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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 the skeletal features. Most individuals come to diagnosis because they have classic features. At birth, affected individuals typically have abnormally large, wide-open fontanelles 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 supernumerary teeth, eruption failure of the permanent teeth, and presence of the second permanent molar with the primary dentition. 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

Diagnosis of CCD spectrum disorder is established in an individual with typical clinical and radiographic findings and/or by the identification of a heterozygous pathogenic variant in *RUNX2* (*CBFA1*).

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. If bone density is below normal, treatment with calcium and vitamin D supplementation is considered. Dental procedures to address retention of deciduous dentition, presence of

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supernumerary teeth, and non-eruption of the permanent dentition. Such procedures may include prosthetic replacements, removal of the supernumerary teeth followed by surgical repositioning of the permanent teeth, and a combination of surgical and orthodontic measures for actively erupting and aligning the impacted permanent teeth. Speech therapy may be required during periods of dental treatment. Aggressive treatment of sinus and middle ear infections; consideration of tympanostomy tubes for recurrent middle ear infections.

Prevention of primary manifestations: Preventive treatment for osteoporosis should be initiated at a young age. Early screening for low bone mineral density and appropriate supplementation with vitamin D and calcium are recommended.

Prevention of secondary complications: Careful planning of anesthetic management due to craniofacial and dental abnormalities. Consultation with an otolaryngologist to assist in securing the airway. Consideration of alternative anesthetic approaches, including neuraxial block, taking into account possible spine abnormalities.

Surveillance: Monitoring of children for orthopedic complications, dental abnormalities, upper-airway obstruction, sinus and ear infections, and hearing loss. Monitoring for osteoporosis 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: Monitoring of affected women during pregnancy for cephalopelvic disproportion.

Genetic counseling

Cleidocranial dysplasia spectrum disorder is inherited in an autosomal dominant manner. The proportion of cases caused by a *de novo RUNX2* pathogenic variant is high. Each child of an individual with CCD spectrum disorder has a 50% chance of inheriting the pathogenic variant. Prenatal testing for pregnancies at increased risk is possible if the pathogenic variant in the family is known.

Diagnosis

Cleidocranial dysplasia (CCD) spectrum disorder is a skeletal dysplasia that represents a continuum of clinical findings ranging from classical presentation (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

Cleidocranial dysplasia (CCD) spectrum disorder **should be suspected** in individuals 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 broad and flat; the cranium is brachycephalic.
- **Frontal and parietal bossing** and **mid-face retrusion**
- **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
- **Hand abnormalities** including brachydactyly, tapering fingers, and short, broad thumbs

- **Short stature** (typically moderate)
- **Normal intellect** in individuals with classic CCD spectrum disorder

Radiographic findings

- **Cranium**
  - Wide-open sutures, patent fontanelles, presence of wormian bones (small sutural bones)
  - Delayed ossification of the skull
  - Poor or absent pneumatization of the paranasal, frontal, and mastoid sinuses
  - Impacted, crowded teeth; supernumerary teeth
- **Thorax** (Figure 2)
  - 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** (Figure 3)
  - 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 by DXA; some affected individuals sustain multiple fractures.

Establishing the Diagnosis

The diagnosis of a CCD spectrum disorder **is established** in a proband with EITHER of the following:

- The above clinical and radiographic findings of classic CCD
- Suggestive clinical findings and a heterozygous pathogenic variant in *RUNX2* (*CBFA1*) identified by molecular genetic testing (see Table 1)

Molecular testing approaches can include **single-gene testing**, **karyotype**, or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *RUNX2* is performed first and followed by gene-targeted deletion/duplication analysis if no pathogenic variant is found.

  Note: Gene-targeted methods will detect deletions ranging from a single exon to whole genes; however, breakpoints of large deletions and/or deletion of adjacent genes may not be determined.

