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TSEN54 Pontocerebellar Hypoplasia

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Summary

Clinical characteristics

TSEN54 pontocerebellar hypoplasia (*TSEN54*-PCH) comprises three PCH phenotypes (PCH2, 4, and 5) that share characteristic neuroradiologic and neurologic findings. The three PCH phenotypes (which differ mainly in life expectancy) were considered to be distinct entities before their molecular basis was known.

- **PCH2.** Children usually succumb before age ten years (those with PCH4 and 5 usually succumb as neonates). Children with PCH2 have generalized clonus, uncoordinated sucking and swallowing, impaired cognitive development, lack of voluntary motor development, cortical blindness, and an increased risk for rhabdomyolysis during severe infections. Epilepsy is present in approximately 50%.
- **PCH4.** Neonates often have seizures, multiple joint contractures ("arthrogryposis"), generalized clonus, and central respiratory impairment.
- **PCH5** resembles PCH4 and has been described in one family.

Diagnosis/testing

The diagnosis of *TSEN54*-PCH is suspected in children with characteristic neuroradiologic and neurologic findings, and is confirmed by the presence of biallelic *TSEN54* pathogenic variants.

Management

Treatment of manifestations: PCH2: Treatment of irritability, swallowing incoordination, epilepsy, and central visual impairment is symptomatic. Physiotherapy can be helpful. Adequate hydration during prolonged periods of high fever may help avoid rhabdomyolysis. PCH4 and PCH5: No specific therapy is available.

Surveillance: PCH2: Routine monitoring of respiratory function, feeding, musculoskeletal and neurologic manifestations, developmental milestones, and family needs.

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Genetic counseling

TSEN54-PCH is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *TSEN54* pathogenic variant, each sib of an affected individual has at conception a 25% chance of inheriting both pathogenic variants and being affected, a 50% chance of inheriting one pathogenic variant and being an unaffected carrier, and a 25% chance of inheriting both normal alleles. Once the *TSEN54* pathogenic variants have been identified in an affected family member, molecular genetic testing to determine carrier status of at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

GeneReview Scope

TSEN54 Pontocerebellar Hypoplasia: Included Phenotypes [1]
• Pontocerebellar hypoplasia type 2 (PCH2) • Pontocerebellar hypoplasia type 4 (PCH4) • Pontocerebellar hypoplasia type 5 (PCH5)

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

Diagnosis

The phenotypic spectrum of *TSEN54* pontocerebellar hypoplasia (*TSEN54*-PCH) includes three PCH phenotypes (thought to be distinct entities before the molecular basis of PCH was known) based on neuroradiologic and neurologic findings: PCH type 2 (PCH2), PCH type 4 (PCH4), and PCH type 5 (PCH5).

Suggestive Findings

TSEN54-PCH **should be suspected** in children with severe neurologic impairment and the following findings on brain imaging [Barth et al 2007, Steinlin et al 2007, Namavar et al 2011].

Brain MRI Findings

Common findings

- Cerebellar hypoplasia and varying degrees of cerebellar atrophy (more severe in PCH4).
- Ventral pontine atrophy, present in the majority of cases (more severe in PCH4).
- Cerebellar hemispheres more affected than cerebellar vermis
- Cerebral cortical atrophy, progressive with age
- Pericerebral CSF accumulation and delayed neocortical maturation in PCH4

Less common findings (not present in all persons) (see Figure 1)

- Striatal hypoplasia or atrophy
- Delayed myelination of the brain in the first years; no demyelination; gliosis in PCH4
- Exceptional: cerebellar hemispheric cysts in PCH2

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

Establishing the Diagnosis

Diagnosis of *TSEN54*-PCH **is established** in a proband with suggestive findings and biallelic *TSEN54* pathogenic (or likely pathogenic) variants identified by molecular genetic testing (see Table 1).

