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Craniometaphyseal Dysplasia, Autosomal Dominant

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Summary

Clinical characteristics

Autosomal dominant craniometaphyseal dysplasia (designated AD-CMD in this review) is characterized by progressive diffuse hyperostosis of cranial bones evident clinically as wide nasal bridge, paranasal bossing, widely spaced eyes with an increase in bizygomatic width, and prominent mandible. Development of dentition may be delayed and teeth may fail to erupt as a result of hyperostosis and sclerosis of alveolar bone. Progressive thickening of craniofacial bones continues throughout life, often resulting in narrowing of the cranial foramina, including the foramen magnum. If untreated, compression of cranial nerves can lead to disabling conditions such as facial palsy, blindness, or deafness (conductive and/or sensorineural hearing loss). In individuals with typical uncomplicated AD-CMD life expectancy is normal; in those with severe AD-CMD life expectancy can be reduced as a result of compression of the foramen magnum.

Diagnosis/testing

Diagnosis is based on clinical and radiographic findings that include diffuse hyperostosis of the cranial base, cranial vault, facial bones, and mandible as well as widening and radiolucency of metaphyses in long bones. Identification of a heterozygous pathogenic variant in *ANKH* by molecular genetic testing can confirm the diagnosis if clinical features are inconclusive.

Management

Treatment of manifestations: Treatment for feeding and respiratory issues per craniofacial team; surgical intervention to reduce compression of cranial nerves and the brain stem / spinal cord at the level of the foramen magnum. Severely overgrown facial bones can be contoured; however, surgical procedures can be technically difficult and bone regrowth is common. Hearing aids; vision aids and surgical treatment for optic nerve impaction; speech therapy; surgical intervention for malocclusion.

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Surveillance: Evaluation for feeding and respiratory issues at least annually. Neurologic evaluation for signs and symptoms of narrowing of the cranial foramina including the foramen magnum at least annually. Hearing and ophthalmologic assessment at least annually.

Genetic counseling

By definition, AD-CMD is inherited in an autosomal dominant manner. Most individuals diagnosed with AD-CMD have an affected parent; the proportion of individuals with AD-CMD caused by a *de novo* pathogenic variant is thought to be very low. Each child of an individual with AD-CMD has a 50% chance of inheriting the pathogenic variant. Once the AD-CMD-causing pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Diagnosis

Formal diagnostic criteria for autosomal dominant craniometaphyseal dysplasia (AD-CMD) have not been established.

Suggestive Findings

AD-CMD **should be suspected** in individuals with the following clinical, radiographic, and laboratory features.

Clinical features

- Obstruction of the nasal sinuses
- Characteristic facial features. Wide nasal bridge, paranasal bossing, hypertelorism with an increase in bizygomatic width, and prominent mandible (see Figure 1)
- Dolichocephaly due to fronto-occipital hyperostosis

Radiographic features

- **Cranial base.** Sclerosis may begin in infancy (see Figure 2). Increasing diffuse hyperostosis of the cranial base leads to narrowing of the foramen magnum.
- **Skull.** Diffuse hyperostosis of cranial vault, facial bones, and mandible increases as the condition progresses [Lamazza et al 2009] with obstruction of the cranial foramina.
- **Long bones.** Metaphyseal widening (described as Erlenmeyer flask- or club-shaped) with thinned cortex and decreased bony density in the metaphyses can be detected early in life. Metaphyseal changes typically develop during early childhood. The flaring is most prominent in the distal femur and tibia (see Figure 3). Diaphyseal sclerosis/hyperostosis can be present in infancy but disappears with age. Bone density of the diaphyses is normal in children and adults; cortical thickness can be increased.
- **Ribs and clavicles** (medial portion [i.e., endochondral]) can be sclerotic in younger children but show normal bone density by age five years [Richards et al 1996].

Laboratory features

- **Blood calcium and phosphate concentrations** are within normal limits [Cheung et al 1997] or decreased [Sheppard et al 2003].
- **Serum alkaline phosphatase activity** can be elevated [Sheppard et al 2003, Wu et al 2016].
- **Parathyroid hormone level** is normal or can be slightly/transiently elevated [Fanconi et al 1988, Cheung et al 1997, Sheppard et al 2003, Wu et al 2016].
- **Osteocalcin** is decreased [Yamamoto et al 1993].

Note: Findings are based on very limited data. Variability of the described parameters can be expected. Abnormal parameters may be transient.