- **Karyotype.** If *RUNX2* testing is not diagnostic and if strong suspicion persists in an individual with features of 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 [Purandare et al 2008, Northup et al 2011].

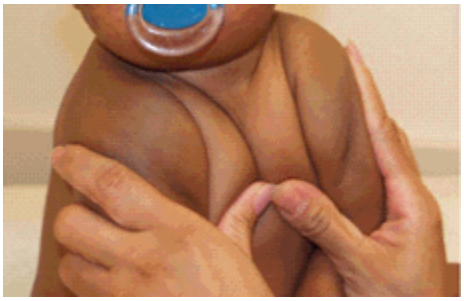

Figure 1. Shoulders in an individual with clavicular hypoplasia may be brought to the midline.

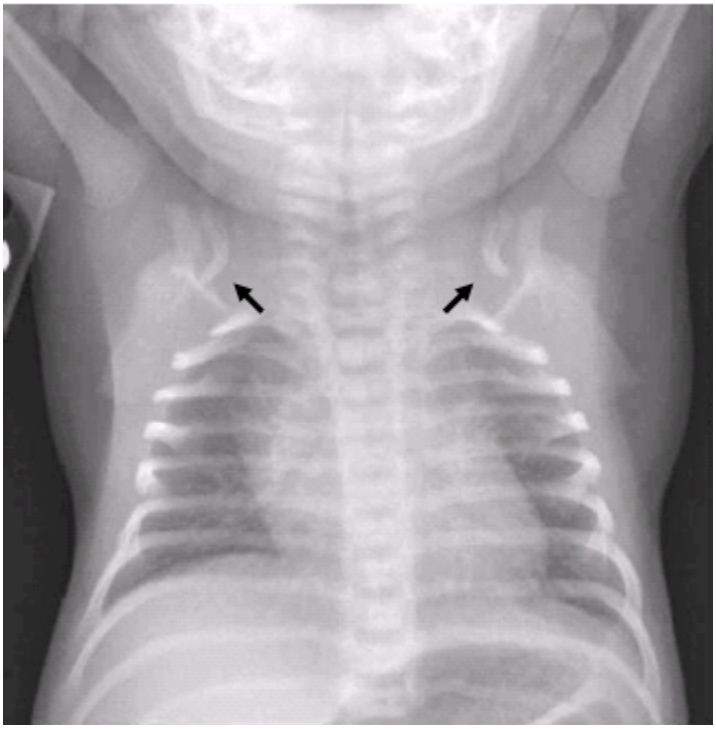

Figure 2. Chest x-ray demonstrates clavicular hypoplasia.

- **A multigene panel** that includes *RUNX2* and other genes of interest (see Differential Diagnosis) may also be considered. 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*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of pathogenic variants in genes that do not explain the underlying phenotype. (3) 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.