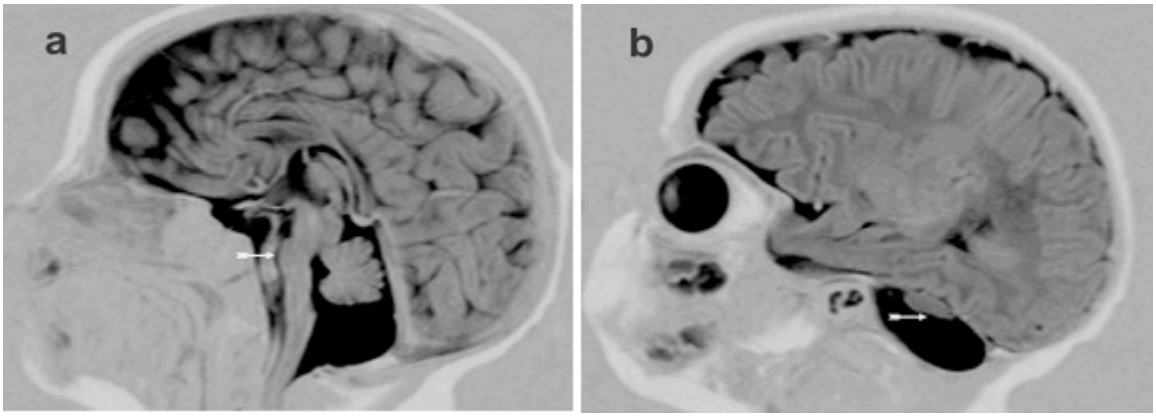

Figure 1. MRI of the brain of an infant age two months with PCH2

a. Midsagittal image showing hypoplastic vermis and flat ventral pons (arrow)

b. Lateral sagittal image showing hypoplastic cerebellar hemisphere (arrow) leaving empty space in the posterior fossa

From Budde et al [2008]

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic *TSEN54* variants of uncertain significance (or of one known *TSEN54* pathogenic variant and one *TSEN54* variant of uncertain significance) does not establish or rule out the diagnosis.

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

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive brain imaging findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of *TSEN54*-PCH has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *TSEN54* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. Typically, if only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications; however, to date such variants have not been identified as a cause of this disorder.

Note: Targeted analysis for the common c.919G>T variant can be performed first, since this is by far the most frequent pathogenic variant in *TSEN54*.

A cerebellar hypoplasia multigene panel that includes *TSEN54* 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*. Of note, given the rarity of *TSEN54* pontocerebellar hypoplasia,

some panels for cerebellar hypoplasia may not include this gene. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

Option 2

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

If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis; however, to date such variants have not been identified as a cause of *TSEN54* pontocerebellar hypoplasia.

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

Table 1. Molecular Genetic Testing Used in *TSEN54* Pontocerebellar Hypoplasia

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
TSEN54	Sequence analysis [3]	100% [4]
	Gene-targeted deletion/duplication analysis [5]	Unknown [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of the Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. No data on detection rate of gene-targeted deletion/duplication analysis are available.

Clinical Characteristics

Clinical Description

To date, at least 131 individuals have been identified with *TSEN54* pontocerebellar hypoplasia (*TSEN54*-PCH) [Namavar et al 2011, Sánchez-Albisua et al 2014].

The phenotypic spectrum of *TSEN54*-PCH comprises the three PCH phenotypes (PCH 2, 4, and 5) thought to be distinct entities before their molecular basis was known. The main difference between the three PCH phenotypes is life expectancy: individuals with PCH2 usually survive into childhood, whereas those with PCH4 and PCH5 usually die as neonates.

Pontocerebellar Hypoplasia Type 2

The following description of the phenotypic features associated with *TSEN54*-PCH type 2 is based on Sánchez-Albisua et al [2014].

Table 2. Select Features of *TSEN54* Pontocerebellar Hypoplasia Type 2

Feature		% of Persons with Feature	Comment
Severe developmental delay		100%	
Neurologic	Choreoathetosis	88%	62% w/pyramidal signs
	Pure spasticity	12%	
	Epileptic seizures	82%	
	Dystonic attacks	33%	
Gastrointestinal	Feeding difficulties	100%	
	GERD	73%	
Sleep disorder		96%	
Apnea		67%	
Recurrent infections		52%	

Based on 33 individuals homozygous for the common missense variant, p.Ala307Ser, from nonconsanguineous parents surviving until age 11 years [Sánchez-Albisua et al 2014]
GERD = gastroesophageal reflux disease

Pregnancy is usually unremarkable. Newborns have no external dysmorphic features and no visceral abnormalities. Birth is usually at term with normal weight, length, and (though always <50th centile) head circumference. Progressive microcephaly is observed during the first year, with the occipitofrontal circumference dropping below two standard deviations.

