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Chondrodysplasia Punctata 1, X-Linked

Synonym: Arylsulfatase E Deficiency

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Summary

Clinical characteristics

X-linked chondrodysplasia punctata 1 (CDPX1) is characterized by chondrodysplasia punctata (stippled epiphyses), brachytelephalangy (shortening of the distal phalanges), and nasomaxillary hypoplasia. Although most affected males have minimal morbidity and skeletal findings that improve by adulthood, some have significant medical problems including respiratory involvement, cervical spine stenosis and instability, mixed conductive and sensorineural hearing loss, and intellectual disability.

Diagnosis/testing

The diagnosis of CDPX1 is established in a male proband with typical clinical and radiographic findings and a hemizygous *ARSL* pathogenic variant identified by molecular genetic testing. Testing of ARSL enzymatic activity is not currently available on a clinical basis.

Management

Treatment of manifestations: Treatment of respiratory difficulty as per ENT and/or pulmonologist including nasal stents and oxygen as needed. Severe maxillary hypoplasia or maxillary retrognathia may require reconstructive surgery in older individuals. Instability of the cervical spine may require a cervical collar or spinal fusion. Decompression for cervical spine stenosis as needed. Hearing aids and pressure equalization tubes may be needed for hearing loss. Therapies and individualized education plan for those with developmental delay and/or learning disorder. Standard treatment for vision issues and cardiac anomalies.

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Surveillance: Routine monitoring for growth deficiency, scoliosis, hearing loss, developmental delay, and ocular abnormalities. Assess for cervical spine instability by flexion-extension radiographs every six to twelve months until growth is completed.

Agents/circumstances to avoid: In individuals with cervical spine instability, extreme neck extension and neck flexion and contact sports should be avoided. In case of general anesthesia, the cervical spine should be assessed by imaging prior to the procedure.

Genetic counseling

CDPX1 is inherited in an X-linked manner. If the mother of a proband has the *ARSL* pathogenic variant identified in the proband, 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 be carriers and thus far have not been affected. Males with CDPX1 pass the pathogenic variant to all of their daughters and none of their sons. Carrier testing for at-risk relatives and prenatal testing for at-risk pregnancies are possible if the *ARSL* pathogenic variant has been identified in the family.

Diagnosis

Suggestive Findings

X-linked chondrodysplasia punctata 1 (CDPX1) should be **suspected** in a **male proband** with the following clinical and radiographic findings.

Clinical findings

- Brachytelephalangy (shortening of the distal phalanges)
- Nasomaxillary hypoplasia
  - Hypoplasia of the anterior nasal spine
  - Flattened nasal base
  - Reduced nasal tip protrusion with short columella
  - Crescent-shaped nostrils
  - Vertical grooves within the alae nasi (in some individuals)
- Postnatal short stature

Radiographic findings

- Chondrodysplasia punctata (stippled epiphyses) are observed on skeletal x-rays in infancy, usually of the ankle and distal phalanges, although they can be more generalized to include epiphyses of long bones, vertebrae, hips, costochondral junctions, and hyoid bone. An inverted triangular shape of the distal phalanges with lateral stippling at the apex is characteristic. Stippling is usually symmetric and age dependent and cannot be seen after normal epiphyseal ossification at age two to three years.
- Calcifications can also occur in the larynx, trachea, and main stem bronchi (structures that do not normally ossify) and cause stenosis.
- Vertebral abnormalities are common and include dysplastic and hypoplastic vertebrae and coronal or sagittal clefts. Cervical vertebral abnormalities can cause cervical kyphosis, cervical stenosis, and atlantoaxial instability.

Laboratory findings. Normal clotting function (PT and PTT) and clotting factors II, VII, IX, and X (See Differential Diagnosis.)

Establishing the Diagnosis

The diagnosis of CDPX1 is **established** in a **male proband** with suggestive findings and a hemizygous pathogenic variant in *ARSL* identified by molecular genetic testing (see Table 1).

