GENEReviews

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Cleidocranial Dysplasia

[*Cleidocranial Dysostosis*]

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Summary

Disease characteristics. Cleidocranial dysplasia (designated as CCD in this *GeneReview*) is a skeletal dysplasia characterized by delayed closure of the cranial sutures, hypoplastic or aplastic clavicles, and multiple dental abnormalities. Manifestations may vary among individuals in the same family. The most prominent clinical findings are abnormally large, wide-open fontanels at birth that may remain open throughout life; mid-face hypoplasia; abnormal dentition, including delayed eruption of secondary dentition, failure to shed the primary teeth, supernumerary teeth with dental crowding, and malocclusion; clavicular hypoplasia resulting in narrow, sloping shoulders that can be apposed at the midline; and hand abnormalities such as brachydactyly, tapering fingers, and short, broad thumbs. Individuals with CCD are shorter than their unaffected sibs and are more likely to have other skeletal/orthopedic problems such as pes planus, genu valgum, and scoliosis. Other medical problems include recurrent sinus infections and other upper airway complications, recurrent ear infections, high incidence of cesarean section, and mild degree of motor delay in children under age five years.

Diagnosis/testing. Diagnosis of CCD is based on clinical and radiographic findings that include imaging of the cranium, thorax, pelvis, and hands. *RUNX2(CBFA1)* is the only gene known to be associated with CCD. Molecular genetic testing of the *RUNX2* gene detects mutations in 60-70% of individuals with a clinical diagnosis of CCD. Such testing is available on a clinical basis.

Management. Treatment of CCD includes dental procedures to address retention of deciduous dentition, presence of supernumerary teeth, and non-eruption of the permanent dentition; these procedures 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. Sinus and middle ear infections need aggressive treatment; tympanostomy tubes are considered for recurrent middle ear infections. If the cranial vault defect is significant, the head needs protection from blunt trauma; helmets may be used for high-risk activities. If bone density is below normal, treatment with calcium and vitamin D supplementation is considered. Preventive treatment for osteoporosis should be initiated at a young age. Children with CCD should be monitored for orthopedic complications, dental

abnormalities, upper airway obstruction, sinus and ear infections, hearing loss, and osteoporosis. Pregnant women with CCD should be monitored for cephalopelvic disproportion.

Genetic counseling. Cleidocranial dysplasia is inherited in an autosomal dominant manner. The proportion of cases caused by a *de novo* mutation is high. If a parent of the proband is affected, the risk to the sibs is 50%. Each child of an individual with CCD has a 50% chance of inheriting the mutation. Prenatal diagnosis for pregnancies at increased risk is possible if the disease-causing mutation has been identified, but requests are not common.

Diagnosis

Clinical Diagnosis

Cleidocranial dysplasia (CCD) is a disorder that affects most prominently those bones derived from endochondral and intramembranous ossification, such as the cranium and the clavicles. Diagnosis is based on clinical and radiographic findings.

The most prominent clinical findings in CCD:

- **Abnormally large, wide-open fontanels 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.
- **Mid-face hypoplasia**
- **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
- **Clavicular hypoplasia,** resulting in narrow, sloping shoulders that can be apposed at the midline (Figure 1)
- **Hand abnormalities** such as brachydactyly, tapering fingers, and short, broad thumbs
- **Normal intellect** in individuals with typical CCD

The most prominent radiographic findings in CCD:

- **Cranium**
  - Wide-open sutures; patent fontanels; 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**
  - Cone-shaped thorax with narrow upper thoracic diameter
  - Clavicular abnormalities ranging from complete absence to hypoplastic or discontinuous clavicles. The lateral and middle thirds of the clavicle are more commonly affected (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
- Large femoral neck and large epiphyses

- **Hands**
  - Pseudoepiphyses of the metacarpal and metatarsal bones, which may result in a characteristic lengthening of the second metacarpal
  - Hypoplastic distal phalanges
  - Deformed and short middle phalanges of the third, fourth, and fifth digits with cone-shaped epiphyses
- **Other**
  - Osteopenia with evidence of decreased bone mineral density by DEXA in some individuals is a non-specific finding.

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.

Gene. To date, *RUNX2(CBFA1*) is the only gene known to be associated with CCD.

Other loci. Although not all cases clinically diagnosed as CCD have mutations in *RUNX2*, there is little additional evidence for locus heterogeneity.

