# CASK-related disorders

*https://www.ncbi.nlm.nih.gov/books/NBK169825/*

SummaryClinical 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 CASKX-linked intellectual disability (XLID) with or without nystagmus, generally associated with hypomorphic CASK pathogenic variantsMICPCH 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.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.

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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.

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DiagnosisCASK 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 FindingsCASK disorders should be considered in individuals with intellectual disability of any degree and any of the following additional findings:Progressive microcephaly up to -10 SDPontine and cerebellar hypoplasiaHypotonia, 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 retinopathySensorineural hearing lossShort statureEstablishing the DiagnosisThe 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 DisordersView in own windowGene 1MethodProportion of Probands with a Pathogenic Variant 2 Detectable by Method

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Suggestive FindingsCASK disorders should be considered in individuals with intellectual disability of any degree and any of the following additional findings:Progressive microcephaly up to -10 SDPontine and cerebellar hypoplasiaHypotonia, 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 retinopathySensorineural hearing lossShort stature

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Establishing the DiagnosisThe 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

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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.

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Clinical CharacteristicsClinical DescriptionCASK 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.FemalesA 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]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.

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 onlyNormal-to-mild ocular findings including congenital nystagmus and strabismusNo additional neurologic signs besides mild tremor or absence seizuresMRI finding: normal or mainly unknownMalesA 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].

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Typically severe diffuse pontocerebellar hypoplasiaSimplified 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 microcephalyDD/ID. SevereNeurologic features. Mild ataxia reported in one male, dystonia/dyskinesia in another male. No seizures.MRI findings. Variable degree of diffuse pontocerebellar hypoplasiaOther findings. NystagmusMortality. One affected male died at age two weeks.

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or without nystagmus typically have CASK hypomorphic pathogenic variants, including missense and splice variants [Moog et al 2015].PenetrancePenetrance 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.NomenclatureAn 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.PrevalenceThe prevalence of CASK disorders is unknown. At least 130 individuals (45 males and 85 females) with a CASK pathogenic variant have been reported.

Clinical DescriptionCASK 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.FemalesA 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.

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Cerebellar hemispheres can be affected asymmetrically.

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Normal- or low normal-sized corpus callosum with low cerebrum / corpus callosum ratio [Takanashi et al 2010]

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Neurologic features. Mild ataxia reported in one male, dystonia/dyskinesia in another male. No

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MRI findings. Variable degree of diffuse pontocerebellar hypoplasia

Other findings. Nystagmus

Mortality. One affected male died at age two weeks.

DD / mild-to-severe ID

Seizures/epilepsy

Congenital nystagmus and other eye findings including strabismus and mild pallor of the optic disc

Genotype-Phenotype CorrelationsIn 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].

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majority of CASK pathogenic variants are germline loss-of-function alterations.

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PenetrancePenetrance 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.

NomenclatureAn 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.

PrevalenceThe 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) DisordersNo phenotypes other than those discussed in this GeneReview are known to be associated with pathogenic variants in CASK.

Differential DiagnosisIntellectual Disability and Microcephaly with Pontine and Cerebellar Hypoplasia (MICPCH)Table 2. Genes of Interest in the Differential Diagnosis of MICPCHView in own windowGene(s)DisorderMOIClinical FeaturesBrain MRI Findings

SEPSECS

TSEN15

TSEN2

TSEN34

VPS53

TSEN54

PCH2ARGeneralized clonus ("jitteriness") w/lack of voluntary motor development & later development of chorea & spasticity, impaired swallowing, & (in some) epilepsyPersons w/PCH2 usually live into childhood.

In persons w/PCH2/PCH4:

Cerebellar hemispheres are more affected than the vermis, → "dragonfly" appearance in coronal images. 2Pontine hypoplasia is more severe than in females w/MICPCH.Corpus callosum is often thin & hypoplastic.

TSEN54

PCH4ARPolyhydramnios, contractures, severe generalized clonus, & central respiratory failure

usually → neonatal deathARXSTXBP1(>80 genes) 1Ohtahara syndromeXLADEarly-infantile epileptic encephalopathy w/suppression burstMay or may not be assoc w/abnormalities on brain MRIAD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; PCH = pontocerebellar hypoplasia; XL = X-linked1. 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) ± NystagmusXLID 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).

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PCH4ARPolyhydramnios, contractures, severe generalized clonus, & central respiratory failure usually → neonatal deathARXSTXBP1(>80 genes) 1Ohtahara syndromeXLADEarly-infantile epileptic encephalopathy w/suppression burstMay or may not be assoc w/abnormalities on brain MRIAD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; PCH = pontocerebellar hypoplasia; XL = X-linked1. 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.