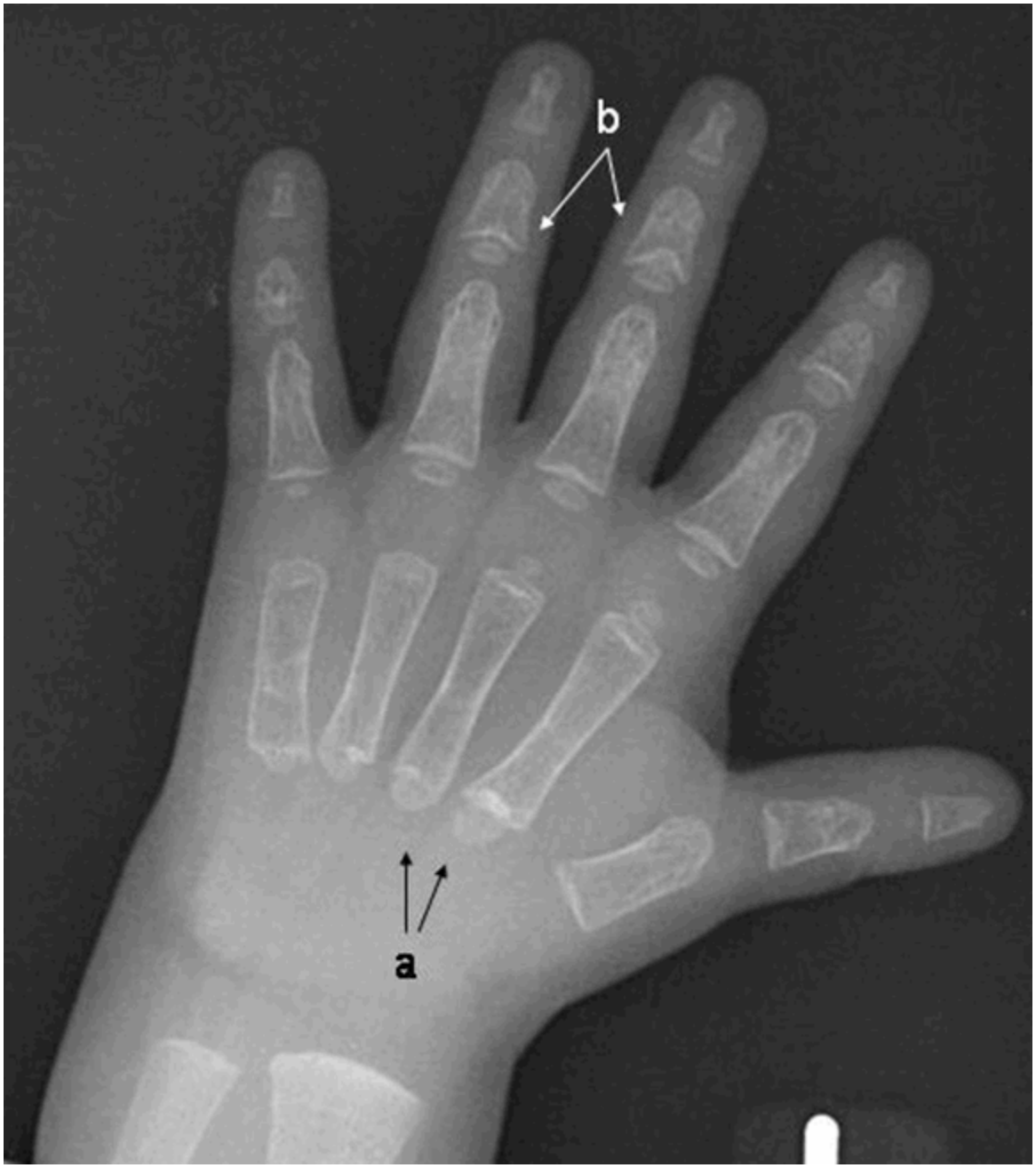

Figure 3. Hand x-ray of a male age 2.5 years with cleidocranial dysplasia spectrum disorder

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 [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
RUNX2	Sequence analysis [3]	~60% [4]
	Gene-targeted deletion/duplication analysis [5]	10% [6, 7]
	Karytoype	See footnote 8
Unknown [9]	NA	

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. Ott et al [2010]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Individuals with these deletions may have a phenotype consistent with a CCD spectrum disorder and additional findings including developmental delay. Gene-targeted methods will detect single-exon up to whole gene deletions; however, breakpoints of large deletions and/or deletion of adjacent genes may not be determined.
7. Ott et al [2010]
8. Two individuals with translocations involving the *RUNX2* locus have been reported [Purandare et al 2008, Northup et al 2011].
9. Not all individuals clinically diagnosed with CCD have an identifiable heterozygous pathogenic variant in *RUNX2*; however, there is little additional evidence for locus heterogeneity.

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 the skeletal features [Golan et al 2000]. Most individuals come to diagnosis 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. Males and females are affected equally.

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**).