Molecular genetic testing: Clinical uses

- Confirmatory diagnostic testing
- Prenatal diagnosis

Molecular genetic testing: Clinical methods

- **Sequence analysis/mutation scanning.** Sequence analysis/mutation scanning of genomic DNA of the coding region of *RUNX2* detects mutations in close to 70% of individuals with a clinical diagnosis of CCD. The mutations in most families are unique.
- **FISH.** Individuals with the CCD phenotype and additional findings including developmental delay may have deletion of all or part of the *RUNX2* gene as well as neighboring genes. Microdeletions may be found in up to 13% of individuals with normal results on sequence analysis [Mendoza-Londono & Lee, unpublished observation of 40 individuals with CCD phenotype]. These deletions can be detected by FISH with specific probes that contain part of the *RUNX2* sequence. *(RUNX2* is covered by three partially overlapping clones: RP11-166H4, RP11-244F24, and RP11-342L7). Probes spanning the *RUNX2* sequence are included in some commercially available chromosomal microarray analysis (CMA) testing platforms.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Cleidocranial Dysplasia

Test Methods	Mutations Detected	Mutation Detection Rate	Test Availability
Genomic DNA sequence analysis	Missense and nonsense mutations, small insertions or deletions, exon-skipping mutations of *RUNX2*	60-70%	Clinical Testing
Chromosomal microarray analysis (CMA) [1]	Large microdeletions involving *RUNX2*		

1. Chromosomal microarray analysis (also known as array comparative genomic hybridization or CGH) evaluates multiple loci; therefore, clinically relevant but unanticipated abnormalities may be identified with this assay.

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

Testing Strategy for a Proband

1. When the diagnosis of CCD is suspected, the clinician should request a skeletal survey that includes: (1) anteroposterior (AP) and lateral projections of the skull and thorax; (2) AP of the pelvis; (3) lateral of the lumbar spine; and (4) AP of the long bones, hands, and feet.
2. Individuals with atypical features and developmental delay should have a karyotype in order to evaluate for visible deletions or rearrangements involving the *RUNX2* locus at 6p21.
3. Molecular genetic testing is appropriate for diagnostic confirmation if the clinical findings do not meet clinical and radiologic diagnostic criteria.

Genetically Related Disorders

To date, no other phenotypes have been associated with mutations in *RUNX2*.

Clinical Description

Natural History

Cleidocranial dysplasia (CCD) is a skeletal dysplasia characterized by delayed closure of the cranial sutures, hypoplastic or aplastic clavicles, and multiple dental abnormalities. Jackson (1951) described an extensive family with CCD. More recently, Cooper et al (2001) recorded the natural history of 90 affected individuals and 56 first- and second-degree relatives.

Manifestations range from isolated dental anomalies to fully manifesting disease with poorly ossified cranium and absent clavicles [Golan et al 2000]. The phenotype may vary among individuals in the same family even though they have the same mutation. Males and females are affected equally.

The main medical problems identified in individuals with CCD include the following:

Height. Individuals with CCD are shorter than their unaffected sibs. Males with CCD are on average six inches shorter than their unaffected brothers and have an average height of 165 cm (±8 cm). Females with CCD 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. Individuals with CCD are more likely to have other bone-related problems. Pes planus (flat feet) are seen in 57% of individuals with CCD. Genu valgum (knock-knee deformity) is seen in 28% and scoliosis in 18% [Cooper et al 2001]. Other less common orthopedic problems include joint dislocation at the shoulder and elbow.

ENT complications. Recurrent sinus infections and other upper airway complications are observed significantly more often in individuals with CCD. Hearing loss occurs in 39% of affected individuals. Individuals with CCD of any age are more likely to have recurrent ear infections.

Dental complications. Up to 94% of persons with CCD 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 CCD 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]. Individuals with CCD are more likely to have an underbite and to have cysts in their gums that usually form around extra teeth [McNamara et al 1999].

Obstetric complications. The primary cesarean section rate among women with CCD is 69%, which is higher than in controls [Cooper et al 2001].

Development. Intelligence is normal in individuals with classic CCD. Children under the age of five years may show a mild degree of motor delay, particularly in gross motor abilities. This delay may be associated with orthopedic complications such as flat feet and knock-knees. No significant differences are observed among children in grade school.