Table 2. Genes of Interest in the Differential Diagnosis of MICPCHView in own windowGene(s)DisorderMOIClinical FeaturesBrain MRI Findings

SEPSECS

TSEN15

TSEN2

TSEN34

VPS53

TSEN54

PCH2ARGeneralized clonus ("jitteriness") w/lack of voluntary motor development & later development of chorea & spasticity, impaired swallowing, & (in some) epilepsyPersons w/PCH2 usually live into childhood.

In persons w/PCH2/PCH4:

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Persons w/PCH2 usually live into childhood.

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.

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; PCH = pontocerebellar hypoplasia; XL = X-linked1. 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.

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AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; PCH = pontocerebellar hypoplasia; XL = X-linked

See Phenotypic Series: Early Infantile Epileptic Encephalopathy for genes associated with this phenotype in OMIM.

In CASK disorders, a "butterfly" pattern is visible that results from diffuse hypoplasia of the hemispheres and vermis.

X-Linked Intellectual Disability (XLID) ± NystagmusXLID 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).

ManagementEvaluations Following Initial DiagnosisTo 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 DisordersView in own windowSystem/ConcernEvaluationComment

Neurologic

Neurologic evalTo incl brain MRI & EEG if not already done

Development

Developmental assessmentTo incl motor, adaptive, cognitive, & speech/language evalEval for early intervention / special education

Psychiatric/

Behavioral

Neuropsychiatric evalFor 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 evalTo 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 evalTo incl eval of aspiration risk & nutritional statusConsider eval for gastric tube placement in those w/dysphagia &/or aspiration risk.

Eyes

Ophthalmologic evalAssess for nystagmus, optic nerve hypoplasia, retinopathy, & strabismus.

Hearing

Audiologic evalAssess for hearing loss.

Cardiovascular

EchocardiogramAssess for rare but possible cardiac anomaly.

Genitourinary

Ultrasound of the kidneysAssess for rare but possible renal/urologic anomaly.

Miscellaneous/

Other

Consultation w/clinical geneticist &/or genetic counselorTo incl genetic counselingFamily

support/resourcesAssess 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 therapyTreatment of ManifestationsTable 4. Treatment of Manifestations in Individuals with CASK DisordersView in own windowManifestation/ConcernTreatmentConsiderations/Other

DD/ID

See Developmental Delay / Intellectual Disability Management Issues.

Epilepsy

Standardized treatment w/ASM by experienced neurologistMany 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 & fallsConsider need for positioning & mobility devices, disability parking placard.

Abnormal vision

&/or strabismus

Standard treatment(s) as recommended by ophthalmologistCommunity 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 nursingConsider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; DD = developmental delay; ID = intellectual disability; OT = occupational therapy; PT = physical therapy1. 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 IssuesThe 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 ConcernsChildren 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.SurveillanceTable 5. Recommended Surveillance for Individuals with CASK DisordersView in own windowSystem/ConcernEvaluationFrequency

Feeding

Measurement of growth parametersEval 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 skillsAt each visit

Eyes

Ophthalmologic evalAnnually

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 visitOT = occupational therapy; PT = physical therapyEvaluation of Relatives at RiskSee Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.Therapies Under InvestigationSearch 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.

Evaluations Following Initial DiagnosisTo 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 DisordersView in own windowSystem/ConcernEvaluationComment

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Musculoskeletal

Orthopedics / physical medicine & rehab / PT & OT evalTo 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 evalTo incl eval of aspiration risk & nutritional statusConsider eval for gastric tube placement in those w/dysphagia &/or aspiration risk.

Eyes

Ophthalmologic evalAssess for nystagmus, optic nerve hypoplasia, retinopathy, & strabismus.

Hearing

Audiologic evalAssess for hearing loss.

Cardiovascular

EchocardiogramAssess for rare but possible cardiac anomaly.

Genitourinary

Ultrasound of the kidneysAssess for rare but possible renal/urologic anomaly.

Miscellaneous/

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Consultation w/clinical geneticist &/or genetic counselorTo incl genetic counselingFamily support/resourcesAssess 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

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Treatment of ManifestationsTable 4. Treatment of Manifestations in Individuals with CASK DisordersView in own windowManifestation/ConcernTreatmentConsiderations/Other

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See Developmental Delay / Intellectual Disability Management Issues.

Epilepsy

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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 & fallsConsider need for positioning & mobility devices, disability parking placard.

