



# Cleidocranial Dysplasia Spectrum Disorder

Synonym: Cleidocranial Dysostosis

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## Summary

### Clinical characteristics

Cleidocranial dysplasia (CCD) spectrum disorder is a skeletal dysplasia that represents a clinical continuum ranging from classic CCD (triad of delayed closure of the cranial sutures, hypoplastic or aplastic clavicles, and dental abnormalities), to mild CCD, to isolated dental anomalies without other skeletal features. Individuals with classic CCD spectrum disorder typically have abnormally large, wide-open fontanelles at birth that may remain open throughout life. Clavicular hypoplasia can result in narrow, sloping shoulders that can be opposed at the midline. Moderate short stature may be observed, with most affected individuals being shorter than their unaffected sibs. Dental anomalies may include delayed eruption of secondary dentition, failure to shed the primary teeth, and supernumerary teeth. Individuals with CCD spectrum disorder are at increased risk of developing recurrent sinus infections, recurrent ear infections leading to conductive hearing loss, and upper airway obstruction. Intelligence is typically normal.

### Diagnosis/testing

The diagnosis of CCD spectrum disorder is established in an individual with typical clinical and radiographic findings and/or a heterozygous pathogenic variant in *RUNX2* identified by molecular genetic testing.

### Management

*Treatment of manifestations:* If the cranial vault defect is significant, the head needs protection from blunt trauma; helmets may be used for high-risk activities. Surgical cosmesis for depressed forehead or lengthening of hypoplastic clavicles can be considered. Careful planning of anesthetic management due to craniofacial and dental abnormalities. Consultation with an otolaryngologist to assist in securing the airway. Consideration of

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alternative anesthetic approaches, including neuraxial block, taking into account possible spine abnormalities. If bone density is below normal, treatment with calcium and vitamin D supplementation. Dental procedures to address retention of primary dentition, presence of supernumerary teeth, and non-eruption of secondary dentition. Such procedures may include prosthetic replacements, removal of the supernumerary teeth followed by surgical repositioning of the secondary teeth, and a combination of surgical and orthodontic measures for actively erupting and aligning the impacted secondary teeth. Speech therapy as needed. Aggressive treatment of sinus and middle ear infections; consideration of tympanostomy tubes for recurrent middle ear infections; regular immunizations including influenza. Sleep study in those with manifestations of obstructive sleep apnea; surgical intervention may be required for upper airway obstruction.

*Surveillance:* Monitor children for orthopedic complications, dental abnormalities, sinus and ear infections, upper airway obstruction, hearing loss, and speech issues. DXA scan to assess bone mineral density beginning in early adolescence and every five to ten years thereafter.

*Agents/circumstances to avoid:* Helmets and protective devices should be worn when participating in high-risk activities.

*Pregnancy management:* Monitor affected women during pregnancy for cephalopelvic disproportion.

## Genetic counseling

CCD spectrum disorder is inherited in an autosomal dominant manner. The proportion of individuals with CCD spectrum disorder caused by a *de novo* pathogenic variant is high. Each child of an individual with CCD spectrum disorder has a 50% chance of inheriting the *RUNX2* pathogenic variant. Once the *RUNX2* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for CCD spectrum disorder are possible.

## Diagnosis

Cleidocranial dysplasia (CCD) spectrum disorder is a skeletal dysplasia that represents a continuum of clinical and radiographic findings ranging from classic CCD (triad of delayed closure of the cranial sutures, hypoplastic or aplastic clavicles, and dental abnormalities), to mild CCD, to isolated dental anomalies without other skeletal features. No formal clinical diagnostic criteria for CCD spectrum disorder have been established.

## Suggestive Findings

CCD spectrum disorder **should be suspected** in probands with the following clinical and radiographic findings.

### Clinical findings

- **Abnormally large, wide-open fontanelles at birth** that may remain open throughout life. The wide-open metopic suture results in separation of the frontal bones by a metopic groove. The forehead is otherwise broad and flat; the cranium is brachycephalic.
- **Additional craniofacial features.** Frontal and parietal bossing, hypertelorism, midface retrusion, and depressed nasal bridge
- **Narrow, sloping shoulders** that can be opposed at the midline due to clavicular hypoplasia or aplasia (see Figure 1).
- **Abnormal dentition** including delayed eruption of secondary dentition, failure to shed the primary teeth, variable numbers of supernumerary teeth along with dental crowding, and malocclusion
- **Digit abnormalities** including brachydactyly, tapering fingers, and short, broad thumbs
- **Short stature** (typically moderate)
- **Normal intellect**

## Radiographic findings

- **Cranium**
  - Wide-open sutures, patent fontanelles, presence of Wormian bones
  - Delayed ossification of the skull
  - Poor or absent pneumatization of the paranasal, frontal, and mastoid sinuses
  - Impacted, crowded teeth; supernumerary teeth
- **Thorax**
  - Cone-shaped thorax with narrow upper thoracic diameter
  - Typically bilateral (but not necessarily symmetric) clavicular abnormalities ranging from complete absence to hypoplastic or discontinuous clavicles. The lateral portions are more affected than the medial aspects of the clavicles (see Figure 2).
  - Hypoplastic scapulae
- **Pelvis**
  - Delayed ossification of the pubic bone with wide pubic symphysis
  - Hypoplasia of the iliac wings
  - Widening of the sacroiliac joints
  - Elongated femoral head with short femoral neck and elongated epiphyses ("chef-hat" appearance)
  - Coxa vara
- **Hands**
  - Pseudoepiphyses of the metacarpal and metatarsal bones, which may result in a characteristic lengthening of the second metacarpal (See Figure 3.)
  - Hypoplastic distal phalanges
  - Deformed and short middle phalanges of the third, fourth, and fifth digits with cone-shaped epiphyses
- **Other.** Osteopenia/osteoporosis with evidence of decreased bone mineral density on DXA scan; some affected individuals sustain multiple fractures.