Genotype-Phenotype Correlations

Although the spectrum of phenotypic variability in CCD ranges from primary dental anomalies to all CCD clinical features plus osteoporosis, no clear phenotype-genotype correlation has been established [Otto et al 2002].

All 24 Japanese individuals evaluated by Yoshida et al (2002) had the classic CCD phenotype, including hypoplastic clavicles and open sutures; however, the other hand, skeletal, and dental findings demonstrated significant genotype-phenotype correlation. They also showed a direct correlation between (1) final height and residual transactivation activity of RUNX2, mediated by the runt domain, with an important additional effect given the individual's genetic background; (2) the number of supernumerary teeth and the degree of short stature; i.e., the more supernumerary teeth, the shorter the individual.

Mutations that result in premature termination upstream or within the runt domain produce classic CCD by abolishing the transactivation activity of the mutant protein with consequent haploinsufficiency. Hypomorphic mutations (R391X, T200A, and 90insC) result in a clinical spectrum ranging from isolated dental anomalies without the skeletal features of CCD to mild CCD to classic CCD. Intrafamilial variability is significant [Zhou et al 1999].

Missense mutations cluster at arginine 225 (R225) of the RUNX2 protein, a critical residue for RUNX2 function. In vitro studies have shown that R225 mutations interfere with nuclear accumulation of RUNX2 protein. In addition, a frameshift mutation in codon 402 has been associated with osteoporosis leading to recurrent bone fractures and scoliosis reflecting the role of RUNX2 in the maintenance of adult bone [Quack et al 1999].

Penetrance

Mutations in *RUNX2* have a high penetrance and extreme variability.

Anticipation

Anticipation has not been observed.

Prevalence

CCD is present at a frequency of one in one million individuals. It affects all ethnic groups.

Differential Diagnosis

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

Other conditions share some characteristics with CCD. The fact that similar skeletal elements are affected suggests that some of these conditions may result from mutations in genes that affect the action of RUNX2 on its downstream targets. Most notable is association of deletions of CBF beta *(CBFB*) with wide-open fontanels and short clavicles [Goto et al 2004]. Because *CBFB* forms a heterodimer with *RUNX2* to activate transcription of downstream targets, haploinsufficiency for this gene would explain the similarity in the phenotypes.

Crane-Heise syndrome (MIM 218090) is a rare disorder characterized by a large head, poorly mineralized calvarium, cleft lip and palate, low-set dysplastic ears, hypoplastic clavicles and scapulae, agenesis of some cervical vertebrae, and genital hypoplasia. Inheritance may be autosomal recessive.

Mandibuloacral dysplasia (MADA, MIM 248370, and MADB MIM 608612) is a progressive disorder characterized by short stature, delayed closure of cranial sutures, mandibular hypoplasia, and dysplastic clavicles. The scalp hair becomes sparse by the third decade and some individuals develop alopecia. The joints become progressively stiff; radiographs reveal acroosteodysplasia of the fingers and toes, with delayed ossification of the carpal bones. Osteolysis of the mandibular body and ramus results in micrognathia. In adolescence, dental crowding is observed; hypoplastic roots lead to early tooth loss. The skin is atrophic with decreased subcutaneous fat. Several individuals develop a hyperpigmented rash over the trunk and hyperkeratotic papular lesions of the extremities. MAD is associated with mutations in the genes *LMNA* or *ZMPSTE24*. Inheritance is autosomal recessive.

Pycnodysostosis (PYCD, MIM 265800) is caused by mutations in the gene that encodes cathepsin K, a lysosomal protease excreted by the osteoclasts for bone matrix degradation. PYCD is characterized by short stature, osteopetrosis with increased bone fragility, short terminal phalanges, and failure of closure of the cranial sutures with persistence of an open fontanel. Radio-opacity of all bones is increased because of increased density of the trabecular bone but not the cortices. Inheritance is autosomal recessive.

Yunis Varon syndrome (MIM 216340) is characterized by prenatal growth deficiency, wide-open fontanels and sutures, unusual mineralization of the skull, and hypoplastic clavicles. The thumbs and great toes are hypoplastic or absent. Inheritance is autosomal recessive.