Abnormal vision

&/or strabismus

Standard treatment(s) as recommended by ophthalmologistCommunity 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

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ASM = anti-seizure medication; DD = developmental delay; ID = intellectual disability; OT = occupational therapy; PT = physical therapy1. 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 IssuesThe 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

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Gross motor dysfunction

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Table 4. Treatment of Manifestations in Individuals with CASK DisordersView in own windowManifestation/ConcernTreatmentConsiderations/Other

DD/ID

See Developmental Delay / Intellectual Disability Management Issues.

Epilepsy

Standardized treatment w/ASM by experienced neurologistMany 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 & fallsConsider need for positioning & mobility devices, disability parking placard.

Abnormal vision

&/or strabismus

Standard treatment(s) as recommended by ophthalmologistCommunity 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 nursingConsider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; DD = developmental delay; ID = intellectual disability; OT = occupational therapy; PT = physical therapy1. 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.

Treatment of Manifestations in Individuals with CASK Disorders

Manifestation/ConcernTreatmentConsiderations/Other

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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 IssuesThe 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.

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.

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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.

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.

Social/Behavioral ConcernsChildren 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.

SurveillanceTable 5. Recommended Surveillance for Individuals with CASK DisordersView in own windowSystem/ConcernEvaluationFrequency

Feeding

Measurement of growth parametersEval 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 skillsAt each visit

Eyes

Ophthalmologic evalAnnually

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 visitOT = occupational therapy; PT = physical therapy

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

Therapies Under InvestigationSearch 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 InheritanceIntellectual 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

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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 TestingOnce 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.

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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.

Prenatal Testing and Preimplantation Genetic TestingOnce 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.

GermanyPhone: +49 (0) 6154 8018537Email: info@cask-kinder-lebenshilfe.de

www.cask-kinder-lebenshilfe.de

American Association on Intellectual and Developmental Disabilities (AAIDD)

Phone: 202-387-1968Fax: 202-387-2193

www.aaidd.org

CDC - Developmental Disabilities

Phone: 800-CDC-INFOEmail: cdcinfo@cdc.gov

Intellectual Disability

MedlinePlus

Intellectual Disability

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

Fax: 202-387-2193

www.aaidd.org

CDC - Developmental Disabilities

Phone: 800-CDC-INFO

Email: cdcinfo@cdc.gov

Intellectual Disability

MedlinePlus

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Molecular GeneticsInformation 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 DatabasesView in own windowGeneChromosome LocusProteinLocus-Specific DatabasesHGMDClinVar

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) View in own window

300172CALCIUM/CALMODULIN-DEPENDENT SERINE PROTEIN KINASE; CASK

300422FG SYNDROME 4; FGS4

300749INTELLECTUAL DEVELOPMENTAL DISORDER WITH MICROCEPHALY AND PONTINE AND CEREBELLAR HYPOPLASIA; MICPCHMolecular PathogenesisCASK 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) domainTwo L27 (L27.1 and L27.2) domainsA PSD-95/discs large/ZO-1 (PDZ) domainAn src homology 3 (SH3)A guanylate kinase (GK) domain at the C-terminusCASK 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].

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CASK

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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.

CASK Disorders: Genes and Databases

GeneChromosome LocusProteinLocus-Specific DatabasesHGMDClinVar

CASK

Xp11.4

Peripheral plasma membrane protein CASK

CASK @ LOVD

CASK

CASK

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Table B.OMIM Entries for CASK Disorders (View All in OMIM) View in own window

300172CALCIUM/CALMODULIN-DEPENDENT SERINE PROTEIN KINASE; CASK

300422FG SYNDROME 4; FGS4

300749INTELLECTUAL DEVELOPMENTAL DISORDER WITH MICROCEPHALY AND PONTINE AND CEREBELLAR HYPOPLASIA; MICPCH

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Molecular PathogenesisCASK 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) domainTwo L27 (L27.1 and L27.2) domainsA PSD-95/discs large/ZO-1 (PDZ) domainAn src homology 3 (SH3)A guanylate kinase (GK) domain at the C-terminusCASK 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].

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

Chapter NotesAuthor NotesWe are interested in determining the phenotypic spectrum and molecular pathogenesis of CASK disorders.AcknowledgmentsWe thank the families with individuals affected by MICPCH who are participating in our research programs.Author HistoryKerstin Kutsche, PhD (2013-present)Ute Moog, MD (2013-present)Gökhan Uyanik, MD; Hanusch Hospital, Vienna (2013-2020)Revision History21 May 2020 (ha) Comprehensive update posted live26 November 2013 (me) Review posted live28 February 2013 (kk) Original submission

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