Note: (1) Identification of a hemizygous *ARSL* variant of uncertain significance does not establish or rule out the diagnosis of this disorder. (2) Testing of ARSL enzymatic activity is not currently available on a clinical basis.

Molecular genetic testing approaches can include the following:

- If an Xp deletion syndrome is suspected (see Genetically Related Disorders), **chromosomal microarray analysis (CMA)** to detect genome-wide large deletions/duplications (including *ARSL*) that cannot be detected by sequence analysis
- **Single-gene testing.** Sequence analysis of *ARSL* 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 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 multigene panel** that includes *ARSL* and other genes of interest (see Differential Diagnosis) can be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

Table 1. Molecular Genetic Testing Used in Chondrodysplasia Punctata 1, X-Linked

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
ARSL (formerly *ARSE*)	Sequence analysis [3, 4]	88% [4]
	Gene-targeted deletion/duplication analysis [5]	12% [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. 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.

Clinical Characteristics

Clinical Description

Affected Males

The most consistent clinical features of X-linked chondrodysplasia punctata 1 (CDPX1) in affected males are chondrodysplasia punctata (CDP), brachytelephalangy, and nasomaxillary hypoplasia. Most affected males have minimal morbidity, and skeletal findings improve by adulthood; however, some have significant medical problems including airway stenosis and cervical spine instability.

To date, approximately 50 individuals with a pathogenic variant in *ARSL* have been reported in the literature. The following description of the phenotypic features associated with this condition is based on the case series from Nino et al [2008] and Matos-Miranda et al [2013].

Table 2. Chondrodysplasia Punctata 1, X-Linked: Frequency of Select Features

Feature	Proportion of Persons w/ Feature [1]	Comment
Chondrodysplasia punctata (CDP)	45/46 [2]	CDP typically not visible on radiographs after age 3 yrs
Nasomaxillary hypoplasia	42/42	
Brachytelephalangy	33/35	
Short stature (height <5th %ile)	12/16	Postnatal onset
Significant respiratory abnormalities	17/23	Frequent respiratory infections, asthma, central apnea, tachypnea, neonatal respiratory distress, mechanical ventilation, tracheotomy, chronic nasal obstruction, nasal stents
Mixed conductive & sensorineural hearing loss	13/18	
Significant cervical spine abnormalities	10/16	Dysplasia or hypoplasia of cervical vertebrae, C1–C2 anterior subluxation, kyphosis, cervical cord compression, spinal canal stenosis
Delayed cognitive development	5/6	

1. From Nino et al [2008], Matos-Miranda et al [2013]. Note: These studies may have an ascertainment bias towards more severely affected children.
2. A child with brachytelephalangy, nasomaxillary hypoplasia, and tracheobronchial calcifications did not have CDP at age 14 months [Casarin et al 2009].

Nasomaxillary hypoplasia. Hypoplasia of the anterior nasal spine results in a characteristic flattened nasal base, reduced nasal tip protrusion with short columella, and in some individuals vertical grooves within the alae nasi. The nostrils are crescent shaped.

Brachytelephalangy. The shortening of the distal phalanges is typically seen in newborns in both hands and feet. Brachytelephalangy persists in the fingers over the life span of individuals with CDPX1 but may become less apparent with age.

Growth measurements tend to be normal at birth; short stature usually develops postnatally but only some affected adults have short stature.

Respiratory insufficiency. Respiratory compromise caused by severe nasal hypoplasia or extensive punctate calcifications along the tracheobronchial tree may require choanal stents, tracheostomy, or tracheal reconstruction [Wolpoe et al 2004].

Hearing loss. Conductive and sensorineural hearing loss have been reported.

Cervical spine abnormalities. Abnormal ossification of the cervical vertebrae can result in cervical spine stenosis and/or instability and spinal cord compression [Garnier et al 2007, Vogel & Menezes 2012].

Developmental delay / intellectual disability. Cognitive delay has been reported in some individuals.

