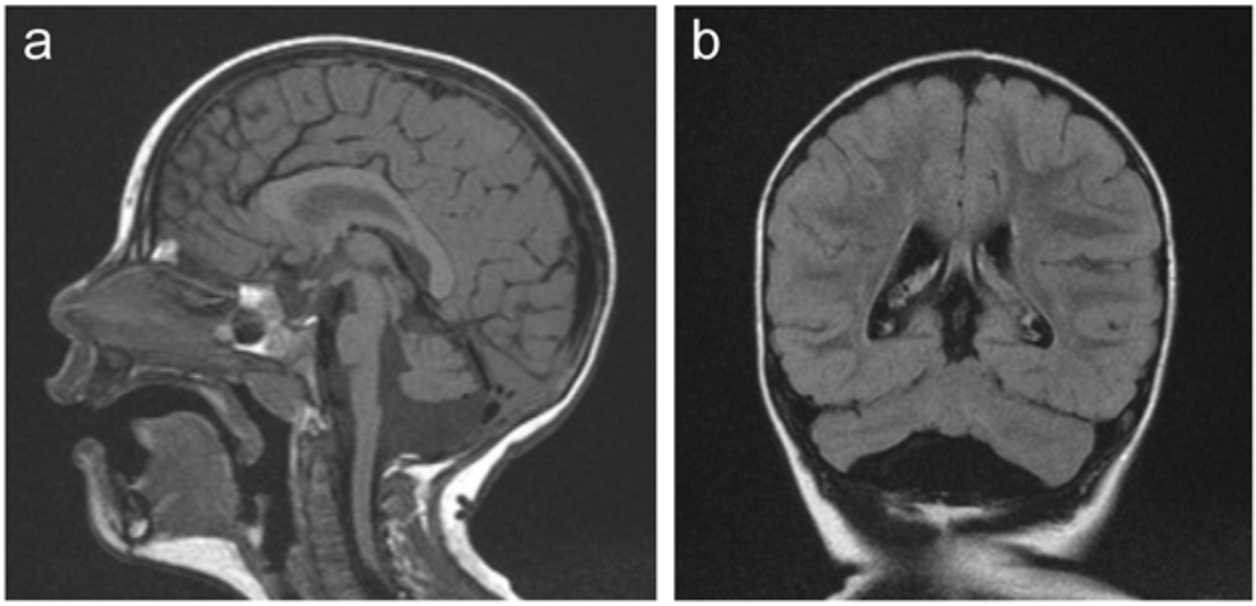

Figure 1. MRI of the brain of a girl age 2.5 years with MICPCH and a heterozygous *CASK* pathogenic variant

a. Sagittal image showing mild pontocerebellar hypoplasia with sparing of pontine bulging. The corpus callosum is normal.

b. Coronal image showing mild cerebellar hypoplasia affecting the vermis and hemispheres proportionally ("butterfly" appearance)

- **Mortality.** One affected male died at age two weeks.

X-Linked Intellectual Disability (XLID) ± Nystagmus

Mild-to-severe XLID with or without nystagmus and/or other anomalies have been reported in a total of 29 males [Moog et al 2015, Dunn et al 2017, Hayashi et al 2017].

- DD / mild-to-severe ID
- Seizures/epilepsy
- Congenital nystagmus and other eye findings including strabismus and mild pallor of the optic disc

Brain MRI has been reported in a minority of individuals only and did not show pontocerebellar hypoplasia.

Other findings include microcephaly, hypotonia, autism spectrum disorder, behavioral problems, tremor and unsteady gait, sensorineural hearing loss, feeding difficulties, constipation, short stature, cryptorchidism, and gastrointestinal and gastroesophageal complications.

Genotype-Phenotype Correlations

In females, microcephaly with pontine and cerebellar hypoplasia (MICPCH) is typically associated with heterozygous *CASK* pathogenic loss-of-function variants [Moog et al 2011, Burglen et al 2012, Hayashi et al 2012, Takanashi et al 2012, Hayashi et al 2017]. The X-linked intellectual disability (XLID) with or without nystagmus phenotype in females is typically associated with *CASK* hypomorphic pathogenic variants.

In males, the three clinically distinguishable groups are associated with different classes of pathogenic *CASK* variants [Moog et al 2015]:

- In males with MICPCH with severe epileptic encephalopathy, the most severe phenotype, the majority of *CASK* pathogenic variants are germline loss-of-function alterations.

- In the group with MICPCH, males are somatic mosaics of a *CASK* loss-of-function variant or carry partly penetrant variants in the hemizygous state.
- The largest group of males with XLID with or without nystagmus typically have *CASK* hypomorphic pathogenic variants, including missense and splice variants [Moog et al 2015].