CDAGS syndrome (MIM 603116) is characterized by **c**raniosynostosis, **d**elayed closure of the fontanels, cranial **d**efects, clavicular hypoplasia, **a**nal and **g**enitourinary malformations, and **s**kin eruption. It brings together the apparently opposing pathophysiologic and developmental processes of accelerated suture closure and delayed ossification [Mendoza-Londono et al 2005]. Inheritance is autosomal recessive.

Hypophosphatasia (MIM 241500) is characterized by a generalized defect of mineralization with delayed ossification of multiple skeletal elements. Children with the infantile form may present with very poorly mineralized cranium, widened cranial sutures, short ribs, and narrow thorax. The alkaline phosphatase activity in serum and tissues is very low [Morava et al 2002]. In one report, an individual with severe CCD was initially thought to have

hypophosphatasia [Unger et al 2002]. Hypophosphatasia is caused by mutations in the gene encoding alkaline phosphatase. Inheritance is autosomal recessive.

Parietal foramina with cleidocranial dysplasia (PFMCCD) is a distinct clinical entity with parietal foramina, mild craniofacial dysmorphisms, and clavicular hypoplasia. This condition is a manifestation of mutations in *MSX2* and is not associated with the dental abnormalities seen in classic CCD (see Enlarged Parietal Foramina/Cranium Bifidum) [Garcia-Minaur et al 2003].

Chromosomal abnormalities. Brueton et al (1992) described apparent CCD associated with abnormalities of 8q22 in three individuals.

The first index case had at birth micrognathia, a large anterior fontanel with a wide sagittal suture, and a narrow upper thorax. X-rays at 27 months showed wormian bones in the skull, underdevelopment of the maxillary bones, and bilateral hypoplastic clavicles. The child's mother had similar physical characteristics, with bilateral hypoplasia of clavicles, micrognathia, and short stature. Cytogenetic studies showed the balanced translocation 46,XX, t(8;10)(q22.1;p12.3).

The third individual, the product of non-consanguineous parents, was noted at four months of age to have a small central palatal cleft, large anterior fontanel, and wide sagittal suture. Her clavicles were rudimentary and hypoplastic. Cranial x-ray revealed wormian bones and micrognathia. Cytogenetic analysis showed a partial duplication of the long arm of chromosome 8 (47, XX, der dup (8)(q13-q22.1).

Hypothyroidism can present with delayed fontanel closure.

Management

Evaluations at Initial Diagnosis to Establish the Extent of Disease

Once the diagnosis is established, individuals with CCD need an initial evaluation to establish the extent of their clinical findings. This evaluation should include:

- Full skeletal survey including the hands and feet
- Audiologic evaluation
- Dental evaluation by a dentist familiar with CCD and its management.

Treatment of Manifestations

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, Lustmann et al 1997; Becker, Shteyer et al 1997.

Speech therapy may be required during periods of dental treatment.

Sinus and middle ear infections need aggressive and timely treatment and tympanostomy tubes should be considered in cases of recurrent middle ear infections [Visosky et al 2003].

The fontanels 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 is indicated.

If bone density is below normal on DEXA, treatment with calcium and vitamin D supplementation should be considered. Preventive treatment for osteoporosis should be initiated at a young age since peak bone mineral density is achieved in the second and third decade.

Surveillance

Children with CCD should be monitored for:

- Orthopedic complications
- Dental abnormalities
- Upper airway obstruction. Because of the craniofacial involvement, signs and symptoms of obstructive upper airway disease should be elicited. When symptoms are suggestive, a sleep study is indicated and surgical intervention may be required.
- 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. DEXA 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 (increased number of fractures), evaluation and treatment should be started earlier.

Pregnant women with CCD should be monitored closely for cephalopelvic disproportion, which may require delivery by cesarean section.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

Individuals with CCD should by followed by their primary care physician and receive regular immunizations and anticipatory guidance as recommended.

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

Cleidocranial dysplasia is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Some individuals diagnosed with cleidocranial dysplasia have an affected parent.
- A proband with cleidocranial dysplasia may have the disorder as the result of a *de novo* gene mutation. The proportion of cases caused by *de novo* mutations is high.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include careful clinical examination and consideration of craniofacial and skeletal x-rays if there are signs suggestive of dental or bony abnormalities.

Note: (1) Although some individuals diagnosed with cleidocranial dysplasia have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members. (2) If the parent is the individual in whom the mutation first occurred, s/he may have somatic mosaicism for the mutation and may be mildly/minimally affected.

