GENEReviews

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Chondrodysplasia Punctata 1, X-Linked Recessive

[*CDPX1, Arylsulfatase E Deficiency*]

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Summary

Disease characteristics. X-linked recessive chondrodysplasia punctata 1 (CDPX1), a congenital disorder of bone and cartilage development, is caused by a deficiency of the Golgi enzyme arylsulfatase E (ARSE). It 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 compromise, cervical spine stenosis and instability, mixed conductive and sensorineural hearing loss, and abnormal cognitive development.

Diagnosis/testing. In approximately 25% of individuals with features of CDPX1, routine karyotype analysis reveals deletions or rearrangements of the short arm of the X chromosome (Xp) that include *ARSE*. FISH for *ARSC* or array genomic hybridization (array GH) can be used to evaluate for smaller interstitial deletion syndromes. Sequence analysis of *ARSE* identifies mutations in up to 60% to 75% of males who meet clinical diagnostic criteria.

Management. *Treatment of manifestations:* Respiratory difficulty can require frequent monitoring, nasal stents, and oxygen. 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. *Surveillance:* routine monitoring of hearing, growth, development, and cervical spine instability.

Genetic counseling. CDPX1 is inherited in an X-linked recessive manner. If the mother of a proband has a disease-causing mutation, the chance of transmitting it in each pregnancy is 50%. Males who inherit the mutation will be affected; females who inherit the mutation will be carriers and will usually not be affected. Males with CDPX1 pass the disease-causing mutation 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 disease-causing mutation has been identified in the family.

Diagnosis

Clinical Diagnosis

X-linked recessive chondrodysplasia punctata 1 (CDPX1), a congenital disorder of bone and cartilage development, is caused by a deficiency of the enzyme, arylsulfatase E (ARSE).

CDPX1 is suspected in a male with the following clinical findings:

- Chondrodysplasia punctata (CDP) (stippled epiphyses) (see Radiographic findings)
- Brachytelephalangy (shortening of the distal phalanges)
- Nasomaxillary hypoplasia in which hypoplasia of the anterior nasal spine results in a characteristic flattened nasal base, reduced nasal tip protrusion with short columella, and in some cases vertical grooves within the alae nasi. The nostrils are crescent-shaped. It may appear as if the child's nose is pressed flat against a window.

Note: Coagulopathy should be explicitly ruled out by measurement of clotting factors II, VII, IX, and X (see Differential Diagnosis).

The diagnosis is confirmed by molecular genetic testing.

Radiographic findings

- Stippled epiphyses are observed on skeletal x-rays in infancy, usually in the ankle and distal phalanges, although they can be more generalized to include epiphyses of long bones, vertebrae, hips, costochondral junctions, hyoid bone, and tracheal cartilage. An inverted triangular shape of the distal phalanges with lateral stippling at the apex is characteristic. Stippling is usually symmetric and tends to disappear radiologically after age two to three years when the epiphyses ossify.
- Vertebral abnormalities are common and include dysplastic and hypoplastic vertebrae and coronal or sagittal clefts. Cervical vertebral abnormalities can cause cervical kyphosis and atlantoaxial instability.

Testing

Arylsulfatase E enzyme activity. A reliable biochemical assay to measure ARSE enzyme activity is not yet available.

Cytogenetic analysis. Routine karyotype analysis reveals Xp deletions or rearrangements that include *ARSE* in approximately 25% of individuals with features of CDPX1. To identify these individuals, karyotype analysis should be performed and consideration given to using either FISH with an *ARSC* probe or array genomic hybridization (array GH) to evaluate for smaller interstitial deletion syndromes [Hou 2005].

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. Mutations in *ARSE* are the only known genetic cause of CDPX1.