## Establishing the Diagnosis

The clinical diagnosis of a CCD spectrum disorder can be **established** in a proband with characteristic clinical and radiographic findings, or a molecular diagnosis can be established in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *RUNX2* identified by molecular genetic testing (see Table 1).

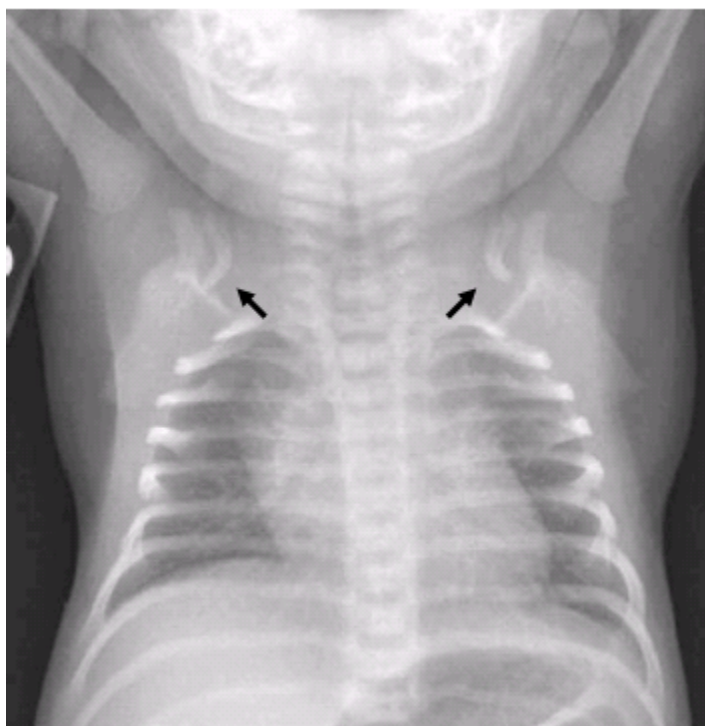
Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic, and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic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

Molecular genetic testing approaches can include a combination of **single-gene testing**, **multigene panel**, and **karyotype**.

- **Single-gene testing.** Sequence analysis of *RUNX2* 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 no variant is detected by the sequencing method used, the next step is to perform *RUNX2* gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.