Penetrance

Penetrance for the MICPCH phenotype (associated with the heterozygous *CASK* pathogenic loss-of-function variants) appears to be complete in the female individuals reported to date.

Penetrance of *CASK* pathogenic variants appears to be complete in males. In males with mosaic *CASK* pathogenic variants the level of somatic mosaicism may be one factor that determines clinical variability. In females heterozygous for a pathogenic hypomorphic *CASK* variant penetrance is incomplete with high clinical variability.

Nomenclature

An FG syndrome (FGS)-like phenotype has been suggested as a distinct *CASK*-related phenotype based on findings in affected males from two families [Piluso et al 2009, Dunn et al 2017]. However, with the exception of FGS1 caused by a recurrent *MED12* pathogenic variant (see *MED12*-Related Disorders), FGS is not clearly defined and FGS4 is not discernible as phenotype. Thus, it seems more appropriate to subsume the phenotype described in these families under XLID with or without nystagmus.

Prevalence

The prevalence of *CASK* disorders is unknown. At least 130 individuals (45 males and 85 females) with a *CASK* pathogenic variant have been reported.

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

Intellectual Disability and Microcephaly with Pontine and Cerebellar Hypoplasia (MICPCH)

Table 2. Genes of Interest in the Differential Diagnosis of MICPCH

Gene(s)	Disorder	MOI	Clinical Features	Brain MRI Findings
SEPSECS *TSEN15* *TSEN2* *TSEN34* *VPS53* *TSEN54*	PCH2	AR	• Generalized clonus ("jitteriness") w/lack of voluntary motor development & later development of chorea & spasticity, impaired swallowing, & (in some) epilepsy • Persons w/PCH2 usually live into childhood.	In persons w/PCH2/PCH4: • Cerebellar hemispheres are more affected than the vermis, → "dragonfly" appearance in coronal images. [2] • Pontine hypoplasia is more severe than in females w/MICPCH. • Corpus callosum is often thin & hypoplastic.
TSEN54	PCH4	AR	Polyhydramnios, contractures, severe generalized clonus, & central respiratory failure usually → neonatal death	

Table 2. continued from previous page.

Gene(s)	Disorder	MOI	Clinical Features	Brain MRI Findings
ARX *STXBP1* (>80 genes) [1]	Ohtahara syndrome	XL AD	Early-infantile epileptic encephalopathy w/suppression burst	May or may not be assoc w/abnormalities on brain MRI

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; PCH = pontocerebellar hypoplasia; XL = X-linked
1. See Phenotypic Series: Early Infantile Epileptic Encephalopathy for genes associated with this phenotype in OMIM.
2. In *CASK* disorders, a "butterfly" pattern is visible that results from diffuse hypoplasia of the hemispheres and vermis.

X-Linked Intellectual Disability (XLID) ± Nystagmus

XLID with nystagmus may be seen in the X-linked disorder Allan-Herndon-Dudley syndrome caused by hemizygous pathogenic variants in *SLC16A2*. These individuals show severe ID, microcephaly, neurologic features (spasticity, dystonia, and ataxia), scoliosis, large ears, and other dysmorphisms. Nystagmus is reported in some individuals.

XLID without nystagmus has a broad differential diagnosis as a multitude of genes are known to cause nonsyndromic and syndromic XLID (see OMIM Phenotypic Series: Nonsyndromic XLID and Syndromic XLID).

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with a *CASK* disorder, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with *CASK* Disorders

System/Concern	Evaluation	Comment
Neurologic	Neurologic eval	To incl brain MRI & EEG if not already done
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech/language eval • Eval for early intervention / special education
Psychiatric/ Behavioral	Neuropsychiatric eval	For individuals age >12 mos: screening for behavior concerns incl sleep disturbances, ADHD, anxiety, &/or traits suggestive of ASD
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills. • Scoliosis. • Mobility, activities of daily living, & need for adaptive devices. • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills).
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl eval of aspiration risk & nutritional status • Consider eval for gastric tube placement in those w/dysphagia &/or aspiration risk.
Eyes	Ophthalmologic eval	Assess for nystagmus, optic nerve hypoplasia, retinopathy, & strabismus.
Hearing	Audiologic eval	Assess for hearing loss.
Cardiovascular	Echocardiogram	Assess for rare but possible cardiac anomaly.
Genitourinary	Ultrasound of the kidneys	Assess for rare but possible renal/urologic anomaly.