Clinical testing

- **Sequence analysis.** Sequencing of all 11 exons of *ARSE* and flanking intronic regions from genomic DNA identifies mutations in 60% to 75% of males who meet clinical diagnostic criteria [Franco et al 1995, Parenti et al 1997, Sheffield et al 1998, Brunetti-Pierri et al 2003, Garnier et al 2007, Nino et al 2008].The failure to achieve higher mutation detection rates could reflect the inclusion of phenocopies, genetic heterogeneity, or mutations in regions of *ARSE* that were not sequenced.
- **Deletion/duplication analysis.** Deletions involving *ARSE* that are not detected by cytogenetic analysis are identified in approximately 10% of individuals with CDPX1.

Table 1 summarizes molecular genetic testing for this disorder.

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

Gene Symbol	Test Method	Mutations Detected	Mutation Detection Frequency by Test Method		Test Availability
			Affected Males [1]	Carrier Females	
ARSE	Sequence analysis	Sequence variants	60%-75% [1,2]	Unknown	Clinical Testing
		Exonic, multiexonic, and whole-gene deletions		0% [3]	
	Deletion/ duplication analysis [4]	Exonic, multiexonic, and whole-gene deletions	See footnote [2]	Unknown	

1. Non-genetic phenocopies contribute to some cases in which *ARSE* sequence analysis is normal [Brunetti-Pierri et al 2003, Eash et al 2003, Nino et al 2008].

2. Sequence analysis can detect putative exonic, multiexonic, and whole-gene deletions on the X chromosome in affected males as a result of amplification by polymerase chain reaction (PCR). The presence of a deletion should be confirmed by a direct testing method.

3. Sequence analysis of genomic DNA cannot detect exonic, multiexonic, or whole-gene deletions on the X chromosome in carrier females.

4. Testing that detects deletions/duplications not readily detectable by sequence analysis of genomic DNA; a variety of methods including quantitative PCR, real-time PCR, multiplex ligation-dependent probe amplification (MLPA), or array GH may be used.

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

To establish the diagnosis in a male proband

- CDP, brachytelephalangy, and nasomaxillary hypoplasia should be present on clinical examination.
- Conduct molecular genetic testing for mutations in *ARSE.*
- If an Xp deletion syndrome is suspected, conduct karyotype analysis before molecular testing.

Carrier testing for at-risk relatives requires prior identification of the disease-causing mutations in the family.

Note: Carriers are heterozygous females who are not known to be at risk of manifesting clinical findings of CDPX1.

Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the disease-causing mutation in the family.

Genetically Related (Allelic) Disorders

Contiguous Xp gene deletions that include *ARSE* have additional phenotypic features that may include ichthyosis, hypogonadotrophic hypogonadism, anosmia, cataracts, and mental retardation. Affected males have Xp terminal deletions, interstitial deletions, or translocations; most involve *SHOX-ARSC* (*STS*) genes. (See also *SHOX*-Related Haploinsufficiency Disorders). In one of the characterized deletion syndromes, the presence of ichthyosis, cataracts, anosmia, and hypogonadotrophic hypogonadism reflects associated deletions of *ARSC* (*STS*) and *KAL1*. (See also Kallman Syndrome.)

Clinical Description

Natural History

Affected males. The most consistent clinical features of X-linked recessive chondrodysplasia punctata 1 (CDPX1) in affected males are 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.

Growth measures tend to be normal at birth; short stature usually develops postnatally but only some affected adults have small stature. The shortening of the distal phalanges may become less apparent with age such that older individuals may show brachytelephalangy only in some digits.

Affected individuals have been thought to have a normal life span; however, recent descriptions have identified persons with more severe morbidity and mortality. These complications include the following:

- Respiratory compromise caused by severe nasal hypoplasia or extensive punctate calcifications along the tracheobronchial tree requiring choanal stents, tracheostomy, or tracheal reconstruction [Wolpoe et al 2004].
- Abnormal ossification of the cervical vertebrae that leads to cervical spine stenosis and instability [Garnier et al 2007].

These complications have led to early death in some cases [Brunetti-Pierri et al 2003, Garnier et al 2007, Nino et al 2008].