Sibs of a proband

- The risk to the sibs of the proband depends upon the genetic status of the proband's parents.
- If a parent of the proband is affected, the risk to the sibs is 50%.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low.
- If the disease-causing mutation cannot be detected in the DNA of either parent, the risk to sibs is low, but greater than that of the general population because of the possibility of germline mosaicism. Germline mosaicism is the most likely explanation for a reported family with two affected sibs and unaffected parents (in whom molecular genetic testing had not been performed) [Zackai et al 1997].

Offspring of a proband. Each child of an individual with cleidocranial dysplasia has a 50% chance of inheriting the mutation.

Other family members of a proband. The risk to other family members depends upon the status of the proband's parents. If a parent is found to be affected, his or her family members are at risk.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation or clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations including alternate paternity or undisclosed adoption could also be explored.

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.

DNA banking. 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 in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Molecular genetic testing. Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about 10-12 weeks' gestation. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed.

Ultrasound examination. 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 (below the 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 [Hassan et al 1997, Stewart et al 2000].

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

Requests for prenatal testing for conditions such as cleidocranial dysplasia are not common. 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. Although most centers would consider decisions about prenatal testing to be the choice of the parents, careful discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified in an affected family member in a research or clinical laboratory. 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 Cleidocranial Dysplasia

Gene Symbol	Chromosomal Locus	Protein Name
RUNX2	6p21	Runt-related transcription factor 2

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 Cleidocranial Dysplasia

119600	CLEIDOCRANIAL DYSPLASIA; CCD
600211	RUNT-RELATED TRANSCRIPTION FACTOR 2; RUNX2

Table C. Genomic Databases for Cleidocranial Dysplasia

Gene Symbol	Entrez Gene	HGMD
RUNX2	860 (MIM No. 600211)	RUNX2

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

Normal allelic variants: Most documented cases of CCD are caused by mutations in the transcription factor *RUNX2* (runt-related transcription factor 2). At the genomic level, *RUNX2* contains nine exons that can be alternatively spliced [Geoffroy et al 1998].

The protein, runt-related transcription factor 2, 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 of independently mediating DNA binding and protein heterodimerization [Zhou et al 1999].

Pathologic allelic variants: Mutations in *RUNX2* include missense, deletion/splice/insertion variants resulting in premature termination and nonsense mutations. The majority of *RUNX2* mutations in individuals with classic CCD affect the runt domain and most mutations are predicted to abolish DNA binding [Lee at al 1997, Mundlos et al 1997, Otto et al 2002]. Microdeletion of the gene is an important cause for CCD. (For more information, see Genomic Databases table above.)

Normal gene product: RUNX2, also known as CBFA1 (core-binding factor, alpha subunit 1), is a transcription factor involved in osteoblast differentiation and skeletal morphogenesis. RUNX2 is essential for the osteoblast differentiation during intramembranous as well as chondrocyte maturation during endochondral ossification [Zheng et al 2005].

Abnormal gene product: Mutations in *RUNX2* result in haploinsufficiency for this gene and are associated with classic CCD. There are exceptions, including the 90insC and T200A mutations, which are associated with mild CCD, isolated dental anomalies, and significant intrafamilial variability. This finding raises the question of whether hypomorphic/neomorphic effects and genetic modifiers alter the clinical expressivity of these mutations.

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.

Children's Craniofacial Association
13140 Coit Road, Suite 307
Dallas, TX 75240
Phone: 800-535-3643; 214-570-8811
Email: contactCCA@ccakids.com
www.ccakids.com

FACES: The National Craniofacial Association
PO Box 11082
Chattanooga, TN 37401

Phone: 800-332-2373; 423-266-1632
Email: faces@faces-cranio.org
www.faces-cranio.org

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

The MAGIC Foundation
6645 West North Avenue
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Fax: 708-383-0899
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www.magicfoundation.org

European Skeletal Dysplasia Network
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Email: Jacky.Taylor@cmmc.nhs.uk
www.esdn.org

International Skeletal Dysplasia Registry
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www.csmc.edu

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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.

