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EXOSC3 Pontocerebellar Hypoplasia

Synonym: Pontocerebellar Hypoplasia Type 1B (PCH1B)

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Summary

Clinical characteristics

EXOSC3 pontocerebellar hypoplasia (*EXOSC3*-PCH) is characterized by abnormalities in the posterior fossa and degeneration of the anterior horn cells. At birth, skeletal muscle weakness manifests as hypotonia (sometimes with congenital joint contractures) and poor feeding. In persons with prolonged survival, spasticity, dystonia, and seizures become evident. Within the first year of life respiratory insufficiency and swallowing difficulties are common. Intellectual disability is severe. Life expectancy ranges from a few weeks to adolescence. To date, 82 individuals (from 58 families) with *EXOSC3*-PCH have been described.

Diagnosis/testing

The diagnosis of *EXOSC3*-PCH is suspected in children with characteristic neuroradiologic and neurologic findings, and is confirmed by the presence of biallelic *EXOSC3* pathogenic variants identified by molecular genetic testing.

Management

Treatment of manifestations: No specific therapy is available. Treatment is symptomatic. Contractures and scoliosis are managed by passive or active movement and bracing as needed. Aspiration risk and seizures are managed in a routine manner. Education is adapted to the level of cognitive abilities.

Surveillance: Regular examinations to address: growth and nutritional status (including problems with feeding and risk of aspiration); respiratory function; joint contractures and scoliosis. Observation for and management of epileptic seizures.

Genetic counseling

EXOSC3-PCH is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an *EXOSC3* pathogenic variant, each sib of an affected individual has at conception a 25% chance of inheriting

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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 *EXOSC3* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

Diagnosis of *EXOSC3* pontocerebellar hypoplasia (*EXOSC3*-PCH) **should be suspected** in children with severe neurologic impairment and characteristic findings on brain imaging.

Neurologic Findings

Common

- Hypotonia (onset is usually at birth, but a later onset is possible)
- Signs of neurogenic muscle atrophy, such as muscle atrophy and decreased tendon reflexes
- Central motor neuron signs (spasticity, dystonia), especially in individuals with prolonged survival
- Lower motor neuron involvement, demonstrated by EMG (abnormal EMG potentials, increased motor unit potentials, fasciculations)

Less common

- Joint contractures (can be present at birth or develop later)
- Swallowing insufficiency
- Ophthalmologic findings of:
  - Small or pale optic discs indicative of optic atrophy
  - Nystagmus
  - Strabismus
- Seizures

Brain MRI Findings Consistent with Pontocerebellar Hypoplasia Type 1 (PCH1) *

Common

- Hypoplasia and/or atrophy of the cerebellum in varying degrees
- Hypoplasia and/or atrophy of the pons in varying degrees
- Cerebellar vermis and cerebellar hemispheres equally affected

Less common

- Intracerebellar cysts [Eggens et al 2014]
- Supratentorial abnormalities, such as widened extracerebellar CSF spaces and widened lateral ventricles due to small basal ganglia

* See Nomenclature.

Family History

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

Establishing the Diagnosis

The diagnosis of *EXOSC3* pontocerebellar hypoplasia **is established** in a proband with suggestive findings and biallelic *EXOSC3* pathogenic (or likely pathogenic) variants identified by molecular genetic testing (see Table 1).

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 *EXOSC3* variants of uncertain significance (or of one known *EXOSC3* pathogenic variant and one *EXOSC3* 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 *EXOSC3*-PHC has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *EXOSC3* 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. 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.

A cerebellar hypoplasia multigene panel that includes *EXOSC3* 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 *EXOSC3*-PCH, 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.

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 *EXOSC3* Pontocerebellar Hypoplasia

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
EXOSC3	Sequence analysis [3]	~99% [4]
	Deletion/duplication analysis [5]	Partial-gene deletion in 1 person [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants.
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. Wan et al [2012], Rudnik-Schöneborn et al [2013], Zanni et al [2013], Eggens et al [2014]
5. Testing that identifies exon or whole-gene deletions/duplications not detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment.
6. Eggens et al [2014]

Clinical Characteristics

Clinical Description

EXOSC3 pontocerebellar hypoplasia (*EXOSC3*-PCH) is characterized at birth by skeletal muscle weakness that manifests as hypotonia (sometimes with congenital joint contractures) and poor feeding. In children with prolonged survival, spasticity, dystonia, and seizures become evident. Respiratory insufficiency and swallowing difficulties are common. Intellectual disability is severe.