**Figure 1.** Shoulders in an individual with clavicular hypoplasia may be brought to the midline.

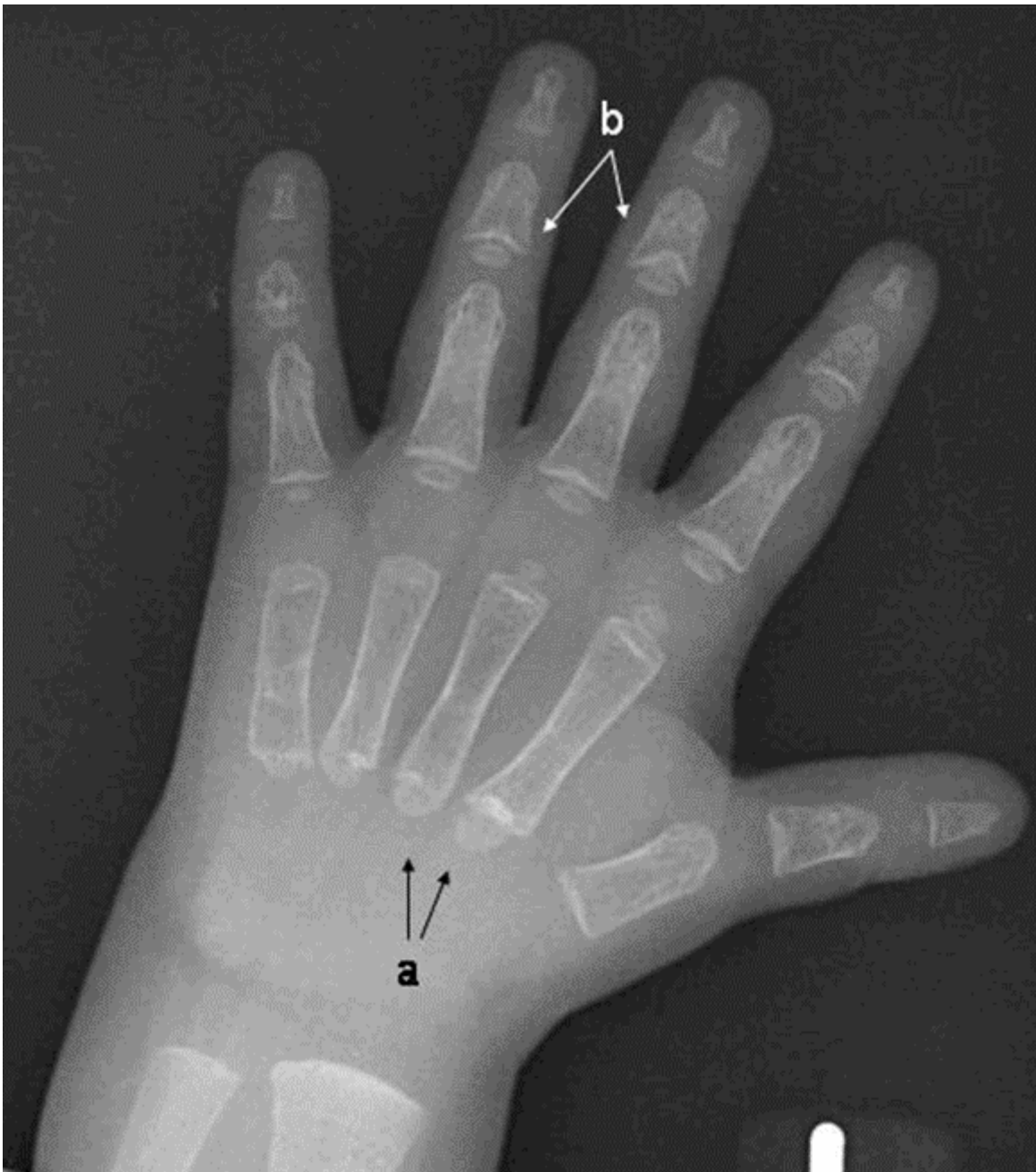


**Figure 2.** Chest x-ray demonstrates clavicular hypoplasia.

- **A multigene panel** that includes *RUNX2* and other genes of interest (see Differential Diagnosis) may 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](#).

- **Karyotype.** If *RUNX2* testing is not diagnostic in an individual with features of a CCD spectrum disorder who also has multiple congenital anomalies and/or developmental delay, a karyotype may be considered to evaluate for complex chromosome rearrangements or translocations that involve 6p21.1 (*RUNX2* locus) but do not result in *RUNX2* copy number changes.



**Figure 3.** Hand x-ray of a male age 2.5 years with cleidocranial dysplasia spectrum disorder

a. Note pseudoepiphyses at the bases of the second and third metacarpals with accessory physes seen at the base of the fourth and fifth metacarpals.

b. Cone-shaped epiphyses are seen involving most predominantly the third and fourth middle phalanges. The phalanges appear abnormally formed, particularly the middle phalanges of the second through fifth digits.

**Table 1.** Molecular Genetic Testing Used in Cleidocranial Dysplasia Spectrum Disorder

Gene <sup>1</sup>	Method	Proportion of Probands with a Pathogenic Variant <sup>2</sup> Detectable by Method
<i>RUNX2</i>	Sequence analysis <sup>3</sup>	~70%-80% <sup>4</sup>
	Gene-targeted deletion/duplication analysis <sup>5</sup>	~15% <sup>4, 6</sup>
	Karyotype	See footnote 7.
Unknown	NA	~5%-15%

NA = not applicable

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on variants detected in these genes.

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. Ott et al [2010], Motaie et al [2021], and data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020] and review of the ClinVar database.

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. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole gene; however, breakpoints of large deletions and/or deletion of adjacent genes (e.g., those described by Puvabanditsin et al [2018]) may not be detected by these methods.

6. Individuals with *RUNX2* deletions may have a phenotype consistent with a CCD spectrum disorder and additional findings including developmental delay.

7. Two individuals with translocations involving the *RUNX2* locus have been reported [Purandare et al 2008, Northup et al 2011].

## Clinical Characteristics

### Clinical Description

Cleidocranial dysplasia (CCD) spectrum disorder is a skeletal dysplasia representing a clinical continuum ranging from classic CCD (triad of delayed closure of the cranial sutures, hypoplastic or aplastic clavicles, and dental abnormalities), to mild CCD, to isolated dental anomalies without other skeletal features [Golan et al 2000]. Most individuals are diagnosed because they have classic features. CCD spectrum disorder affects most prominently those bones derived from intramembranous ossification, such as the cranium and the clavicles, although bones formed through endochondral ossification can also be affected. Cooper et al [2001] recorded the natural history of 90 probands and 56 first- and second-degree relatives; findings highlight the clinical variability of this condition within affected members of the same family who harbor the same pathogenic variant. Roberts et al [2013] reviewed their experience with more than 100 affected individuals in South Africa.

**Classic CCD.** The most prominent clinical findings in individuals with classic CCD are listed in Suggestive Findings and include: abnormally large, wide-open fontanelles at birth that may remain open throughout life; clavicular hypoplasia resulting in narrow, sloping shoulders that can be opposed at the midline; and abnormal dentition (see **Dental complications** in this section).

Further medical problems identified in individuals with CCD spectrum disorder include short stature, skeletal/orthopedic findings, dental complications, ENT complications, endocrine findings, and mild developmental delay.

**Height.** Individuals with CCD spectrum disorder are often shorter than their unaffected sibs and present with postnatal growth deficiency.

- Males are on average six inches shorter than their unaffected brothers and have an average height of 165 cm ( $\pm 8$  cm).
- Females are on average three inches shorter than their unaffected sisters and have an average height of 156 cm ( $\pm 10$  cm) [Cooper et al 2001].