Neurologic findings

- Bucco-pharyngeal incoordination with reduced grasping of the nipple and incoordination of sucking and swallowing
- Generalized clonus (often described as "jitteriness") present in the majority
- Impaired motor and cognitive development: lack of voluntary motor development; unsupported sitting or voluntary reaching and grasping rarely achieved
- Severe chorea often developing during the first six months, usually accompanied by spasticity. Those children who never develop chorea remain tetraspastic.
- Impaired central vision. Note that primary optic nerve atrophy has not been observed.
- Epilepsy (in ~50%); usually generalized tonic clonic seizures often provoked by fever, although other types of seizures including infantile spasms have been observed.

Other. Subclinical myopathy, associated with elevated creatine kinase, may lead to rhabdomyolysis following severe infections.

Life expectancy. Death is often before age ten years, although survival beyond age 20 years has been reported. Improved care, especially gastrostomy feeding, has probably improved survival. Typical complications are sudden and unexpected death while the child is sleeping (crib death) in infancy and death from hyperthermic crises.

Pontocerebellar Hypoplasia Type 4

Prenatal findings include polyhydramnios in many (but not all) pregnancies.

Central respiratory impairment (probably the result of brain stem failure) at birth results in prolonged or perpetual dependence on mechanical ventilation. Respiratory complications occur at a later stage when weaning is difficult or plainly impossible.

Microcephaly is usually present at birth. About 50% of neonates have contractures (arthrogryposis) at birth. Generalized clonus, provoked by handling or noise, may be extreme.

Life expectancy. Infants with PCH4 usually die in the neonatal period from these complications.

Neuropathology of PCH2 and PCH4

[Barth et al 2007]

- **Cerebellum**
  - Hypoplasia and reduced branching of the folia; segmental degeneration of the cerebellar cortex and dentate nucleus; variable degeneration of Purkinje cells; relative sparing of the flocculus and vermis
  - PCH4. Denuding of the dorsal part of the cerebellar hemispheric cortex; relative sparing of the flocculus and vermis
- **Pons.** Neuronal death within the ventral pons; relative sparing of the tegmentum
- **Cerebral cortex and striatum.** Variable neuronal degeneration
- **Medulla oblongata.** Variable neuronal degeneration; hypoplasia and segmental degeneration of the inferior olivary nuclei; loss of arcuate nuclei
- **Myelin.** Not involved in PCH2; widespread gliosis variably seen in PCH4

Pontocerebellar Hypoplasia Type 5

Described in only one family, findings of PCH5 are similar to those of PCH4 except that the degenerative process occurs in the cerebellar vermis rather than the cerebellar hemispheres [Patel et al 2006]. There is fetal onset of seizure-like activity. Death occurs very shortly after birth.

Genotype-Phenotype Correlations

The following clinical data, supported by pathogenic data, strongly suggest a genotype-phenotype correlation.

The common c.919G>T missense variant is strongly associated with a dragonfly-like cerebellar pattern on MRI.

In general, infants with the PCH4 phenotype who are compound heterozygotes for a pathogenic nonsense or splice site variant and a pathogenic missense variant have poorer survival than children with the PCH2 phenotype who are homozygous for a missense variant [Budde et al 2008, Namavar et al 2011].

Nomenclature

Pontocerebellar hypoplasia 2 (PCH2) refers to the phenotype; its subtypes are identified by the gene in which causative variants occur:

- PCH2A (*TSEN54*)
- PCH2B (*TSEN2*)
- PCH2C (*TSEN34*)
- PCH2D (*SEPSECS*)

Prevalence

The prevalence of *TSEN54*-PCH is unknown. To date, at least 131 individuals have been identified with *TSEN54*-PCH.