To date, 82 individuals (in 58 families) with *EXOSC3*-PCH have been described [Wan et al 2012, Biancheri et al 2013, Rudnik-Schöneborn et al 2013, Schwabova et al 2013, Zanni et al 2013, Eggens et al 2014, Halevy et al 2014, Di Giovambattista et al 2017, Schottmann et al 2017, Ivanov et al 2018, Le Duc et al 2020, Saugier-Veber et al 2020].

Pregnancy is unremarkable in the majority. Fetal akinesia resulting in prenatal-onset joint contractures and polyhydramnios may occur in 1%-2% of cases [Rudnik-Schöneborn et al 2013].

Birth weight and length are normal; birth head circumference varies from normal to small. Hypotonia, the most common initial finding, is present at birth in most infants and not evident until age three to six months in the remainder.

In relatively older individuals, central motor (pyramidal or extrapyramidal) and signs of peripheral motor involvement may coexist.

Infections and respiratory failure due to muscle weakness are among the reported causes of death. In most severe cases, respiratory problems start soon after birth. In the majority of children onset of respiratory failure begins within the first year of life. In rare cases, onset is during childhood [Rudnik-Schöneborn et al 2013].

Joint contractures can be present at birth in the most severe cases, or can develop after a few years. Motor milestones are delayed or not achieved at all. Unsupported crawling, sitting, or walking is reported in a few [Zanni et al 2013, Le Duc et al 2020]; however, these abilities are often lost when the disease progresses. In individuals who are able to sit or stand upright, scoliosis can result from muscle weakness. Speech is usually absent, but may be limited to short sentences in a few.

Some infants can be bottle-fed or breast-fed in the first weeks of life [Eggens et al 2014]. Although on occasion infants are able to eat without aid [Zanni et al 2013], swallowing insufficiency in the majority necessitates tube feeding sometime between birth and a few years of age [Rudnik-Schöneborn et al 2013].

Vision is hard to assess in young children. Many are unable to fix and follow, and many show strabismus and/or nystagmus. Possibly, the nystagmus in some children results from early-onset visual impairment, but clear evidence is lacking.

Seizures mainly occur in individuals who survive beyond infancy [Rudnik-Schöneborn et al 2013, Eggens et al 2014]. A few have infantile spasms (West syndrome). Around 25% of those with prolonged survival develop spasticity and/or epileptic seizures.

Age of death ranges from a few weeks to adolescence and can be correlated with certain pathogenic variants (see Genotype-Phenotype Correlations).

Neuropathologic findings

- **Common**
  - Muscle. Typical findings of anterior horn involvement (i.e., neurogenic muscle atrophy): grouped atrophy, type II muscle fiber atrophy
  - Spinal cord. Degeneration and loss of motor neurons in the anterior spinal horn
  - Cerebellum. Loss of Purkinje cells, folial atrophy, degeneration of dentate nuclei, and loss of ventral pontine nuclei and transverse pontine nerve fibers
- **Less common.** Spinal cord. Depletion of neurons in the dorsal spinal horn [Eggens et al 2014]

Genotype-Phenotype Correlations

Clear genotype-phenotype correlations exist for certain *EXOSC3* pathogenic variants.

Phenotypes associated with the pathogenic variant c.395A>C (p.Asp132Ala) include the following:

- Children homozygous for this variant could be described as having a relatively "mild" clinical course. Some have the ability to walk or speak single words, and the disease course is prolonged with possible survival into puberty. Brain MRI shows a normal-size pons and cerebellar hypoplasia that is mild compared to that observed in children with other *EXOSC3* pathogenic variants [Biancheri et al 2013, Rudnik-Schöneborn et al 2013, Eggens et al 2014].
- Two sibs, compound heterozygotes for the pathogenic variants c.395A>C (p.Asp132Ala) and c.238G>T (p.Val80Phe), had a similarly "mild" phenotype [Zanni et al 2013].
- Two sibs, compound heterozygotes for the pathogenic variants c.395A>C (p.Asp132Ala) and c.572G>A (p.Gly191Asp), also had a mild disease course [Le Duc et al 2020].