**Skeletal/orthopedic findings.** Affected individuals are more likely to have other bone-related problems:

- Pes planus (flat feet) in 57%
- Genu valgum (knock-knee deformity) in 28%
- Scoliosis in 18% [Cooper et al 2001]
- Osteoporosis, found in 8/14 (57%) affected individuals; and osteopenia, identified in 3/14 (21%) individuals [Dinçsoy Bir et al 2017]

Other less common orthopedic problems include joint dislocation at the shoulder and elbow [El-Gharbawy et al 2010].

**Dental complications.** Up to 94% of persons with CCD spectrum disorder have dental findings, including delayed eruption of secondary dentition and failure to shed the primary teeth [Golan et al 2003]. The most consistent dental findings in individuals with a CCD spectrum disorder are the presence of the second permanent molar with the primary dentition (80%), wide spacing in the lower incisor area, supernumerary tooth germs (70%), and parallel-sided ascending rami [Cooper et al 2001, Golan et al 2003, Golan et al 2004, Bufalino et al 2012]. Individuals with a CCD spectrum disorder are more likely to have an underbite and to have gingival cysts that usually form around extra teeth [McNamara et al 1999].

**ENT complications.** Recurrent sinus infections and other upper airway complications are observed significantly more often in individuals with CCD spectrum disorder than in the general population. When symptoms are suggestive of upper airway obstruction, a sleep study is indicated, and surgical intervention may be required. Conductive hearing loss occurs in 39% of affected individuals. Individuals with CCD spectrum disorder of any age are more likely to have recurrent ear infections.

**Endocrinology.** Individuals with CCD spectrum disorder can have low insulin-like growth factor 1 levels. Low vitamin D with no consistent association with osteoporosis has also been reported [Dinçsoy Bir et al 2017]. Rarely, individuals with CCD spectrum disorder have low levels of alkaline phosphatase [Morava et al 2002, Unger et al 2002, El-Gharbawy et al 2010].

**Development.** Intelligence is typically normal. Children younger than age five years may show mild motor delay, particularly in gross motor abilities. This delay may be associated with orthopedic complications such as flat feet and genu valgum. No significant differences are observed among elementary school-age children.

## Genotype-Phenotype Correlations

Some genotype-phenotype correlations have been established for the dental manifestations seen in CCD spectrum disorder. No clear correlation has been established between genotype and clavicular involvement [Otto et al 2002, Bufalino et al 2012, Jaruga et al 2016].

- Heterozygous *RUNX2* pathogenic variants located in the runt domain (or predicting a premature termination upstream of or within the runt domain) that abolish the transactivation activity of the mutated protein with consequent haploinsufficiency result in classic CCD.
- Short stature and dental anomalies were found to be milder in individuals with a classic CCD phenotype who had an intact runt domain and higher residual *RUNX2* activity when compared to individuals with a classic CCD phenotype in whom the pathogenic variant affected the runt domain [Yoshida et al 2002].
- A clinical spectrum ranging from isolated dental anomalies without the skeletal features of CCD, to mild CCD, to classic CCD results from hypomorphic pathogenic variants that result in partial loss of protein

function (c.1171C>T [p.Arg391Ter], c.598A>G [p.Thr200Ala], and c.90dupC [p.Ser31LeufsTer130]) (see Molecular Genetics). Intrafamilial variability is significant [Zhou et al 1999].

- Osteoporosis leading to recurrent bone fractures and scoliosis has been associated with a heterozygous pathogenic frameshift variant c.1205dupC, reflecting the role of RUNX2 in the maintenance of adult bone [Quack et al 1999].

## Penetrance

Pathogenic variants in *RUNX2* have high penetrance. To date, there are no reports of incomplete penetrance.

## Nomenclature

Cleidocranial dysplasia spectrum disorder was originally described as dento-osseous dysplasia affecting several individuals in a large pedigree.

While the term "cleidocranial dysostosis" has been used, the disease is more correctly considered a dysplasia given that RUNX2 has important functions both during skeletal formation and in bone maintenance.

## Prevalence

Stevenson et al [2012] found the frequency to be 0.12 in 10,000 individuals in the Utah (US) population, suggesting that the frequency may be higher than previously recognized.

## Genetically Related (Allelic) Disorders

Partial intragenic duplication of *RUNX2* has been associated with metaphyseal dysplasia, maxillary hypoplasia, and brachydactyly (MDMHB) (OMIM 156510). Affected individuals have short stature, long bone and spinal abnormalities, dystrophic teeth, and enlargement of the medial half of the clavicle bones.

Complete duplications of *RUNX2* have been described in individuals with craniosynostosis and oligodontia [Mefford et al 2010, Greives et al 2013, Molin et al 2015].

## Differential Diagnosis

Other conditions share some characteristics with cleidocranial dysplasia (CCD) spectrum disorder. The fact that similar skeletal elements are affected suggests that some of these conditions may result from mutation of genes (most notably *CBFB*) that affect the action of RUNX2 on its downstream targets (*CBFB* forms a heterodimer with RUNX2 to activate transcription of downstream targets).