Further medical problems identified in individuals with CCD spectrum disorder include the following:

Height. Individuals with CCD spectrum disorder are often shorter than their unaffected sibs:

- Males are on average six inches shorter than their unaffected brothers and have an average height of 165 cm (±8 cm).

- Females are on average three inches shorter than their unaffected sisters and have an average height of 156 cm (±10 cm) [Cooper et al 2001].

Skeletal/orthopedic problems. 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 (57.1%) affected individuals; and osteopenia, identified in 3/14 (21.4%) individuals with CCD spectrum disorder [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 supernumerary teeth (they often do not lose their primary teeth) and eruption failure of the permanent 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 cysts in their gums 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 IGF-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. 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) (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 protein in the maintenance of adult bone [Quack et al 1999].

Penetrance

Pathogenic variants in *RUNX2* have a high penetrance and extreme variability.

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

CCD spectrum disorder is present at a frequency of one in 1,000,000 individuals worldwide. It affects all ethnic groups. Stevenson et al [2012] found the frequency to be 0.12 per 10,000 individuals in the Utah (USA) 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 CCD spectrum disorder. The fact that similar skeletal elements are affected suggests that some of these conditions may result from mutation of genes that affect the action of RUNX2 on its downstream targets. Most notable is the association of 16q22.1 deletion that includes *CBFB* with wide-open fontanelles and short clavicles [Goto et al 2004]. Because CBFB forms a heterodimer with RUNX2 to activate transcription of downstream targets, CBFB haploinsufficiency would explain the similarity in the phenotypes.

Table 2. Disorders to Consider in the Differential Diagnosis of Cleidocranial Dysplasia (CCD) Spectrum Disorder

Disorder Name or Genetic Mechanism	Gene(s)	MOI	Clinical Features	
			Shared w/CCD spectrum disorder	Distinguishing from CCD spectrum disorder
16q22 deletion (incl deletion of *CBFB*) (OMIM 614541)	*CBFB*		Wide-open fontanelles & short clavicles	• Failure to thrive • Delayed psychomotor development • Congenital heart defect

Table 2. continued from previous page.

Disorder Name or Genetic Mechanism	Gene(s)	MOI	Clinical Features	
			Shared w/CCD spectrum disorder	Distinguishing from CCD spectrum disorder
Crane-Heise syndrome (OMIM 218090)	Unknown	AR?	• Large head • Poorly mineralized calvarium • Cleft lip & palate • Low-set, dysplastic ears • Hypoplastic clavicles & scapulae • Hypoplasic/absent phalanges • Absence of cervical vertebrae • Genital hypoplasia	• Lethal condition • IUGR • Multiple joint contractures • Severe vertebral & limb anomalies w/absence of cervical vertebrae
Mandibuloacral dysplasia (OMIM PS248370)	*LMNA*, *ZMPSTE24*	AR	• Short stature, delayed closure of cranial sutures, mandibular hypoplasia, & dysplastic clavicles • Scalp hair sparse by 3rd decade • Progressively stiff joints • Acroosteodysplasia of fingers & toes w/delayed ossification of carpal bones • Micrognathia • Early tooth loss • Atrophic skin w/↓ subcutaneous fat	• Acroosteolysis • Hyperpigmentation • Lipodystrophy • Alopecia
Pycnodysostosis	*CTSK*	AR	• Short stature, osteopetrosis w/↑ bone fragility, short terminal phalanges • Failure of closure of cranial sutures w/persistence of an open fontanelle • Radio-opacity of all bones ↑ due to ↑ density of the trabecular bone but not the cortices	• Osteopetrosis • Acrosteolysis
Yunis Varon syndrome (OMIM 216340)	*FIG4*	AR	• Prenatal growth deficiency • Wide-open fontanelles & sutures, unusual mineralization of the skull, & hypoplastic clavicles • Hypoplastic or absent thumbs & great toes	• Absence/hypoplasia of thumbs, halluces & distal phalanges • Gracile bones • Brain malformations
CDAGS syndrome (OMIM 603116)	Unknown	AR	• Craniosynostosis, delayed closure of fontanelles, cranial defects, clavicular hypoplasia [1] • Anal & genitourinary malformations • Skin eruption	• Craniosynostosis • Anal anomalies • Skin lesions (porokeratosis)

Table 2. continued from previous page.