In a retrospective review of clinical features associated with CDPX1 and proven mutations in *ARSE,* the following were observed [Nino et al 2008]:

- Significant respiratory abnormalities (30%)
- Mixed conductive and sensorineural hearing loss (~25%)
- Significant cervical spine abnormalities (20%)
- Delayed cognitive development (16%)

Less frequently seen findings included the following:

- Ophthalmologic abnormalities (cataracts, optic disc atrophy, small optic nerves)
- Cardiac abnormalities (PDA, VSD, ASD)
- Gastroesophageal reflux
- Feeding difficulties

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

Genotype-Phenotype Correlations

The absence of common mutations precludes identifying correlations between genotype and phenotype.

The severity of the phenotype differed significantly between two brothers with the missense allele p.Ile40Ser, demonstrating variable intrafamilial disease expression [Nino et al 2008].

Thus far, affected individuals with gene deletions do not appear to be more severely affected than those with missense alleles.

Penetrance

The penetrance appears to be complete; however, in one report, the mutation p.Gly137Ala was identified in a proband and his maternal grandfather, the latter of whom was considered asymptomatic [Sheffield et al 1998]. This missense substitution involving a conserved amino acid was identified in a second unrelated, clinically affected proband [Nino et al 2008], implicating it as pathologic. Considering that physical features of CDPX1 improve with age, it is uncertain if this case represents non-penetrance.

Nomenclature

CDPX1 refers specifically to a deficiency of ARSE 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 to be 1:500,000 [Malou et al 2001], but it is likely more common.

CDPX1 is pan ethnic.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Brachytelephalangic chondrodysplasia punctata (BCDP)

Stippled calcifications are observed in a wide variety of disorders including single gene disorders, chromosomal abnormalities, and intrauterine infections or drug exposure (for a

review see Patel et al 1999). A number of those disorders with radiographic stippling are also associated with shortening of the distal phalanges.

Genetic conditions associated with BCDP

- **Keutel syndrome.** This autosomal recessive disorder has features that overlap with X-linked recessive chondrodysplasia punctata 1 (CDPX1), but with more diffuse and progressive calcification of cartilage including nose, auricles, and respiratory tract. Peripheral pulmonic stenosis is also observed. Defects in the vitamin K-dependent matrix Gla protein (MGP) cause Keutel syndrome [Munroe et al 1999].
- **Deficiency of vitamin K epoxide reductase subunit 1 (VKORC1**). Defects in VKORC1 cause both warfarin resistance and multiple coagulation factor deficiency type 2, an autosomal recessive disorder that also may include BCDP [Pauli et al 1987, Rost et al 2004].
- **Xp contiguous deletion syndromes.** See Genetically Related Disorders.
- **Multiple sulfatase deficiency** is a rare autosomal recessive disorder characterized by impaired activity of all known sulfatases including ARSE [Cosma et al 2003].

Teratogenic conditions associated with BCDP. Both male and female infants with BCDP have been described. In the case of an affected male, no specific clinical features distinguished CDPX1 from these non-genetic conditions [Nino et al 2008].

- **Prenatal exposure to warfarin**. BCDP is well described in infants born to mothers receiving warfarin in early gestation [Hall et al 1980]. Warfarin interferes with the recycling of vitamin K.
- **Reduced intestinal absorption of vitamin K**. BCDP was reported in infants whose mothers had presumed vitamin K deficiency as a result of severe hyperemesis gravidarum [Brunetti-Pierri et al 2007], 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], and cholelithiasis [Jaillet et al 2005]. Maternal vitamin K deficiency was indirectly documented in one case [Khau Van Kien et al 1998] and suspected in the others. In one of these cases *ARSE* molecular analysis was negative [Eash et al 2003].
- **Hydantoins.** Both stippling and brachytelephalangy have been reported after exposure to hydantoins [Howe et al 1995]. It is unclear whether this is a result of the known effect of hydantoins on vitamin K cycling.
- **Alcohol.** Occasionally, infants with other evidence for intrauterine consequences of maternal alcoholism have stippled epiphyses similar to that seen in BCDP [Leicher-Düber et al 1990].