**Table 2.** Genes of Interest in the Differential Diagnosis of Cleidocranial Dysplasia Spectrum Disorder

Gene / Genetic Mechanism	Disorder	MOI	Craniofacial & Dental Features	Skeletal Features	Other Features
<i>ALPL</i>	Hypophosphatasia <sup>1</sup>	AR AD <sup>2</sup>	<ul style="list-style-type: none"> <li>Children w/ infantile form may present w/ very poorly mineralized cranium &amp; widened cranial sutures.</li> <li>Premature deciduous tooth loss</li> </ul>	<ul style="list-style-type: none"> <li>Generalized defect of mineralization w/delayed ossification of multiple skeletal elements</li> <li>Children w/ infantile form may present w/short ribs &amp; narrow thorax.</li> <li>Clavicles least affected</li> <li>Rachitic skeletal changes</li> </ul>	<ul style="list-style-type: none"> <li>Very low alkaline phosphatase activity in serum &amp; tissues</li> <li>Nephrocalcinosis</li> <li>Hypercalcemia</li> </ul>
<i>CBFB</i> (intragenic pathogenic variants)	<i>CBFB</i> -related CCD (OMIM 620099)	AD	<ul style="list-style-type: none"> <li>Delayed closure of fontanelle</li> <li>Delayed/absent eruption of deciduous teeth</li> <li>Supernumerary teeth</li> </ul>	<ul style="list-style-type: none"> <li>Hypoplastic or absent clavicles, clavícula bipartita</li> <li>Metacarpal/ metatarsal pseudoepiphyses</li> <li>Delayed ossification of pubic &amp; carpal bones</li> <li>Short distal phalanges</li> </ul>	<ul style="list-style-type: none"> <li>Normal stature</li> <li>DD (mild to moderate)</li> </ul>
<i>CBFB</i> (16q22.1 deletions involving <i>CBFB</i> )	Chromosome 16q22 deletion syndrome (OMIM 614541)	AD	Wide-open fontanelles	<ul style="list-style-type: none"> <li>Short clavicles <sup>3</sup></li> <li>Short stature</li> <li>Short distal phalanges</li> <li>Delayed ossification of skull</li> </ul>	<ul style="list-style-type: none"> <li>Poor weight gain</li> <li>DD</li> <li>Congenital heart defect</li> </ul>
<i>CTSK</i>	Pycnodysostosis	AR	Failure of closure of cranial sutures w/ persistence of open fontanelles	<ul style="list-style-type: none"> <li>Acro-osteolysis</li> <li>Osteopetrosis; radio-opacity of all bones ↑ due to ↑ density of trabecular bone but not cortices</li> <li>Short stature w/↑ bone fragility, short terminal phalanges</li> </ul>	
<i>FIG4</i>	Yunis Varon syndrome (OMIM 216340)	AR	<ul style="list-style-type: none"> <li>Wide-open fontanelles &amp; sutures</li> <li>Unusual mineralization of skull</li> </ul>	<ul style="list-style-type: none"> <li>Hypoplastic clavicles</li> <li>Absence/ hypoplasia of thumbs, halluces, &amp; distal phalanges</li> <li>Gracile bones</li> </ul>	<ul style="list-style-type: none"> <li>Prenatal growth deficiency</li> <li>Brain malformations</li> </ul>

Table 2. continued from previous page.

Gene / Genetic Mechanism	Disorder	MOI	Craniofacial & Dental Features	Skeletal Features	Other Features
<i>LMNA</i> <i>ZMPSTE24</i>	Mandibuloacral dysplasia (OMIM PS248370)	AR	<ul style="list-style-type: none"> <li>• Delayed closure of cranial sutures</li> <li>• Micrognathia</li> <li>• Early tooth loss</li> </ul>	<ul style="list-style-type: none"> <li>• Dysplastic clavicles</li> <li>• Acro-osteodysplasia of fingers &amp; toes w/ delayed ossification of carpal bones</li> <li>• Progressively stiff joints</li> <li>• Short stature</li> </ul>	<ul style="list-style-type: none"> <li>• Alopecia; scalp hair sparse by 3rd decade</li> <li>• Atrophic skin w/↓ subcutaneous fat</li> <li>• Skin hyperpigmentation</li> </ul>
<i>MSX2</i> (intragenic pathogenic variants)	Parietal foramina w/ CCD <sup>4</sup>	AD	<ul style="list-style-type: none"> <li>• Enlarged parietal foramina</li> <li>• Broad forehead w/frontal bossing</li> <li>• Not assoc w/ dental abnormalities</li> </ul>	Clavicular hypoplasia	
<i>MSX2</i> (microduplications upstream of <i>MSX2</i> )	<i>MSX2</i> -related CCD w/synpolydactyly <sup>5</sup>	AD	Phenocopy of CCD	Phenocopy of CCD	Synpolydactyly in some

AR = autosomal recessive; AD = autosomal dominant; CCD = cleidocranial dysplasia; DD = developmental delay; MOI = mode of inheritance

1. In one report, an individual with severe CCD was initially thought to have hypophosphatasia [Unger et al 2002].

2. Perinatal and infantile hypophosphatasia are typically inherited in an autosomal recessive manner. The milder forms, especially adult hypophosphatasia and odontohypophosphatasia, may be inherited in an autosomal recessive or autosomal dominant manner depending on the effect that the *ALPL* pathogenic variant has on TNSALP activity.