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Chapter Notes

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www.imgen.bcm.tmc.edu/molgen/facultyaz/blee.html
www.hhmi.org/research/investigators/leebhl.html
www.texaschildrenshospital.org/findadoctor/displaybio.asp?person_id=60
imgen.bcm.tmc.edu/molgen/cg/clinics/sd_index.html

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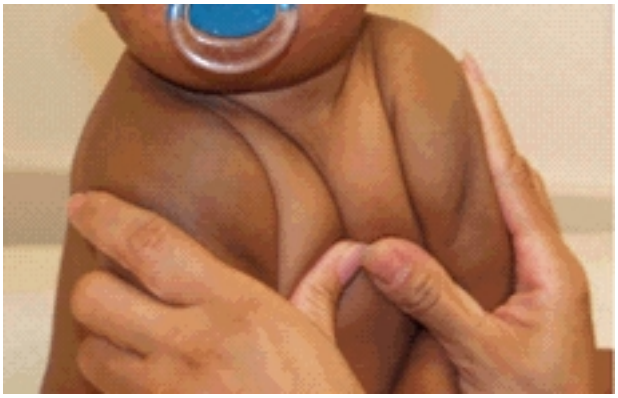

Figure 1. Shoulders in an individual with clavicular hypoplasia may be brought to the midline.

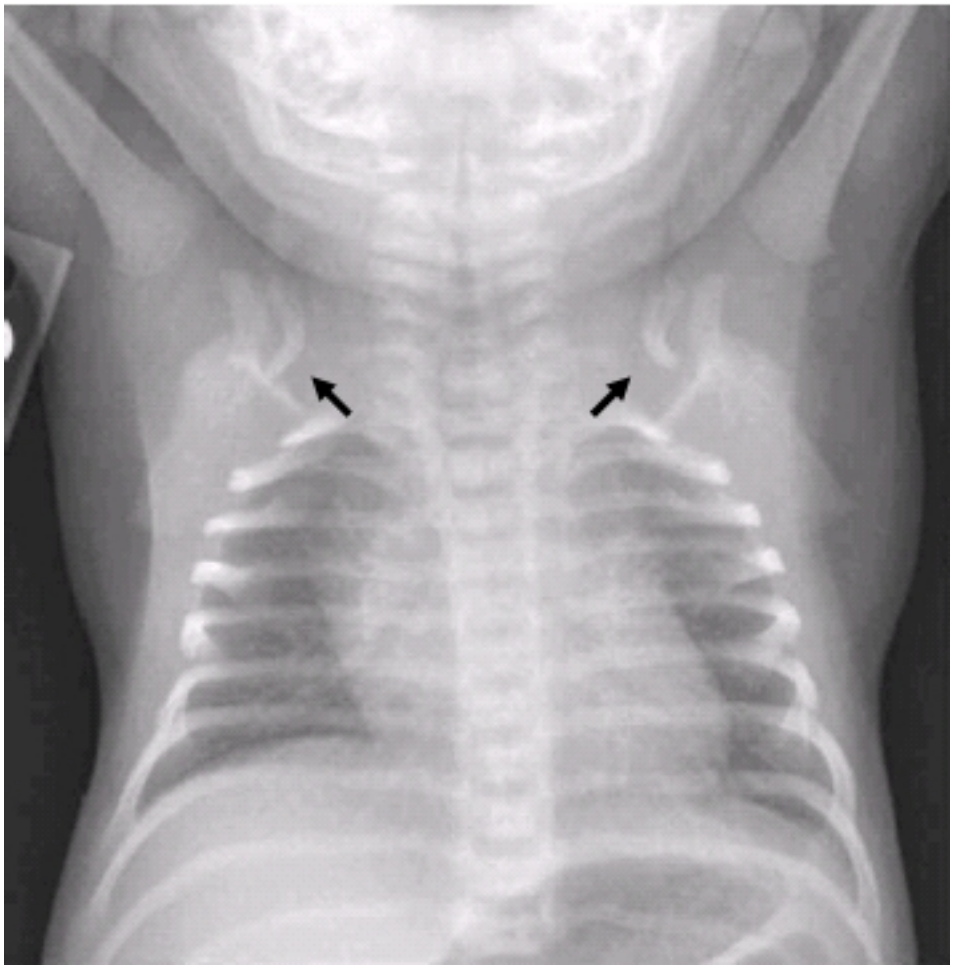

Figure 2. Chest x-ray demonstrates clavicular hypoplasia.