Phenotypes associated with the pathogenic variant c.92G>C (p.Gly31Ala) include the following:

- Individuals homozygous for this variant represent the severe end of the *EXOSC3*-PCH spectrum, often manifesting at birth or in the first months of life severe hypotonia and respiratory failure. Survival is poor [Rudnik-Schöneborn et al 2013, Eggens et al 2014].
- More recently, two sibs with this variant had severe growth retardation, fetal akinesia, microlissencephaly, and cerebellar malformations consistent with rhombencephalosynapsis [Saugier-Veber et al 2020].

Nomenclature

Pontocerebellar hypoplasia 1 (PCH1) refers to the phenotype defined by brain imaging findings. Its subtypes, designated by letter (e.g., PCH1B), are identified by the gene in which causative pathogenic variants occur.

Prevalence

The prevalence of *EXOSC3*-PCH in the general population is unknown.

About 50% of individuals with pontocerebellar hypoplasia 1 (PCH1) have pathogenic variants in *EXOSC3*.

To date, 82 individuals (in 58 families) have been described with *EXOSC3*-PCH [Wan et al 2012, Biancheri et al 2013, Rudnik-Schöneborn et al 2013, Schwabova et al 2013, Zanni et al 2013, Eggens et al 2014, Halevy et al 2014, Di Giovambattista et al 2017, Schottmann et al 2017, Ivanov et al 2018, Le Duc et al 2020, Saugier-Veber et al 2020].

c.395A>C (p.Asp132Ala) is the most prevalent pathogenic variant with an ancestral origin [Wan et al 2012, Rudnik-Schöneborn et al 2013], with an allele frequency of 0.1% among European Americans (Exome Variant Server). See Table 6.

The c.92G>C (p.Gly31Ala) pathogenic variant is a founder variant in the Roma population [Rudnik-Schöneborn et al 2013, Schwabova et al 2013]. A carrier frequency of about 4% was found in the Roma population of the Czech Republic [Schwabova et al 2013]. See Table 6.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with biallelic pathogenic variants in *EXOSC3*.

Differential Diagnosis

Key disorders to consider in the differential diagnosis of pontocerebellar hypoplasia type 1 (PCH1) include *EXOSC8*-, *SLC25A46*-, and *VRK1*-related PCH1, PCH2/4 (*TSEN54*-related PCH), spinal muscular atrophy type 1, PCH10, and PCH12 (see Table 2).

PCH1. About 50% of individuals with PCH1 have pathogenic variants in *EXOSC3* (i.e., *EXOSC3*-PCH). In children with *EXOSC3*-PCH, neonatal death, delayed nerve conduction velocities, and congenital respiratory and feeding difficulties occur less frequently than in those without identifiable *EXOSC3* pathogenic variants [Rudnik-Schöneborn et al 2014].

PCH2/4. Dyskinesias and seizures are common in PCH2, the most common type of PCH. PCH4 is a severe form of PCH2, often with congenital contractures and polyhydramnios. In children with *EXOSC3*-PCH, central motor findings (together with the typical brain MRI findings of cerebellar or pontocerebellar hypoplasia) may falsely suggest a diagnosis of PCH2. Compared to findings in *EXOSC3*-PCH, the findings in PCH2 are:

- No abnormalities of the spinal cord (whereas in PCH1 anterior horn cells are involved);
- Attenuation of the pons on brain MRI (whereas in PCH1 the pons can be unaffected).

Table 2. Genes of Interest in the Differential Diagnosis of *EXOSC3* Pontocerebellar Hypoplasia

Gene(s)	Phenotype/ Disorder	MOI	Brain MRI Findings	Clinical Characteristics
Key differential diagnosis disorders (in order of relevance)				

Table 2. continued from previous page.