3. Goto et al [2004]

4. See [Enlarged Parietal Foramina](#).

5. Ott et al [2012]

### Other disorders/conditions in the differential diagnosis of CCD spectrum disorder

- **Crane-Heise syndrome** (OMIM 218090). A lethal condition of unknown genetic cause associated with a poorly mineralized calvarium; macrocephaly; cleft lip and palate; low-set, dysplastic ears; severe vertebral and limb anomalies with absence of cervical vertebrae; hypoplastic clavicles and scapulae; hypoplastic and absent phalanges; multiple joint contractures; intrauterine growth restriction; and genital hypoplasia.
- **CDAGS syndrome** (OMIM 603116). A disorder caused by biallelic pathogenic variants in small nuclear RNA encoding *RNU12* [Xing et al 2021] that combines the apparently opposing pathophysiologic and developmental processes of accelerated suture closure and delayed ossification [Mendoza-Londono et al 2005]. CDAGS syndrome is associated with delayed closure of the fontanelles, clavicular hypoplasia, craniosynostosis, anal anomalies, genitourinary malformations, and skin lesions (porokeratosis).
- **Familial supernumerary teeth**. Nonsyndromic supernumerary premolar teeth [Bae et al 2017]
- **Hypothyroidism**. Can be associated with delayed fontanelle closure

## Management

No clinical practice guidelines for cleidocranial dysplasia (CCD) spectrum disorder have been published.

## Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with CCD spectrum disorder, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

**Table 3.** Recommended Evaluations Following Initial Diagnosis in Individuals with Cleidocranial Dysplasia Spectrum Disorder

System/Concern	Evaluation	Comment
<b>Skeletal</b>	<ul style="list-style-type: none"> <li>Clinical assessment for skeletal manifestations</li> <li>Full skeletal survey incl hands &amp; feet</li> </ul>	
	DXA scan	Should be done in early adolescence due to risk of osteopenia
<b>Dental</b>	Dental eval by dentist familiar w/CCD spectrum disorder & its mgmt	
<b>Hearing</b>	Audiologic eval	
<b>Genetic counseling</b>	By genetics professionals <sup>1</sup>	To inform affected persons & their families re nature, MOI, & implications of CCD spectrum disorder to facilitate medical & personal decision making

CCD = cleidocranial dysplasia; DXA = dual-energy x-ray absorptiometry; MOI = mode of inheritance

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

## Treatment of Manifestations

**Supportive care** to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 4).

**Table 4.** Treatment of Manifestations in Individuals with Cleidocranial Dysplasia Spectrum Disorder

Manifestation/Concern	Treatment	Considerations/Other
<b>Craniofacial manifestations</b>	<ul style="list-style-type: none"> <li>If cranial vault defect is significant, protect head from blunt trauma; helmets may be advised for high-risk activities. In these persons, eval by craniofacial surgeon &amp; rehabilitation services are indicated.</li> <li>Affected persons may consider correction of metopic groove for cosmetic reasons.<sup>1</sup></li> </ul>	Fontanelles close w/time in majority of persons & cranial remodeling is usually not necessary.
<b>Airway management w/ anesthesia</b>	<ul style="list-style-type: none"> <li>Careful planning for anesthetic mgmt</li> <li>ENT consult to assist in securing airway</li> <li>Consider alternative anesthetic approaches, incl neuraxial block, taking into account possible spine abnormalities.<sup>2</sup></li> </ul>	Dental & craniofacial abnormalities result in predictably difficult airway mgmt.
<b>Hypoplastic clavicles</b>	Affected persons may consider lengthening hypoplastic clavicles for cosmetic reasons. <sup>1</sup>	
<b>Osteoporosis</b>	Calcium & vitamin D supplementation for those w/ bone density below normal on DXA scan	
<b>Dental manifestations</b>	Early referral to dental clinic familiar w/CCD allows for timely planning of necessary procedures.	Generally, an aggressive approach to coordinate multiple oral surgeries for removal of primary dentition & exposure of permanent dentition is

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
	Dental manifestations that require treatment: <ul style="list-style-type: none"> <li>Retention of primary dentition</li> <li>Presence of supernumerary teeth</li> <li>Non-eruption of secondary dentition</li> </ul>	recommended; watchful waiting for spontaneous eruption after initial delay is not effective. <sup>3</sup>
	Goals of treatment: <ul style="list-style-type: none"> <li>Improve appearance</li> <li>Provide functioning masticatory mechanism</li> </ul>	
	Goals may be achieved w/: <ul style="list-style-type: none"> <li>Prosthetic replacements, w/ or w/o prior extractions</li> <li>Removal of supernumerary teeth followed by surgical repositioning of secondary teeth</li> <li>Combination of surgical &amp; orthodontic measures for actively erupting teeth &amp; aligning impacted secondary teeth</li> </ul>	
<b>Speech issues</b>	Speech therapy as needed during periods of dental treatment &/or in those w/speech issues related to hearing impairment.	
<b>Sinus &amp; middle ear infections</b> <sup>4</sup>	<ul style="list-style-type: none"> <li>Aggressive &amp; timely treatment</li> <li>Tympanostomy tubes should be considered when middle ear infections are recurrent.</li> <li>Regular immunizations incl influenza</li> </ul>	
<b>Upper airway obstruction</b>	<ul style="list-style-type: none"> <li>Sleep study in those w/manifestations of obstructive sleep apnea</li> <li>Surgical intervention may be required.</li> </ul>	
<b>Short stature</b>	No treatment recommended	<ul style="list-style-type: none"> <li>Efficacy of GH therapy in CCD has not been proven.</li> <li>Possible adverse effects of GH therapy on primary chondrodysplastic growth plate are theoretically possible, as <i>RUNX2</i> is directly involved in chondrocyte differentiation &amp; growth plate maintenance.<sup>5</sup></li> </ul>

CCD = cleidocranial dysplasia; DXA = dual-energy x-ray absorptiometry; GH = growth hormone

1. There have been reports of successful surgical interventions for metopic groove & hypoplastic clavicles in a very small number of affected individuals [Kang et al 2009, Sewell et al 2013].