Disorder Name or Genetic Mechanism	Gene(s)	MOI	Clinical Features	
			Shared w/CCD spectrum disorder	Distinguishing from CCD spectrum disorder
Hypophosphatasia [2]	*ALPL*	AR AD [3]	• Generalized defect of mineralization w/delayed ossification of multiple skeletal elements • Children w/infantile form may present w/very poorly mineralized cranium, widened cranial sutures short ribs, & narrow thorax. • Very low alkaline phosphatase activity in serum & tissues	• Clavicles least affected • No supernumerary teeth • Premature deciduous tooth loss • Rachitic skeletal changes • Nephrocalcinosis • Hypercalcemia
Parietal foramina with cleidocranial dysplasia [4]	*MSX2*	AD	• Parietal foramina • Mild craniofacial dysmorphisms • Clavicular hypoplasia	Not associated w/dental abnormalities seen in classic CCD [5]
Microduplications upstream of *MSX2*			Phenocopy of cleidocranial dysplasia [6]	Synpolydactyly in some
Familial supernumerary teeth		AD	Supernumerary premolar teeth	Nonsyndromic supernumerary premolar teeth [7]
Hypothyroidism			Delayed fontanelle closure	

IUGR = intrauterine growth restriction; MOI = mode of inheritance

1. CDAGS syndrome brings together the apparently opposing pathophysiologic and developmental processes of accelerated suture closure and delayed ossification [Mendoza-Londono et al 2005].

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

3. Perinatal and infantile hypophosphatasia are inherited in an autosomal recessive manner. The milder forms, especially adult 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.

4. See Enlarged Parietal Foramina.

5. Garcia-Miñaur et al [2003]

6. Ott et al [2012]

7. Bae et al [2017]

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with cleidocranial dysplasia (CCD) spectrum disorder, the following evaluations are recommended if they have not already been completed:

- Full skeletal survey including the hands and feet
- DXA scan for those in early adolescence and older
- Dental evaluation by a dentist familiar with CCD and its management
- Audiologic evaluation
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Craniofacial. The fontanelles close with time in the majority of individuals and cranial remodeling is usually not necessary.

- If the cranial vault defect is significant, the head should be protected from blunt trauma; helmets may be advised for high-risk activities. In these cases, evaluation by a craniofacial surgeon and rehabilitation services are indicated.
- Affected individuals may consider having correction of the depressed forehead or lengthening of the hypoplastic clavicles for cosmetic reasons. There have been reports of successful surgical interventions in a very small number of affected individuals [Kang et al 2009, Sewell et al 2013].

Skeletal. If bone density is below normal on DXA, treatment with calcium and vitamin D supplementation should be considered.

Dental. Early referral to a dental clinic familiar with CCD allows for timely planning of necessary procedures.

- The dental problems that need to be addressed include the retention of deciduous dentition, the presence of supernumerary teeth, and the non-eruption of the permanent dentition.
- The goal of treatment is to improve appearance and to provide a functioning masticatory mechanism. The goals may be achieved with prosthetic replacements, with or without prior extractions; by removal of the supernumerary teeth followed by surgical repositioning of the permanent teeth; and by a combination of surgical and orthodontic measures for actively erupting and aligning the impacted permanent teeth. For a detailed review, see Becker et al [1997a], Becker et al [1997b], and Roberts et al [2013].
- Generally, an aggressive approach to coordination of multiple oral surgeries for removal of primary dentition and exposure of permanent dentition is recommended, as watchful waiting for spontaneous eruption after initial delay is not effective.