Gene(s)	Phenotype/ Disorder	MOI	Brain MRI Findings	Clinical Characteristics
EXOSC8 *SLC25A46* *VRK1*	PCH1 [1, 2]	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. [3]
TSEN54	*TSEN54*-PCH (PCH2, 4, & 5)	AR	• Severe pontocerebellar hypoplasia w/relative sparing of pons • Profound supratentorial atrophy in PCH4	• Generalized clonus, impaired swallowing, dystonia, chorea, progressive microcephaly in PCH2 • PCH4 is a severe type of PCH2, w/congenital contractures & polyhydramnios.
SMN1	Spinal muscular atrophy type 1	AR	Normal	• Early-onset (birth-6 mos) disease is characterized by muscle weakness & lack of motor development. • Cognitive function is normal. • EMG reveals denervation; muscle biopsy shows grouped atrophy.
CLP1	PCH10 (OMIM 615803)	AR	Mild cerebellar atrophy/ hypoplasia	Very rare disorder characterized by DD, microcephaly, spasticity, axonal motor & sensory neuropathy, abnormal muscle tone, seizures, motor neuron degeneration
COASY	PCH12 (OMIM 618266)	AR	Prenatal-onset microcephaly; hypoplasia of cerebellum, brain stem, spinal cord	Severe prenatal-onset PCH, microcephaly, arthrogryposis w/ hypoplasia of spinal cord & brain stem, multiple congenital contractures, polyhydramnios, motor neuron degeneration
Other disorders to consider (in alphabetic order by gene)				

Table 2. continued from previous page.

Gene(s)	Phenotype/ Disorder	MOI	Brain MRI Findings	Clinical Characteristics
B3GALNT2 *B4GAT1* *DAG1* *FKRP* *FKTN* *GMPPB* *ISPD* *LARGE1* *POMGNT1* *POMGNT2* *POMK* *POMT1* *POMT2* *RXYLT1* [4]	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 pons) & severe cerebellar hypoplasia (PCH)	• 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 [1]	AR	MRI findings similar to PCH1B	Microcephaly, delayed walking, variable foot deformities, chorea, dystonic posturing, impaired cognition
PCLO	PCH3 [1]	AR		
>40 genes (e.g., *PMM2* [5])	Congenital disorders of glycosylation (CDG) (See also PMM2-CDG.)	AR (XL)	Pontocerebellar hypoplasia w/ superimposed atrophy, delayed myelination	Dysmorphic features, ataxia; organ failure in neonatal period
RARS2	PCH6 [1]	AR		• Very rare • ↑ CSF lactate concentration
RELN	Lissencephaly 2 (OMIM 257320)	AR	Classic lissencephaly w/ coexistent cerebellar & pontine hypoplasia	
SEPSECS	PCH2 [1]	AR	Progressive cerebello-cerebral atrophy closely resembles mild PCH.	Clinical findings closely resemble mild PCH2.
TOE1	PCH7 [1]	AR	PCH	Disorders of sex development
VLDLR	*VLDLR* cerebellar hypoplasia	AR	Gross cerebellar hypoplasia, flat ventral pons, simplified gyri	Ataxia & ID

AR = autosomal recessive; DD = developmental delay; ID = intellectual disability; MOI = mode of inheritance; PCH = pontocerebellar hypoplasia; XL = X-linked

1. van Dijk et al [2018]

2. OMIM Phenotypic Series: Pontocerebellar hypoplasia

3. 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.

4. OMIM Phenotypic Series: Muscular dystrophy-dystroglycanopathy, type A

5. PMM2-CDG (*CDG-Ia*) is the most common of a group of disorders of abnormal glycosylation of N-linked oligosaccharides.

Other conditions 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 (gestational age <28 weeks); 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 *EXOSC3* pontocerebellar hypoplasia (*EXOSC3*-PCH), 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 of *EXOSC3* Pontocerebellar Hypoplasia

System/Concern	Evaluation	Comment
Constitutional	Measure length & weight.	See **Gastrointestinal/Feeding** if 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.
Neurologic	Eval by pediatric neurologist	Assess for: • Evidence of severe generalized clonus; • Chorea, spasticity; • Seizures (to incl EEG); • Impaired central vision.
Hearing loss	Eval by audiologist	
Vision	Eval by pediatric ophthalmologist	• Assess visual acuity. • Fundoscopy to assess optic nerve
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 persons & their families re nature, MOI, & implications of *EXOSC3*-PCH to facilitate medical & personal decision making
Family support/ resources	Assess: • Use of community or online resources incl 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, or certified advanced genetic nurse

Treatment of Manifestations

No specific treatment for *EXOSC3*-PCH exists; the goals are to maximize function and reduce complications.