2. Ioscovich et al [2010]

3. For a detailed review, see Becker et al [1997a], Becker et al [1997b], Roberts et al [2013], and Farrow et al [2018].

4. See Visosky et al [2003].

5. Zheng et al [2005]

## Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 5 are recommended.

**Table 5.** Recommended Surveillance for Individuals with Cleidocranial Dysplasia Spectrum Disorder

System/Concern	Evaluation	Frequency
<b>Skeletal</b>	Orthopedic assessment for skeletal manifestations (pes planus, genu valgum, scoliosis, recurrent shoulder or elbow dislocations)	At each visit throughout childhood
	DXA scan to measure bone mineral density (to assess for osteoporosis)	Every 5-10 yrs beginning in early adolescence or earlier in those w/manifestations of osteopenia (e.g., ↑ fractures)
<b>Dental</b>	Dental eval by dentist familiar w/CCD spectrum disorder & its mgmt	Every 6 mos or more frequently as recommended by dentist beginning at age 3 yrs
<b>ENT</b>	<ul style="list-style-type: none"> <li>Assess for recurrent sinus &amp; ear infections.</li> <li>Assess for manifestations of upper airway obstruction.</li> </ul>	At each visit
	Audiology eval	Annually in persons w/recurrent ear infections
<b>Development</b>	Assessment of speech	At each visit during times of dental treatment & in those w/recurrent ear infections &/or hearing issues

DXA = dual-energy x-ray absorptiometry

## Agents/Circumstances to Avoid

To avoid head trauma, helmets and protective devices should be worn when participating in high-risk sports and activities.

## Evaluation of Relatives at Risk

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

## Pregnancy Management

Pregnant women with CCD spectrum disorder should be monitored closely for cephalopelvic disproportion, which may require delivery by cesarean section. The primary cesarean section rate among women with a CCD spectrum disorder is 69%, which is higher than in controls [Cooper et al 2001].

## Therapies Under Investigation

Search [ClinicalTrials.gov](https://clinicaltrials.gov) in the US and [EU Clinical Trials Register](https://clinicaltrialsregister.eu) 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

Cleidocranial dysplasia (CCD) spectrum disorder is inherited in an autosomal dominant manner.

## Risk to Family Members

### Parents of a proband

- Some individuals diagnosed with CCD spectrum disorder have an affected parent.
- A proband with CCD spectrum disorder may have the disorder as the result of a *de novo* *RUNX2* pathogenic variant. The proportion of individuals with CCD spectrum disorder caused by a *de novo* pathogenic variant is high.
- If the proband appears to be the only affected family member (i.e., a simplex case), recommendations for the evaluation of the parents of the proband include:
  - Detailed clinical examination and consideration of craniofacial and skeletal x-rays if there are signs suggestive of dental or bone abnormalities. (Note: The phenotype may vary between parent and child even though they have the same pathogenic variant.)
  - Molecular genetic testing (if a molecular diagnosis has been established in the proband) to confirm the genetic status of the parents and to allow reliable recurrence risk counseling.
- If the proband has a known pathogenic variant that is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism\* [Pal et al 2007, Qian et al 2018, Muurinen et al 2022]. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.
    - \* A parent with somatic and germline mosaicism for a *RUNX2* pathogenic variant may be mildly/minimally affected.
- The family history of some individuals diagnosed with CCD spectrum disorder may appear to be negative because of failure to recognize the disorder in family members. Therefore, an apparently negative family history cannot be confirmed without appropriate clinical examination (with skeletal x-rays) of the parents and/or molecular genetic testing (to establish that neither parent is heterozygous for the pathogenic variant identified in the proband).

**Sibs of a proband.** The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs is 50%.
- The phenotype may vary among sibs who inherit the same *RUNX2* pathogenic variant (although the penetrance of *RUNX2* pathogenic variants is high, significant clinical variability is observed between affected family members; see Genotype-Phenotype Correlations and Penetrance).
- If the proband has a known *RUNX2* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism. Germline mosaicism has been demonstrated in a family with three affected sibs and an apparently unaffected mother [Pal et al 2007].
- If the parents are clinically unaffected but their genetic status is unknown, the risk to the sibs of a proband appears to be low but increased over that of the general population because of the possibility of parental germline mosaicism.

**Offspring of a proband.** Each child of an individual with CCD spectrum disorder has a 50% chance of inheriting the *RUNX2* pathogenic variant.

**Other family members.** The risk to other family members depends on the status of the proband's parents: if a parent has features of CCD spectrum disorder and/or is known to be heterozygous for a *RUNX2* pathogenic variant, the parent's family members may be at risk.