Other. Less frequently seen findings:

- Ophthalmologic abnormalities (e.g., cataracts, optic disc atrophy, small optic nerves)
- Cardiac anomalies (e.g., patent ductus arteriosus, ventricular septal defect, atrial septal defect, pulmonary artery stenosis)
- Gastroesophageal reflux
- Feeding difficulties

Prognosis. Affected individuals most often have a normal life span; however, some males experience severe morbidity and early mortality due to respiratory compromise, cervical spine stenosis, and/or cervical instability [Brunetti-Pierri et al 2003, Garnier et al 2007, Nino et al 2008].

Heterozygotes

Affected carrier females have not been described, presumably because they have sufficient levels of ARSE enzyme activity expressed from both X chromosomes. Some heterozygous females may have smaller-than-expected stature [Sheffield et al 1998, Brunetti-Pierri et al 2003].

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Penetrance

Penetrance may be incomplete. *ARSL* pathogenic variant p.Gly137Ala was identified in an affected proband and his unaffected maternal grandfather [Sheffield et al 1998]. A deletion of exons 7-10 was identified in an affected proband and his asymptomatic maternal grandfather [Casarin et al 2009]. Considering that physical features of CDPX1 improve with age, it is uncertain whether such instances represent non-penetrance.

Nomenclature

CDPX1 refers specifically to a deficiency of ARSL enzyme activity.

Brachytelephalangic chondrodysplasia punctata (BCDP) is a descriptive term associated with CDPX1 and its non-genetic phenocopies.

Prevalence

The prevalence of CDPX1 is unknown; in one study it was estimated at 1:500,000 [Malou et al 2001], but it is likely more common.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline intragenic pathogenic variants in *ARSL* (formerly *ARSE*).

Contiguous Xp gene deletions that include *ARSL* have additional phenotypic features that may include ichthyosis, hypogonadotropic hypogonadism, anosmia, cataracts, intellectual disability, and autism. Affected males have Xp terminal deletions, interstitial deletions, or translocations (e.g., SHOX Deficiency Disorders).

Differential Diagnosis

Genetic Disorders

Table 3a. Disorders with Brachytelephalangic Chondrodysplasia Punctata (BCDP) in the Differential Diagnosis of CDPX1

Gene(s)	Disorder	MOI	Additional Overlapping Feature	Findings Distinguishing the Disorder from CDPX1
GGCX *VKORC1*	Combined deficiency of vitamin K-dependent clotting factor 1 (OMIM 277450) & factor 2 (OMIM 607473)	AR	Nasal hypoplasia	Bleeding disorder due to variably ↓ levels of coagulation factors II, VII, IX, & X, & protein C, protein S, & protein Z
MGP	Keutel syndrome (OMIM 245150)	AR		More diffuse & progressive calcification of cartilage incl nose, auricles, & respiratory tract

AR = autosomal recessive; CDPX1 = chondrodysplasia punctata 1, X-linked; MOI = mode of inheritance

Table 3b. Disorders with Non-Brachytelephalangic Chondrodysplasia Punctata and Cervical Spine Anomalies in the Differential Diagnosis of CDPX1

Gene(s)	Disorder	MOI	Findings Distinguishing the Disorder from CDPX1	
			Clinical Features	Biochemical Findings
AGPS *GNPAT* *PEX5* *PEX7*	RDCP1, 2, 3, & 5 (OMIM PS215100)	AR	• Rhizomelia, profound growth restriction, congenital cataract • Absence of nasal hypoplasia	Deficiency of peroxisomal plasmalogen (measured in erythrocytes) is diagnostic.
EBP	CDPX2 [1]	XL	• Asymmetric rhizomesomelia, sectorial cataracts, patchy alopecia, ichthyosis, & atrophoderma • Affected individuals are typically female • Absence of nasal hypoplasia	↑ 8(9)-cholestenol & 8-dehydrocholesterol levels in plasma
NSDHL [2]	CHILD syndrome (See *NSDHL*-Related Disorders.)	XL	• Male lethal, unilateral CDP, rhizomelia, polydactyly, skin findings; one side of the body affected • Absence of nasal hypoplasia	↑ 4-methyl- & carboxysterols levels in cultured lymphoblasts (but only occasionally in plasma) [2]