Ideally, each affected individual is managed by a multidisciplinary team of relevant specialists including developmental pediatricians, neurologists, occupational therapists, physical therapists, physiatrists, orthopedists, nutritionists, pulmonologists, and psychologists depending on the clinical manifestations (see Table 4).

Table 4. Treatment of Manifestations in Individuals with *EXOSC3* Pontocerebellar Hypoplasia

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.
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:

- 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 participatin 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.

Surveillance

Table 5. Recommended Surveillance for Individuals with *EXOSC3* Pontocerebellar Hypoplasia

System/Concern	Evaluation	Frequency
Respiratory	Assess airway & pulmonary function & secretion management.	Monitoring of respiratory function may be necessary to detect sleep apnea.
Gastrointestinal/ Feeding	• Aspiration risk & nutritional status • Monitor for constipation.	Annually; more frequently if needed
Musculoskeletal	• PT/OT eval • Assess 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

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

EXOSC3 pontocerebellar hypoplasia (*EXOSC3*-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 *EXOSC3* 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 an *EXOSC3* pathogenic variant and to allow reliable recurrence risk assessment. (*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 an *EXOSC3* 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.
- Although some intrafamilial variability has been described, sibs who inherit biallelic *EXOSC3* pathogenic variants typically have a clinical presentation similar to the proband (see Genotype-Phenotype Correlations).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. Individuals with *EXOSC3*-PCH are not likely to have offspring because of severe intellectual disability and the likelihood of early death.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *EXOSC3* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *EXOSC3* pathogenic variants in the family.

See Related Genetic Counseling Issues, **Population screening** for information about carrier testing in individuals who do not have a family history of *EXOSC3*-PCH.

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.

Population screening. Persons of Roma ancestry may choose to have carrier testing for the c.92G>C (p.Gly31Ala) founder variant (see Prevalence).

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 *EXOSC3* 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. EXOSC3 Pontocerebellar Hypoplasia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
EXOSC3	9p13.2	Exosome complex component RRP40	EXOSC3 @ LOVD	EXOSC3	EXOSC3

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 EXOSC3 Pontocerebellar Hypoplasia (View All in OMIM)

606489	EXOSOME COMPONENT 3; EXOSC3
614678	PONTOCEREBELLAR HYPOPLASIA, TYPE 1B; PCH1B

Molecular Pathogenesis

EXOSC3 encodes a subunit of the exosome complex which plays a role in RNA processing and degradation. Other pontocerebellar hypoplasia (PCH) types are caused by variants in genes involved in RNA processing as well; for example, biallelic variants in *TSEN54* cause PCH2, PCH4, and PCH5 (see *TSEN54*-Related Pontocerebellar Hypoplasia). The exact molecular pathway underlying PCH is unknown.

Mechanism of disease causation. The authors suggest that *EXOSC3* pathogenic variants lead to loss of function or reduced function of the EXOSC3 protein, since individuals with a nonsense variant are more severely affected than those with missense variants.

Table 6. Notable *EXOSC3* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_016042.3 NP_057126.2	c.92G>C	p.Gly31Ala	Founder variant in Roma population [Wan et al 2012, Rudnik-Schöneborn et al 2013]
	c.238G>T	p.Val80Phe	Milder clinical course (See Genotype-Phenotype Correlations.) [Zanni et al 2013]
	c.395A>C	p.Asp132Ala	• Most prevalent pathogenic variant w/ancestral origin (allele frequency of 0.1% in European Americans) [Wan et al 2012, Rudnik-Schöneborn et al 2013] • Milder clinical course [Rudnik-Schöneborn et al 2013, Eggens et al 2014] (See Genotype-Phenotype Correlations.) [Zanni et al 2013]
	c.572G>A	p.Gly191Asp	Milder clinical course [Le Duc et al 2020] (See Genotype-Phenotype Correlations.) [Zanni et al 2013]

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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