Note: Prenatal exposure to warfarin, fetal vitamin K deficiency, and vitamin K epoxide reductase deficiency have been associated with brain malformation [Menger et al 1997, Van Driel et al 2002, Puetz et al 2004, Brunetti-Pierri et al 2007]. However, brain abnormalities have not been reported to date in persons with *ARSE* mutations.

Maternal autoimmune disease. BCDP was reported in infants born to mothers with systemic lupus erythematosus (SLE), Sjogren syndrome, and unclassified autoimmune disorders [Kozlowski et al 2004, Kirkland et al 2006, Nino et al 2008, Shanske et al 2007]. It was proposed that antibodies against ARSE or a component of the biochemical pathway are causative.

Non-brachytelephalangic CDP and other conditions with CDP that are clinically distinguishable from BCDP

- **Conradi-Hunermann-Happle syndrome (CDPX2)** [Herman et al 2002] and **CHILD syndrome** (**c**ongenital **h**emidysplasia, **i**chthyosis, and **l**imb **d**efects) [Konig et al 2000] are a result of defects in cholesterol synthesis; they are X-linked dominant and typically lethal in males:
  - CDPX2 is caused by defects in sterol 8-isomerase (encoded by *EBP*). Affected females have asymmetric rhizomesomelia, sectorial cataracts, patchy alopecia, ichthyosis, and atrophoderma. Rare males with a 47, XXY karyotype or mosaic for defects in *EBP* have been reported [Aughton et al 2003].
  - CHILD syndrome results from defects in the NAD(P)-dependent steroid dehydrogenase-like enzyme. Affected females have unilateral distribution of ichthyosis, limb defects, CDP, and visceral anomalies.
- **Rhizomelic chondrodysplasia punctata** is an autosomal recessive disorder caused by a deficiency of the peroxisomal step of ether phospholipid synthesis [Braverman et al 2002] (see Rhizomelic Chondrodysplasia Punctata Type 1).
- **Tibial-metacarpal type CDP (CDP-TM)** is inherited in an autosomal dominant manner; the gene defect is unknown [Savarirayan et al 2004].
- **Humeral-metacarpal type CDP** may include brachytelephalangy as well as hypoplasia of the humeri and metacarpals [Fryburg & Kelly 1996]. All instances have been sporadic.
- **Toriello-type CDP** is a rare and presumably autosomal recessive disorder with multiple dysmorphic features, colobomata, short stature, and stippling of the proximal humeral epiphyses [Toriello et al 1993].
- **Smith-Lemli-Opitz syndrome**, resulting from a defect in conversion of 7-dehydrocholesterol to cholesterol, can also present with stippled calcifications.
- **Peroxisome biogenesis disorders (PBD), Zellweger syndrome spectrum** can have stippling in the knees and hips.
- Stippling is occasionally present in GM1 gangliosidosis, Cornelia de Lange syndrome, trisomy 18, and trisomy 21.

Nasomaxillary dysplasia

- **Binder phenotype**, a term describing nasomaxillary dysplasia similar to that observed in CDPX1, does not represent a single nosologic entity. A subset of individuals with Binder syndrome may have defects in *ARSE*, but this remains to be determined [Carach et al 2002, Cuillier et al 2005].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with X-linked recessive chondrodysplasia punctata 1 (CDPX1), the following evaluations are recommended:

- Full skeletal survey
- Flexion, neutral, and extension lateral views of the C-spine in every patient. If clinical evidence suggests cervical myelopathy, or if significant instability is demonstrated radiographically, a cervical MRI should be performed. Special consideration should

be given to performing this study in flexion and extension positions as spinal cord compression may only occur with these movements (i.e., a normal neutral cervical MRI does not rule out dynamic compression).