AR = autosomal recessive; CDP = chondrodysplasia punctata; CDPX = X-linked chondrodysplasia punctata; CHILD = congenital hemidysplasia, ichthyosis, limb defects; MOI = mode of inheritance; RCDP = rhizomelic chondrodysplasia punctata; XL = X-linked

1. Also referred to as Conradi-Hünermann syndrome and Happle syndrome.

2. NSDHL encodes a cholesterol biosynthetic 4-methylsterol dehydrogenase. The enzyme, part of a 4-methylsterol demethylase complex, occurs one step proximal to the EBP sterol isomerase.

Teratogen Exposures

Warfarin embryopathy and other vitamin K deficiencies (including vitamin K epoxide reductase deficiency) are phenotypically similar to CDPX1 with especially severe hypoplasia of the nasal bone ("Binder anomaly"), distal phalangeal abnormalities, and punctata of the axial skeleton.

BCDP was reported in infants whose mothers had presumed vitamin K deficiency as a result of severe hyperemesis gravidarum [Brunetti-Pierri et al 2007], Crohn disease [Toriello et al 2013], small intestinal obstruction [Eash et al 2003], postoperative small bowel syndrome [Menger et al 1997, Khau Van Kien et al

1998], untreated celiac disease [Menger et al 1997], pancreatitis [Herman et al 2002], cholelithiasis [Jaillet et al 2005], and liver fibrosis due to transfusional iron overload [Xie et al 2013]. Maternal vitamin K deficiency was indirectly documented in three instances [Khau Van Kien et al 1998, Alessandri et al 2010, Xie et al 2013] and suspected in the others. Molecular genetic testing did not identify an *ARSL* pathogenic variant in the infant described by Eash et al [2003].

Maternal autoimmune disease (systemic lupus erythematosus) [Blask et al 2018, Alkhunaizi et al 2020], mixed connective tissue disease, and scleroderma [Chitayat et al 2008, Schulz et al 2010] can cause CDP with rhizomelic limb shortening.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with X-linked chondrodysplasia punctata 1 (CDPX1), the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Chondrodysplasia Punctata 1, X-Linked

System/Concern	Evaluation	Comment
Respiratory	Assessment of upper & lower airways by ENT & pulmonologist	If stridor is present
Obstructive sleep apnea	Polysomnography	If sleep apnea is suspected
Skeletal	• Growth assessment • Skeletal survey • Assessment for scoliosis	To determine extent of CDP & skeletal anomalies
Cervical spine instability	Flexion, neutral, & extension lateral radiographs of the cervical spine	• Cervical spine MRI if clinical evidence of cervical myelopathy or significant instability on radiographs • Special consideration when performing this study in flexion & extension positions as spinal cord compression may only occur w/these movements (i.e., normal neutral cervical spine MRI does not rule out dynamic compression). • Consider brain MRI at time of cervical spine MRI. [1]
Audiology	Hearing assessment	To assess for sensorineural & conductive hearing loss
Developmental delay	Developmental assessment	
Ophthalmologic abnormalities	Ophthalmologic eval	To evaluate for cataracts, optic disc atrophy, & small optic nerves
Cardiac anomalies	Echocardiogram	To evaluate for patent ductus arteriosus, ventricular septal defect, atrial septal defect, pulmonary artery stenosis
Genetic counseling	By genetics professionals [2]	To inform affected persons & families re nature, MOI, & implications of CDPX1 in order to facilitate medical & personal decision making