Speech therapy may be required during periods of dental treatment.

Upper airway obstruction. When symptoms are suggestive, a sleep study is indicated and surgical intervention may be required.

Sinus and middle ear infections require aggressive and timely treatment; tympanostomy tubes should be considered when middle ear infections are recurrent [Visosky et al 2003].

Endocrinology. The effectiveness of growth hormone (GH) therapy for short stature in this condition has not been proven. Possible adverse effects of GH therapy on the primary chondrodysplastic growth plate are theoretically possible, as *RUNX2* is directly involved in chondrocyte differentiation and growth plate maintenance [Zheng et al. 2005].

Prevention of Primary Complications

Preventive treatment for osteoporosis should be initiated at a young age since peak bone mineral density is achieved in the second and third decade. Early screening for low bone mineral density and appropriate supplementation with vitamin D and calcium are recommended.

Prevention of Secondary Complications

Anesthetic management of those with CCD spectrum disorder needs to be carefully planned since affected individuals may present with a large brachycephalic head with mandibular prognathism and maxillary underdevelopment. In addition, the depressed nasal bridge and hypoplastic sinuses disturb nasal breathing. The dental and craniofacial abnormalities result in predictably difficult airway management. If this is anticipated, an otolaryngologist should be consulted to assist in securing the airway. Alternative anesthetic approaches,

including neuraxial block, should be considered, taking into account possible spine abnormalities [Ioscovich et al 2010].

Surveillance

Children with CCD spectrum disorder should be monitored for the following:

- Orthopedic complications
- Dental abnormalities
- Signs and symptoms of upper-airway obstruction
- Sinus and ear infections
- Hearing loss. Regular audiometry in individuals with repeated ear infections allows the identification and early management of hearing loss if it develops.
- Osteoporosis. DXA to measure bone mineral density should be done early in adolescence and every five to ten years thereafter. If there are clinical signs of osteopenia (i.e., increased number of fractures), evaluation and treatment should be started earlier.

All affected individuals should by followed by their primary care physician and receive regular immunizations and anticipatory guidance as recommended.

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 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, 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. —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* heterozygous *RUNX2* pathogenic variant. The proportion of cases caused by a *de novo* pathogenic variant is high.
- If the pathogenic variant found in the proband cannot be detected in leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. Germline mosaicism has been reported [Pal et al 2007].
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include careful 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 for the parents of a proband with an apparent *de novo* pathogenic variant may also be considered.
- 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 unless a clinical examination with skeletal x-rays and/or molecular genetic testing has been performed on the parents of the proband.

Note: If the parent is the individual in whom the pathogenic variant first occurred, s/he may have somatic mosaicism for the pathogenic variant and may be mildly/minimally affected.

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, the risk to the sibs is 50%. (Note: The phenotype may vary among sibs who inherit the *RUNX2* pathogenic variant.)
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low.
- If the pathogenic variant cannot be detected in the leukocyte DNA of either parent, the empiric recurrence risk to sibs is approximately 1% 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].

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 the *RUNX2* pathogenic variant, his or her family members are at risk.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with CCD spectrum disorder has the *RUNX2* pathogenic variant identified in the proband or clinical evidence of the disorder, the *RUNX2* pathogenic variant is likely *de novo*. However, possible non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

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 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, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the *RUNX2* pathogenic variant has been identified in an affected family member, prenatal testing and preimplantation genetic testing for cleidocranial dysplasia 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, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. 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)
- **Children's Craniofacial Association (CCA)**
  13140 Coit Road
  Suite 517
  Dallas TX 75240
  Phone: 800-535-3643 (toll-free)
  Email: contactCCA@ccakids.com
  www.ccakids.org
- **FACES: The National Craniofacial Association**
  PO Box 11082
  Chattanooga TN 37401
  Phone: 800-332-2373 (toll-free)
  Email: faces@faces-cranio.org
  www.faces-cranio.org
- **Human Growth Foundation (HGF)**
  997 Glen Cove Avenue