- Growth measures
- Developmental assessment
- Hearing assessment
- Assessment of upper and lower airways if stridor is present
- Polysomnography if clinical findings suggest increased upper-airway resistance, disordered breathing in sleep, or apnea
- Ophthalmologic evaluation
- Cardiac ultrasound examination
- Brain imaging studies

Treatment of Manifestations

Management is supportive.

Respiratory difficulty can require frequent monitoring, nasal stents, and oxygen.

Severe maxillary hypoplasia or maxillary retrognathia may require reconstructive surgery in older individuals [Carach et al 2002].

Instability of the cervical spine may require a cervical collar or spinal fusion.

Surveillance

Surveillance of the following is according to recommended pediatric practice, with closer follow-up recommended if abnormalities are identified:

- Hearing
- Growth
- Development
- Thoracic and lumbar spine (for scoliosis)

Testing 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 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.

Other

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

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

Risk to Family Members

Parents of the proband

- The father of an affected male will not have the disease nor will he be a carrier of the mutation. In a family with more than one affected individual, the mother of an affected male is an obligate carrier.
- If pedigree analysis reveals that the proband is the only affected family member, the mother may be a carrier or the affected male may have a *de novo* gene mutation, in which case the mother is not a carrier.
- If a woman has more than one affected son and the disease-causing mutation cannot be detected in her DNA, she has germline mosaicism.
- When an affected male is the only affected individual in the family, several possibilities regarding his mother's carrier status need to be considered:
  - He has a *de novo* disease-causing mutation in the *ARSE* gene and his mother is not a carrier.
  - His mother has a *de novo* disease-causing mutation in the *ARSE* gene, either a) as a "germline mutation" (i.e., present at the time of her conception and therefore in every cell of her body); or b) as "germline mosaicism" (i.e., present in some of her germ cells only).
  - His mother has a disease-causing mutation that she inherited from a maternal female ancestor.

Sibs of the proband

- The risk to sibs depends on the carrier status of the mother.
- If the mother of the proband has a disease-causing mutation, the chance of transmitting it in each pregnancy is 50%. Male sibs who inherit the mutation will be affected; female sibs who inherit the mutation will be carriers and will usually not be affected.
- If the disease-causing mutation cannot be detected in the DNA of the mother of the only affected male in the family, the risk to sibs is low but greater than that of the general population because of the possibility of germline mosaicism.

Offspring of a proband. Males with CDPX1 will pass the disease-causing mutation to all of their daughters and 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 gender, may be at risk of being carriers or of being affected.

Carrier Detection

Carrier testing of at-risk female relatives is possible if the disease-causing mutation has been identified in the family. See Testing.

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 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 at risk of being carriers.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant when the sensitivity of currently available testing is less than 100%. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

If the *ARSE* mutation has been identified in a family member, prenatal testing is possible for pregnancies at increased risk. The usual procedure is to determine fetal sex by performing chromosome analysis on fetal cells obtained by chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation or by amniocentesis usually performed at approximately 15-18 weeks' gestation. If the karyotype is 46,XY, DNA from fetal cells can be analyzed for the known disease-causing mutation. For laboratories offering custom prenatal testing, see Testing.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Chondrodysplasia Punctata 1, X-Linked Recessive

Gene Symbol	Chromosomal Locus	Protein Name
ARSE	Xp22.3	Arylsulfatase E

Data are compiled from the following standard references: gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Chondrodysplasia Punctata 1, X-Linked Recessive

300180	ARYLSULFATASE E; ARSE
302950	CHONDRODYSPLASIA PUNCTATA 1, X-LINKED RECESSIVE; CDPX1

Table C. Genomic Databases for Chondrodysplasia Punctata 1, X-Linked Recessive

Gene Symbol	Entrez Gene	HGMD
ARSE	415 (MIM No. 300180)	ARSE

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Normal allelic variants: *ARSE* spans 29.5 kb of genomic DNA and contains 11 exons and ten introns. It encodes a 2.2-kb full-length transcript. Several polymorphic variations occur in the coding region. *ARSE* is located in Xp22.3, close to the pseudoautosomal boundary within a cluster of evolutionary related sulfatase genes that include *ARSD, ARSF, ARSG,* and *ARSC* (*STS*), which encodes steroid sulfatase. These genes escape X-inactivation and have a pseudogene on the Y chromosome [Sardiello et al 2005].