## Related Genetic Counseling Issues

### Family planning

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

**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

**Molecular genetic testing.** Once the *RUNX2* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for CCD spectrum disorder are possible.

**Ultrasound examination.** Classic CCD can be diagnosed by ultrasound examination in the offspring of an affected parent as early as 14 weeks' gestation. The most consistent features are abnormal clavicles, which are either short (<5th centile for gestational age) or partially or totally absent. Other less specific findings include brachycephalic skull with undermineralization, frontal bossing, and generalized immature ossification [Stewart et al 2000, Hermann et al 2009].

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

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](#).*

- **About Kids Health**  
Canada  
[Cleidocranial Dysplasia \(CCD\)](#)
- **CCD Smiles**  
[www.ccdsmiles.org](http://www.ccdsmiles.org)
- **Children's Craniofacial Association**  
**Phone:** 800-535-3643  
**Email:** [contactCCA@ccakids.com](mailto:contactCCA@ccakids.com)  
[www.ccakids.org](http://www.ccakids.org)

- **FACES: National Craniofacial Association**  
**Phone:** 800-332-2373; 423-266-1632  
**Email:** [info@faces-cranio.org](mailto:info@faces-cranio.org)  
[www.faces-cranio.org](http://www.faces-cranio.org)
- **Human Growth Foundation**  
[www.hgfound.org](http://www.hgfound.org)
- **MAGIC Foundation**  
**Phone:** 800-362-4423  
**Email:** [contactus@magicfoundation.org](mailto:contactus@magicfoundation.org)  
[www.magicfoundation.org](http://www.magicfoundation.org)
- **UCLA International Skeletal Dysplasia Registry (ISDR)**  
**Phone:** 310-825-8998  
[International Skeletal Dysplasia Registry](http://InternationalSkeletalDysplasiaRegistry.org)

## 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.** Cleidocranial Dysplasia Spectrum Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
<a href="#">RUNX2</a>	6p21.1	Runt-related transcription factor 2	<a href="#">RUNX2 database</a>	<a href="#">RUNX2</a>	<a href="#">RUNX2</a>

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 Cleidocranial Dysplasia Spectrum Disorder ([View All in OMIM](#))

<a href="#">119600</a>	CLEIDOCRANIAL DYSPLASIA 1; CLCD1
<a href="#">600211</a>	RUNT-RELATED TRANSCRIPTION FACTOR 2; RUNX2

## Molecular Pathogenesis

*RUNX2* encodes runt-related transcription factor 2 (RUNX2), a transcription factor involved in osteoblast differentiation and skeletal morphogenesis. RUNX2 is essential for osteoblast differentiation during intramembranous ossification as well as chondrocyte maturation during endochondral ossification [Zheng et al 2005]. RUNX2 contains an N-terminal stretch of consecutive polyglutamine and polyalanine repeats known as the Q/A domain, a runt domain, and a C-terminal proline/serine/threonine-rich (PST) activation domain. The runt domain is a 128-amino-acid polypeptide motif originally described in the *Drosophila* runt gene that has the unique ability to independently mediate DNA binding and protein heterodimerization [Zhou et al 1999].

The majority of *RUNX2* pathogenic variants in individuals with classic CCD affect the runt domain and most are predicted to abolish DNA binding [Lee et al 1997, Mundlos et al 1997, Otto et al 2002]. Pathogenic missense variants cluster at arginine 225 (p.Arg225) of RUNX2, a critical residue for RUNX2 function. In vitro studies have shown that pathogenic missense variants at p.Arg225 interfere with nuclear accumulation of RUNX2.



Hypomorphic *RUNX2* alleles with partial loss of protein function, c.90dupC and c.598A>G, are associated with mild CCD, isolated dental anomalies, and significant intrafamilial variability.

**Mechanism of disease causation.** Loss of function

***RUNX2*-specific laboratory technical considerations.** At the genomic level, the longest *RUNX2* transcript variant (NM\_001024630.4) contains nine exons. Transcript variants that encode different protein isoforms [Geoffroy et al 1998] result from the use of alternate promoters and alternate splicing.

**Table 6.** Notable *RUNX2* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_001024630.4 NP_001019801.3	c.90dupC	p.Ser31LeufsTer130	Hypomorphic allele (See Genotype-Phenotype Correlations.)
	c.598A>G	p.Thr200Ala	
	c.673C>T	p.Arg225Trp	See Molecular Pathogenesis.
	c.674G>T	p.Arg225Leu	
	c.674G>A	p.Arg225Gln	
	c.1171C>T	p.Arg391Ter	Hypomorphic allele (See Genotype-Phenotype Correlations.)
	c.1205dupC	p.Pro403AlafsTer87 <sup>1</sup>	Assoc w/osteoporosis → recurrent bone fractures [Quack et al 1999]

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](http://varnomen.hgvs.org)). See [Quick Reference](#) for an explanation of nomenclature.

1. Published as frameshift variant in codon Pro402 [Quack et al 1999]

## Chapter Notes

### Author Notes

Dr Keren Machol's web pages: [Texas Children's Hospital](#) and [Baylor College of Medicine](#)

Dr Mendoza-Londono's [web page](#)

Dr Lee's web pages: [Baylor College of Medicine, People](#) and [Baylor College of Medicine, Find a Physician](#)

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