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	To incl genetic counseling
	Family support/resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; OT = occupational therapy; PT = physical therapy

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with *CASK* Disorders

Manifestation/ Concern	Treatment	Considerations/Other
DD/ID	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]
Poor weight gain / Failure to thrive	Feeding therapy; gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study if clinical signs or symptoms of dysphagia
Spasticity	Orthopedics / physical medicine & rehab / PT & OT incl stretching to help avoid contractures & falls	Consider need for positioning & mobility devices, disability parking placard.
Abnormal vision &/or strabismus	Standard treatment(s) as recommended by ophthalmologist	Community vision services through early intervention or school district
Hearing	Hearing aids may be helpful as per otolaryngologist.	Community hearing services through early intervention or school district
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; DD = developmental delay; ID = intellectual disability; OT = occupational therapy; PT = physical therapy

1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

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).
- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox®, anti-parkinsonian medications, or orthopedic procedures.

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

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

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.

Social/Behavioral 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 serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

Table 5. Recommended Surveillance for Individuals with *CASK* Disorders

System/Concern	Evaluation	Frequency
Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	At each visit
Neurologic	Monitor those w/seizures as clinically indicated.	
	Assess for new manifestations incl seizures, changes in tone, movement disorders.	
Development	Monitor developmental progress & educational needs.	At each visit
Psychiatric/ Behavioral	Behavioral assessment for anxiety, attention, & aggressive or self-injurious behavior	
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	At each visit
Eyes	Ophthalmologic eval	Annually
Hearing	Audiologic eval	
Miscellaneous/ Other	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.	At each visit

OT = occupational therapy; PT = physical therapy

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

Intellectual disability and microcephaly with pontine and cerebellar hypoplasia (MICPCH) and X-linked intellectual disability (XLID) with or without nystagmus are caused by pathogenic variants in *CASK* and are inherited in an X-linked manner.

Risk to the family members of a proband with a *CASK* disorder depends on the phenotype (i.e., MICPCH or XLID ± nystagmus) in the proband.

Risk to Family Members

Parents of a female proband

- **MICPCH.** Most females with MICPCH represent simplex cases (i.e., the only affected family member) and have the disorder as the result of a *de novo CASK* pathogenic variant. However, it is possible (though not likely) that a female with MICPCH inherited a *CASK* pathogenic variant from a mother or a father with somatic and/or germline mosaicism.

  If the parents of the proband are asymptomatic, they are unlikely to have the pathogenic variant because penetrance of the MICPCH phenotype appears to be complete. However, it is possible (though not likely) that a parent of the proband has somatic and/or germline mosaicism.

- **XLID ± nystagmus.** A female with XLID ± nystagmus may have the disorder as the result of a *de novo* pathogenic variant or a pathogenic variant inherited from her mother. (Because hemizygous males are affected, it is unlikely that a female with XLID ± nystagmus would have inherited a pathogenic variant from her father.)

- Molecular genetic testing of the mother (and possibly the father) may help to determine if the *CASK* pathogenic variant was inherited.

- Note: If the *CASK* pathogenic variant cannot be detected in either parent, the pathogenic variant most likely occurred *de novo* in the proband. Another possible explanation is that the proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism.

Parents of a male proband

- The father of a male with a *CASK* disorder will not have the disorder nor will he be hemizygous for the *CASK* pathogenic variant; therefore, he does not require further evaluation/testing.

- **MICPCH.** Most males with MICPCH with or without severe epileptic encephalopathy represent simplex cases (i.e., the only affected family member) and have the disorder as the result of a *de novo* or somatic mosaic *CASK* pathogenic variant.

  If the mother of the proband is asymptomatic, she is unlikely to be heterozygous for the pathogenic variant because penetrance of the MICPCH phenotype appears to be complete. However, it is possible (though not likely) that the mother has somatic and/or germline mosaicism. (Mosaicism for a *CASK* deletion has been described in an asymptomatic other of an affected male [Saitsu et al 2012].)

- **XLID ± nystagmus.** If a male is the only affected family member, the mother may be a heterozygote* or the affected male may have a *de novo* pathogenic variant (as most males have been identified as the result of evaluating families with XLID, it is unknown how many affected males represent simplex cases). In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote.

  Molecular genetic testing of the mother is recommended to confirm her genetic status. (Note: If a woman has more than one affected child and no other affected relatives and if the *CASK* pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism.)

  * Heterozygous females are typically asymptomatic but may display mild-to-severe ID with or without ocular features, absence seizures, and/or tremor.

- Note: If the *CASK* pathogenic variant cannot be detected in the mother, the pathogenic variant most likely occurred *de novo* in the proband. Another possible explanation is that the proband inherited a pathogenic variant from a mother with germline (or somatic and germline) mosaicism. Testing of maternal leukocyte DNA may not detect all instances of somatic mosaicism.

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

- **MICPCH.** If the proband represents a simplex case, the recurrence risk to sibs appears to be low but greater than that of the general population because of the possibility of germline mosaicism in the mother (presenting a risk to male and female sibs) or the father (presenting a risk to female sibs).
- **XLID ± nystagmus.** If the mother of the proband has a *CASK* pathogenic variant, the chance of transmitting it in each pregnancy is 50% (males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will typically be asymptomatic but may display mild-to-severe ID with or without ocular features, absence seizures and/or tremor). If the *CASK* pathogenic variant cannot be detected in maternal leukocyte DNA, the risk to sibs is greater than that of the general population because of the possibility of parental germline mosaicism.