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

CDP = chondrodysplasia punctata; CDPX1 = chondrodysplasia punctata 1, X-linked; MOI = mode of inheritance
1. Although not reported in individuals with CDPX1, cortical dysplasia was reported in two infants with brachytelephalangic chondrodysplasia punctata due to maternal vitamin K deficiency [Brunetti-Pierri et al 2007, Bhoj et al 2013]. It is suspected that cortical dysplasia could occur in individuals with CDPX1 [Author, personal observation].
2. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 5. Treatment of Manifestations in Individuals with Chondrodysplasia Punctata 1, X-Linked

Manifestation/Concern	Treatment
Respiratory difficulty	Treatment per ENT/pulmonologist incl nasal stents & oxygen
Severe maxillary hypoplasia or maxillary retrognathia	Reconstructive surgery in older individuals as needed [1]
Cervical spine instability	Cervical collar or spinal fusion as needed
Cervical spine stenosis	Decompression as needed
Hearing loss	• Hearing aids • Pressure equalization tube placement as needed
Developmental delays	• Adjuvant therapies incl PT, OT, & speech therapy for persons w/identified developmental delays • Individualized education plans for learning disorders & school performance issues
Vision issues	Treatment per ophthalmologist
Cardiac anomalies	Treatment per cardiologist

OT = occupational therapy; PT = physical therapy
1. Carach et al [2002]

Surveillance

Table 6. Recommended Surveillance for Individuals with Chondrodysplasia Punctata 1, X-Linked

System/Concern	Evaluation	Frequency
Short stature	Growth assessment	Annually
Scoliosis	Clinical assessment of thoracic & lumbar spine	As needed
Cervical spine instability	• Flexion-extension radiograph • Flexion-extension MRI if instability & compression on radiographs or limited interpretation on radiographs	• Every 6-12 mos until growth is completed & prior to anesthesia to assess for cervical spine instability • Note: Some individuals have developed cervical spine instability later in the disease course [Vogel & Menezes 2012].

Table 6. continued from previous page.

System/Concern	Evaluation	Frequency
Hearing loss	Hearing assessment	As needed
Developmental delay	Monitor developmental progress & educational needs.	
Ocular abnormalities	Ophthalmologic eval	

Agents/Circumstances to Avoid

In individuals with cervical spine instability, extreme neck extension and neck flexion and contact sports should be avoided.

In case of general anesthesia, the cervical spine should be assessed by imaging prior to the procedure.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk male relatives of an individual with CDPX1 in order to identify as early as possible those who would benefit from evaluation for cervical spine instability and early screening for cardiac anomalies, ophthalmologic abnormalities, and hearing loss.

See Genetic Counseling for issues related to evaluation 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

X-linked chondrodysplasia punctata 1 (CDPX1) is inherited in an X-linked manner.

Risk to Family Members

Parents of a male proband

- The father of an affected male will not have the disorder nor will he be hemizygous for the *ARSL* (formerly *ARSE*) pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote (carrier). Note: If a woman has more than one affected child and no other affected relatives and if the *ARSL* pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism.

- If a male is the only affected family member (i.e., a simplex case), the mother may be a carrier or the affected male may have a *de novo ARSL* pathogenic variant, in which case the mother is not a carrier.
- To date, CDPX1 caused by a *de novo ARSL* pathogenic variant has not been reported. All mothers of males with a detectable *ARSL* pathogenic variant tested to date were found to be carriers [Nino et al 2008, Matos-Miranda et al 2013].

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

- If the mother of the proband has an *ARSL* 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 be carriers and have thus far not been affected (see Clinical Description, Heterozygotes).
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the *ARSL* pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of the mother, the risk to sibs is low but greater than that of the general population because of the theoretic possibility of maternal germline mosaicism.

Offspring of a male proband. Males with CDPX1 transmit the *ARSL* pathogenic variant to:

- All of their daughters, who will be carriers (heterozygotes) and will not be expected to have clinical manifestations of CDPX1 (affected carrier females have not been reported to date);
- None of their sons.