The carrier frequency of the common *TSEN54* pathogenic variant c.919G>T (p.Ala307Ser) among 451 Dutch and 279 German individuals was 0.004 [Budde et al 2008].

Like many autosomal recessive disorders, PCH2 has been reported to be more common in isolated populations or populations with a high rate of consanguinity. PCH2 was originally identified in an isolated population in Volendam, the Netherlands [Barth et al 1995].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* have been associated with mutation of *TSEN54*.

Differential Diagnosis

Table 3. Genes of Interest in the Differential Diagnosis of *TSEN54* Pontocerebellar Hypoplasia

Gene(s)	Phenotype/Disorder	MOI	Brain MRI Findings	Clinical Characteristics
B3GALNT2 *B4GAT1* *DAG1* *FKRP* *FKTN* *GMPPB* *ISPD* *LARGE1* *POMGNT1* *POMGNT2* *POMK* *POMT1* *POMT2* *RXYLT1* [1]	Alpha-dystroglycanopathies	AR	Wide spectrum of brain malformations incl cobblestone lissencephaly & hydrocephalus	Muscle weakness & ophthalmologic abnormalities
CASK	ID & microcephaly w/pontine & cerebellar hypoplasia (See *CASK* Disorders.)	XL	Neocortical dysplasia (simplified gyral pattern, thin brain stem w/flattening of the pons) & severe cerebellar hypoplasia (pontocerebellar hypoplasia)	• Heterozygous females have severe or profound ID & structural brain anomalies incl mild congenital microcephaly & severe postnatal microcephaly. • Hemizygous males are more severely affected.
CHMP1A	PCH8 [2]	AR	MRI findings similar to those of PCH2	Microcephaly, delayed walking, variable foot deformities, chorea, dystonic posturing, & impaired cognition
EXOSC3 *EXOSC8* *SLC25A46* *VRK1*	PCH1 [2, 3] (See *EXOSC3*-PCH.)	AR	Pontine atrophy may not be present in some individuals.	• Lower motor neuron deficits due to loss of anterior horn cells; manifestations of peripheral denervation incl weakness & muscle hypotonia from birth • Mixed central (spastic, dystonic) & peripheral pareses may be present in those w/ prolonged survival; some children w/PCH1 die at an early age. [4]

Table 3. continued from previous page.

Gene(s)	Phenotype/Disorder	MOI	Brain MRI Findings	Clinical Characteristics
>40 genes (e.g., *PMM2* [5])	Congenital disorders of glycosylation (CDG); see also PMM2-CDG (*CDG-Ia*).	AR (XL)	Pontocerebellar hypoplasia w/ superimposed atrophy, delayed myelination	Dysmorphic features, ataxia, organ failure in neonatal period
PCLO	PCH3 [2]	AR		
RARS2	PCH6 [2]	AR		Very rare; ↑ CSF lactate concentration
RELN	Lissencephaly 2 (OMIM 257320)	AR	Classic lissencephaly w/ coexistent cerebellar & pontine hypoplasia	
SEPSECS	PCH2 [2]	AR	Progressive cerebello-cerebral atrophy closely resembles mild PCH2.	Clinical findings closely resemble mild PCH2.
TOE1	PCH7 [2]	AR	PCH	Disorders of sex development
VLDLR	*VLDLR* cerebellar hypoplasia	AR	Gross cerebellar hypoplasia, a flat ventral pons, & simplified gyri	Ataxia & ID

AR = autosomal recessive; ID = intellectual disability; MOI = mode of inheritance; PCH = pontocerebellar hypoplasia; XL = X-linked
1. OMIM Phenotypic Series: Muscular dystrophy-dystroglycanopathy, type A
2. van Dijk et al [2018]
3. OMIM Phenotypic Series: Pontocerebellar hypoplasia
4. Children with *EXOSC3* pathogenic variants other than c.395A>C (p.Asp132Ala) have a more severe phenotype that includes severe pontine and cerebellar hypoplasia, joint contractures, and death in infancy.
5. PMM2-CDG (*CDG-Ia*) is the most common of a group of disorders of abnormal glycosylation of N-linked oligosaccharides.