Sibs of a male proband. The risk to the sibs of a proband depends on the genetic status of the mother:

- **MICPCH.** If the proband represents a simplex case, the recurrence risk to sibs appears to be low but greater than that of the general population because of the possibility of maternal germline mosaicism.
- **XLID ± nystagmus.** If the mother is heterozygous for the *CASK* pathogenic variant, the chance of transmitting the variant in each pregnancy is 50%. (Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will typically be asymptomatic but may display mild-to-severe ID with or without ocular features, absence seizures, and/or tremor.) If the *CASK* pathogenic variant cannot be detected in maternal leukocyte DNA, the risk to sibs is greater than that of the general population because of the possibility of maternal germline mosaicism.

Offspring of female proband

- **MICPCH.** To date, females with MICPCH are not known to reproduce.
- **XLID ± nystagmus.** A female with XLID ± nystagmus has a 50% chance of transmitting the *CASK* pathogenic variant to each child.

Offspring of a male proband. To date, males with a *CASK* disorder are not known to reproduce.

Other family members. A male proband's maternal aunts and maternal cousins may be at risk of having the pathogenic variant. Note: Molecular genetic testing may be able to identify the family member in whom a *de novo* pathogenic variant arose, information that could help determine genetic risk status of the extended 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 women who are heterozygous (asymptomatic or symptomatic) or are at risk of being heterozygous.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once the *CASK* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for a *CASK* disorder 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 choice, 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.

- **CASK Kinder- und Lebenshilfe e. V.**
  Germany
  Phone: +49 (0) 6154 8018537
  Email: info@cask-kinder-lebenshilfe.de
  www.cask-kinder-lebenshilfe.de
- **American Association on Intellectual and Developmental Disabilities (AAIDD)**
  Phone: 202-387-1968
  aaidd.org
- **CDC - Child Development**
  Phone: 800-232-4636
  Developmental Disability Basics
- **MedlinePlus**

Intellectual Disability

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. CASK Disorders: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CASK	Xp11.4	Peripheral plasma membrane protein CASK	CASK @ LOVD	CASK	CASK

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 CASK Disorders (View All in OMIM)

300172	CALCIUM/CALMODULIN-DEPENDENT SERINE PROTEIN KINASE; CASK
300422	FG SYNDROME 4; FGS4
300749	INTELLECTUAL DEVELOPMENTAL DISORDER WITH MICROCEPHALY AND PONTINE AND CEREBELLAR HYPOPLASIA; MICPCH

Molecular Pathogenesis

CASK encodes the calcium-/calmodulin-dependent serine protein kinase (CASK), a multidomain protein of the membrane-associated guanylate kinase (MAGUK) family. Although expressed in different tissues, CASK is widely distributed in different regions of the brain.

CASK contains:

- An N-terminal calmodulin dependent protein kinase (CamK) domain
- Two L27 (L27.1 and L27.2) domains
- A PSD-95/discs large/ZO-1 (PDZ) domain
- An src homology 3 (SH3)
- A guanylate kinase (GK) domain at the C-terminus

CASK plays a critical role in brain development and function. It controls synapse formation and activity by (1) presynaptic organization and regulation of neurotransmitter release, (2) maintaining the morphology of dendritic spines and trafficking of glutamate receptors to postsynaptic sites, and (3) regulating the transcription of genes involved in cortical development [Hsueh 2006, Hsueh 2009].

Mechanism of disease causation. The majority of *CASK* pathogenic variants in females with MICPCH and males with MICPCH with or without severe epileptic encephalopathy are predicted null alleles and associated with a severe phenotype [Najm et al 2008, Moog et al 2011, Burglen et al 2012, Hayashi et al 2012, Moog et al 2015, Hayashi et al 2017]. Males with hemizygous pathogenic loss-of-function variants are more severely affected than females.

A few heterozygous missense variants identified in females with MICPCH specifically impair binding of CASK to the interaction partner Mint1 or neurexin. The question remains whether this impairment is sufficient to cause the severe phenotype in females [LaConte et al 2018, LaConte et al 2019].

The hypomorphic *CASK* pathogenic variants in males (and the rare females) with X-linked intellectual disability with or without nystagmus are mainly missense and splice variants. These variants may interfere with specific functions of the CASK protein, while leaving other functions of CASK intact [Moog et al 2015].

Chapter Notes

Author Notes

We are interested in determining the phenotypic spectrum and molecular pathogenesis of *CASK* disorders.

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