Pathologic allelic variants: See Table 2. Eighteen unique mutations, two partial deletions, and three complete gene deletions have thus far been identified in 30 probands. A few recurrent mutations were reported in two unrelated probands: p.Gly137Ala, p.Thr481Met, and p.Pro578Ser. The nonsense mutation p.Trp581X was reported in five probands. The Gly137 residue was also mutated to Val (p.Gly137Val) in another individual [Franco et al 1995,Sheffield et al 1998,Brunetti-Pierri et al 2003,Garnier et al 2007,Nino et al 2008].

Table 2. *ARSE* Pathologic Allelic Variants Discussed in this *GeneReview*

DNA Nucleotide Change	Protein Amino Acid Change	Reference Sequence
c.119T>G	p.Ile40Ser	NM_000047.2 NP_000038.2
c.410G>C	p.Gly137Ala	
c.410G>T	p.Gly137Val	
c.1442C>T	p.Thr481Met	
c.1732C>T	p.Pro578Ser	
c.1743G>A	p.Trp581X	

See Quick Reference for an explanation of nomenclature. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org).

Normal gene product: The protein encoded by *ARSE* comprises 589 amino acid residues. 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), the catalytic residue in the active site, is generated from a cysteine [Cosma et al 2003]. The ARSE protein has been studied in an in vitro expression system in COS7 cells, where it localized to Golgi membranes [Daniele et al 1998]. Although its physiologic substrate has not yet been identified, ARSE enzyme hydrolyzes the fluorogenic artificial substrate, 4-methylumbelliferyl (4-MU) sulfate. It is active at neutral pH, heat labile, and inactive toward steroid sulfates [Daniele et al 1998]. ARSE enzyme activity is inhibited in vitro by warfarin, an anticoagulant that inhibits VKORC1, and therefore the regeneration of active vitamin K [Rost et al 2004]. Given the well-documented phenotypic similarities between CDPX1 and warfarin embryopathy, it was proposed that

ARSE was the vitamin K-dependent protein inhibited by warfarin. Alternatively, ARSE could act downstream of a vitamin K-dependent metabolic pathway.

Abnormal gene product: Several missense alleles were experimentally evaluated and shown to have reduced function [Daniele et al 1998, Brunetti-Pierri et al 2003].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

CDPX1 Family Support Group
Email: thegillums@cox.net

Human Growth Foundation
997 Glen Cove Avenue Suite 5
Glen Head NY 11545
Phone: 800-451-6434
Fax: 516-671-4055
Email: hgf1@hgfound.org
www.hgfound.org

Little People of America (LPA)
5289 NE Elam Young Parkway Suite F-100
Hillsboro OR 97124
Phone: 888-LPA-2001 (888-572-2001); 503-846-1562
Fax: 503-846-1590
Email: info@lpaonline.org
www.lpaonline.org

The MAGIC Foundation
6645 West North Avenue
Oak Park IL 60302
Phone: 800-362-4423; 708-383-0808
Fax: 708-383-0899
Email: info@magicfoundation.org
www.magicfoundation.org

my baby's hearing
This site, developed with support from the National Institute on Deafness and Other Communication Disorders, provides information about newborn hearing screening and hearing loss.
www.babyhearing.org

International Skeletal Dysplasia Registry
Medical Genetics Institute
8635 West Third St. Suite 665
Los Angeles CA 90048
Phone: 800-CEDARS-1 (800-233-2771)
Fax: 310-423-0462
www.csmc.edu

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

Literature Cited

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Chapter Notes

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