Suite 5
Glen Head NY 11545
Phone: 800-451-6434 (toll-free)
Fax: 516-671-4055
Email: hgf1@hgfound.org
www.hgfound.org

- **MAGIC Foundation**
  4200 Cantera Drive #106
  Warrenville IL 60555
  Phone: 800-362-4423 (Toll-free Parent Help Line); 630-836-8200
  Fax: 630-836-8181
  Email: contactus@magicfoundation.org
  www.magicfoundation.org

- **International Skeletal Dysplasia Registry**
  UCLA
  615 Charles E. Young Drive
  South Room 410
  Los Angeles CA 90095-7358
  Phone: 310-825-8998
  Fax: 310-206-5266
  Email: Salon@mednet.ucla.edu
  International Skeletal Dysplasia Registry

- **Skeletal Dysplasia Network, European (ESDN)**
  Institute of Genetic Medicine
  Newcastle University, International Centre for Life
  Central Parkway
  Newcastle upon Tyne NE1 3BZ
  United Kingdom
  Email: info@esdn.org
  www.esdn.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
RUNX2	6p21.1	Runt-related transcription factor 2	RUNX2 database	RUNX2	RUNX2

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)

119600	CLEIDOCRANIAL DYSPLASIA; CCD

Table B. continued from previous page.

600211	RUNT-RELATED TRANSCRIPTION FACTOR 2; RUNX2

Gene structure. Most documented cases of CCD spectrum disorder are caused by a heterozygous pathogenic variant in the transcription factor *RUNX2* (known previously as *CBFA1*). At the genomic level, the longest *RUNX2* transcript variant (NM_001024630.3) contains nine exons. Transcript variants that encode different protein isoforms [Geoffroy et al 1998] result from the use of alternate promoters as well as alternate splicing [provided by RefSeq, July 2008]. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Pathogenic variants in *RUNX2* include missense variants, deletion/splice/insertion variants resulting in premature termination, and nonsense variants. The majority of *RUNX2* pathogenic variants in individuals with classic CCD affect the runt domain and most pathogenic variants 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 the RUNX2 protein, a critical residue for RUNX2 function. In vitro studies have shown that pathogenic missense variants at p.Arg225 interfere with nuclear accumulation of RUNX2 protein. Microdeletion of the gene is also an important cause of CCD. (For more information, see Table A.)

Table 3. *RUNX2* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Reference Sequences
c.90dupC (90insC)	p.Ser31LeufsTer130	NM_001024630.3 NP_001019801.3
c.598A>G	p.Thr200Ala	
c.673C>T	p.Arg225Trp	
c.674G>T	p.Arg225Leu	
c.674G>A	p.Arg225Gln	
c.1171C>T	p.Arg391Ter	
c.1205dupC	p.Pro403AlafsTer87 [2]	

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.
1. Variant designation that does not conform to current naming conventions
2. Published as frameshift variant in codon Pro402 [Quack et al 1999]

Normal gene product. The protein, runt-related transcription factor 2 (RUNX2), is 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].

Abnormal gene product. Pathogenic variants in *RUNX2* result in haploinsufficiency for the protein and are associated with classic CCD. There are exceptions, including the hypomorphic alleles with partial loss of protein function (c.90dupC and c.598A>G), which are associated with mild CCD, isolated dental anomalies, and significant intrafamilial variability. This finding raises the question of whether hypomorphic/neomorphic effects

of the other *RUNX2* allele and/or other genetic modifiers alter the clinical expressivity of these pathogenic variants [Zhou et al 1999].

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Chapter Notes

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Dr. Mendoza-Londono's website

Dr. Lee's websites:
Baylor College of Medicine, People
Baylor College of Medicine, Find a Physician
Howard Hughes Medical Institute

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