Other disorders to consider in the differential diagnosis

- Lissencephalies without known gene defects exhibiting two-layered cortex, extreme microcephaly, and cerebellar and pontine hypoplasia [Forman et al 2005]
- Pontocerebellar hypoplasia in extremely premature infants (<28 weeks' gestational age); an acquired phenocopy to be considered [Volpe 2009, Pierson & Al Sufiani 2016]

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *TSEN54* pontocerebellar hypoplasia (*TSEN54*-PCH), the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended. Note that recommendations are based only on PCH2 caused by homozygosity for the*TSEN54* pathogenic variant c.919G>T, as all other subtypes are very rare.

Table 4. Recommended Evaluations Following Initial Diagnosis of *TSEN54* Pontocerebellar Hypoplasia Type 2

System/Concern	Evaluation	Comment
Constitutional	Measure length, weight.	See **Gastrointestinal/Feeding** recommendations if there is evidence of failure to thrive.
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	Assess swallowing & feeding to determine safety of oral vs gastrostomy feeding.
Respiratory	Assess airway & pulmonary function & secretion management.	Consult pulmonologist.

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Neurologic	Eval by pediatric neurologist	Assess for evidence of severe generalized clonus; chorea, spasticity; seizures; impaired central vision.
Musculoskeletal	Multidisciplinary neuromuscular clinic assessment by orthopedist, physical medicine, OT/PT	To incl assessment of: • Contractures, clubfoot, & kyphoscoliosis • Need for positioning devices
Palliative care	Refer to palliative care specialist.	When deemed appropriate by family & care providers
Genetic counseling	By genetics professionals [1]	To inform affected individuals & their families re nature, MOI, & implications of *TSEN54*-PCH2 to facilitate medical & personal decision making
Family support/ resources	Assess: • Use of community or online resources such as Parent to Parent; • Need for social work involvement for parental support; • Need for home nursing referral.	

MOI = mode of inheritance; OT = occupational therapist; PT = physical therapist
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

PCH4 and **PCH5.** No specific therapy is available. Respiratory support is usually given for a limited time. Weaning from respiratory support may be possible for only short periods.

PCH2. Although there is no specific treatment, the goals are to maximize function and reduce complications. Ideally each affected individual is managed by a multidisciplinary team of relevant specialists such as developmental pediatricians, neurologists, occupational therapists (OT), physical therapists (PT), physiatrists, orthopedists, nutritionists, pulmonologists, and psychologists depending on the clinical manifestations (see Table 5).

Of note, adequate hydration during prolonged periods of high fever may help avoid rhabdomyolysis.

Table 5. Treatment of Manifestations in Individuals with *TSEN54* Pontocerebellar Hypoplasia Type 2

Manifestation/Concern	Treatment	Considerations/Other
Seizures	Per standard practice	By neurologist experienced in epilepsy management
Irritability	None	Often related to chorea (involuntary movements)
Musculoskeletal	Multidisciplinary neuromuscular clinic physical medicine, OT/PT	• Maximize gross motor & fine motor skills through PT/OT & use of adaptive devices. • Alternative casting/splinting & stretching
	Orthopedics	Manage contractures, clubfoot, & scoliosis w/bracing &/or surgical intervention.
Feeding/ Dysphagia	Gastroenterology / nutrition / feeding team	Modify food consistency to ↓ aspiration risk &/or consider NG feeding & gastrostomy.
Speech	Speech/language eval	Consider involving speech therapist & OT to improve communication skills.

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Respiratory	Manage pulmonary complications; treatment of respiratory infections	Per treating pulmonologist
Neurodevelopmental	Early intervention / individual education program based on needs	See Developmental Delay / Intellectual Disability Management Issues.

NG = nasogastric, OT = occupational therapy, PT = physical therapy

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:

- Individualized education plan (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.
  - A vision consultant should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.

- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Surveillance

Table 6. Recommended Surveillance for Individuals with *TSEN54* Pontocerebellar Hypoplasia Type 2

System/Concern	Evaluation	Frequency
Respiratory	Assess airway & pulmonary function & secretion management.	Monitoring of respiratory function may be needed to detect sleep apnea.
Gastrointestinal/ Feeding	• Aspiration risk & nutritional status • Monitor for constipation.	Annually; more frequently if needed
Musculoskeletal	• PT/OT eval • Assessment for contractures, scoliosis, & foot deformities. • Hip/spine x-rays	
Neurologic	• Monitor those w/seizures as clinically indicated. • Monitor for dystonia & choreic movements.	
Development	Monitor developmental milestones.	
Family support & resources	Family needs	

OT = occupational therapy; PT = physical therapy

Agents/Circumstances to Avoid

Although hyperthermic episodes have been documented in individuals with PCH2, no special risk appears to be associated with generalized anesthesia.

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

TSEN54 pontocerebellar hypoplasia (*TSEN54*-PCH) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., presumed to be carriers of one *TSEN54* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *TSEN54* pathogenic variant and allow reliable recurrence risk assessment. (Although a *de novo* pathogenic variant has not been reported in *TSEN54*-PCH to date, *de novo* variants are known to occur at a low but appreciable rate in autosomal recessive disorders [Jónsson et al 2017].)
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a *TSEN54* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. Individuals with *TSEN54*-PCH are not likely to have offspring because of severe intellectual disability and the likelihood of death before the age of fertility.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *TSEN54* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *TSEN54* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are carriers or are at risk of being carriers.

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). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *TSEN54* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **National Library of Medicine Genetics Home Reference**
  Pontocerebellar hypoplasia

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. TSEN54 Pontocerebellar Hypoplasia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
TSEN54	17q25.1	tRNA-splicing endonuclease subunit Sen54	TSEN54 database	TSEN54	TSEN54

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 TSEN54 Pontocerebellar Hypoplasia (View All in OMIM)

225753	PONTOCEREBELLAR HYPOPLASIA, TYPE 4; PCH4
277470	PONTOCEREBELLAR HYPOPLASIA, TYPE 2A; PCH2A
608755	tRNA SPLICING ENDONUCLEASE, SUBUNIT 54; TSEN54
610204	PONTOCEREBELLAR HYPOPLASIA, TYPE 5; PCH5

Molecular Pathogenesis

The genes of the TSEN complex encode subunits of tRNA splicing endonuclease. The tRNA splicing endonuclease (TSEN) complex has a role in RNA processing [Paushkin et al 2004, Trotta et al 2006]:

- It is involved in tRNA maturation; 6% of human tRNAs carry an intron in a premature state that is spliced out by the TSEN.
- The TSEN complex is also involved in mRNA 3' end formation. The precise role of the TSEN complex in this process remains elusive; however, it is known that in vitro knockdown of TSEN2 protein leads to impaired mRNA 3' end formation.

The TSEN complex comprises four different subunits: two catalytic subunits encoded by *TSEN2* and *TSEN34*; and two structural subunits encoded by*TSEN15* and *TSEN54*.

Mechanism of disease causation. Because individuals with nonsense variants are more seriously affected than those with missense variants, the authors suggest that pathogenic variants lead to loss of function or reduced function of *TSEN54*.

Table 7. Notable *TSEN54* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_207346.2 NP_997229.2	c.919G>T	p.Ala307Ser	Accounts for ~88% of PCH2 [Budde et al 2008, Namavar et al 2011]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

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Revision History

- 28 May 2020 (bp) Comprehensive update posted live
- 14 July 2016 (pgb) Revision: clarification of muscle problem in PCH2
- 18 February 2016 (pgb) Revision: Agents/Circumstances to Avoid
- 24 October 2013 (me) Comprehensive update posted live
- 22 September 2009 (cd) Revision: sequence analysis and prenatal testing is available clinically for *TSEN2* and *TSEN34* pathogenic variants.
- 8 September 2009 (me) Review posted live
- 1 May 2009 (fb) Original submission

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