Other family members. The proband's maternal aunts may be at risk of being carriers and the aunts' offspring, depending on their sex, may be at risk of being carriers or of being affected.

Note: Molecular genetic testing may be able to identify the family member in whom a *de novo* pathogenic variant arose, information that could help determine genetic risk status of the extended family.

Carrier Detection

Molecular genetic testing of at-risk female relatives to determine their genetic status is most informative if the *ARSL* pathogenic variant has been identified in the proband.

Note: (1) Females who are heterozygous (carriers) for this X-linked disorder will usually not be affected. (2) Identification of female heterozygotes requires either (a) prior identification of the *ARSL* pathogenic variant in the family or, (b) if an affected male is not available for testing, molecular genetic testing first by sequence analysis, and if no pathogenic variant is identified, by gene-targeted deletion/duplication analysis.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk male relatives for the purpose of early diagnosis and treatment.

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 affected, are carriers, or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the *ARSL* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for CDPX1 are possible.

Ultrasound examination. Abnormal spinal curvature [He et al 2019] as well as hypoplastic nose and nasal bone [Nino et al 2008] have been identified on prenatal ultrasound examination in trimesters two and three in affected male fetuses.

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.

- **CDPX1 Family Support Group**

  Email: thegillums@cox.net

- **BabyHearing.org**

  This site, developed with support from the National Institute on Deafness and Other Communication Disorders, provides information about newborn hearing screening and hearing loss.

  babyhearing.org

- **Human Growth Foundation**

  www.hgfound.org

- **Little People of America**

  Phone: 888-LPA-2001; 714-368-3689

  Fax: 707-721-1896

  Email: info@lpaonline.org

  lpaonline.org

- **MAGIC Foundation**

  Phone: 800-362-4423

  Email: contactus@magicfoundation.org

  www.magicfoundation.org

- **UCLA International Skeletal Dysplasia Registry (ISDR)**

  Phone: 310-825-8998

  International Skeletal Dysplasia Registry

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. Chondrodysplasia Punctata 1, X-Linked: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ARSL	Xp22.33	Arylsulfatase L	ARSE @ LOVD	ARSL	ARSL

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 Chondrodysplasia Punctata 1, X-Linked (View All in OMIM)

300180	ARYLSULFATASE L; ARSL
302950	CHONDRODYSPLASIA PUNCTATA 1, X-LINKED RECESSIVE; CDPX1

Molecular Pathogenesis

ARSL encode arylsulfatase L (ARSE), a sulfatase that localizes to Golgi membranes [Daniele et al 1998]. Sulfatase enzymes hydrolyze sulfate ester bonds in glycosaminoglycans, sulfolipids, steroid sulfates, and other compounds. All sulfatases undergo a post-translational processing event by the enzyme SUMF1 in which a C-alpha-formylglycine (FGly) is generated from a cysteine [Cosma et al 2003].

Although its physiologic substrate has not yet been identified, ARSE enzyme activity is inhibited in vitro by the anticoagulant warfarin [Rost et al 2004]. Given the well-documented phenotypic similarities between CDPX1 and warfarin embryopathy, ARSE may be the enzyme inhibited by warfarin.

Mechanism of disease causation. The majority of missense variants studied showed negligible activity using a gene expression system and the artificial substrate, fluorogenic 4-methylumbelliferyl (4-MU) sulfate [Daniele et al 1998, Brunetti-Pierri et al 2003, Matos-Miranda et al 2013]. Individuals with *ARSL* gene deletions, nonsense variants, or missense variants present with indistinguishable phenotypes, supporting loss of function as the disease mechanism [Matos-Miranda et al 2013].

***ARSL*-specific laboratory technical considerations.** *ARSL* has a pseudogene on the Y chromosome, which may complicate detection of exon-level deletions for some exons.

Table 7. Notable *ARSL* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000047.2 NP_000038.2	c.410G>C	p.Gly137Ala	Incomplete penetrance reported in one family [Sheffield et al 1998]

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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