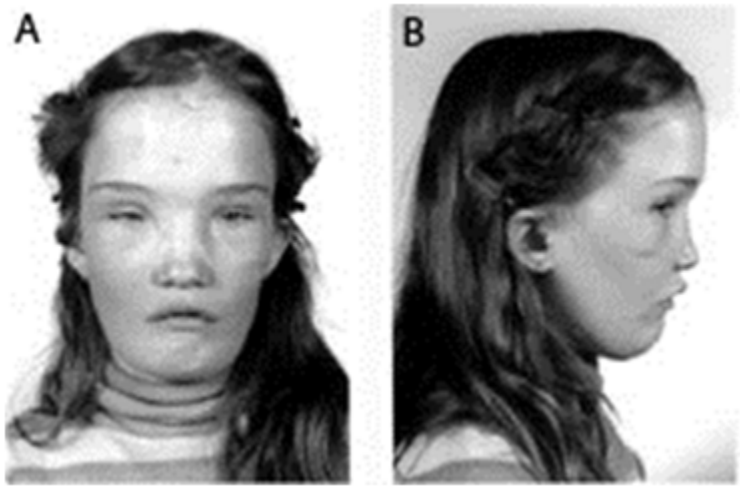

Figure 1. Facial features of a girl age 13 years with AD-CMD

Reprinted from Reichenberger et al [2001] with permission from Elsevier

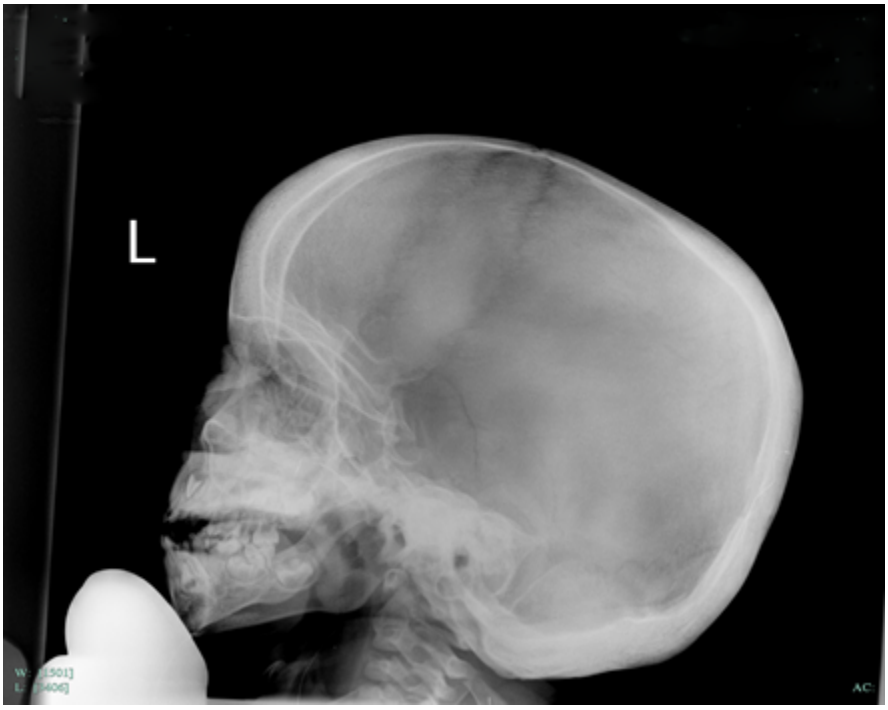

Figure 2. Increased thickness of craniofacial bones in a child age three years with AD-CMD

Establishing the Diagnosis

The diagnosis of AD-CMD **is established** in a proband with characteristic craniofacial hyperostosis and flaring and undertrabeculation of long bone metaphyses and/or a heterozygous pathogenic variant in *ANKH* identified by molecular genetic testing (see Table 1).

Note: Identification of a heterozygous *ANKH* variant of uncertain significance does not establish or rule out the diagnosis of this disorder.

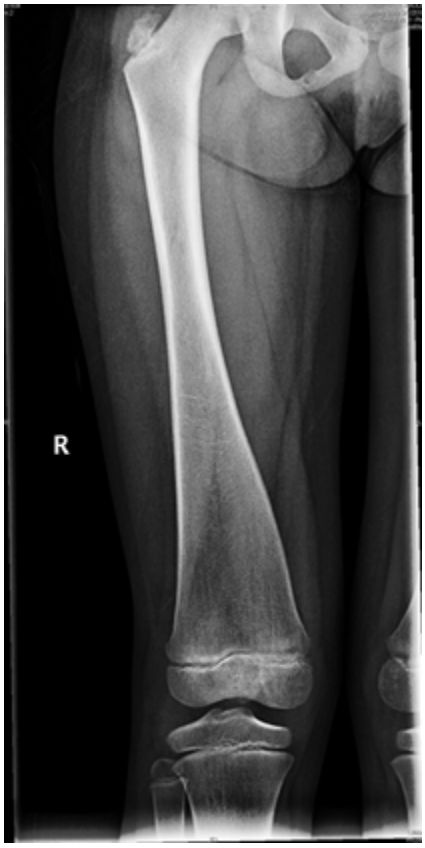

Figure 3. Metaphyseal widening of long bones, specifically prominent at the knee joint

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing and multigene panel) and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of AD-CMD is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with hyperostosis are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of AD-CMD, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *ANKH* 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 gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications. Note: To date such variants have not been identified as a cause of this disorder.
- **A multigene panel** that includes *ANKH* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition at the most reasonable cost 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.

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by hyperostosis, **comprehensive genomic testing**, which does not require the clinician to determine which gene is likely involved, is most likely to establish the diagnosis. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

If exome sequencing is not diagnostic – and particularly when evidence supports autosomal dominant inheritance – **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis. Note: To date such variants have not been identified as a cause of this disorder.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Autosomal Dominant Craniometaphyseal Dysplasia

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
ANKH	Sequence analysis [3]	~90% [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [6]
Unknown [7]	NA	~10%

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. Nürnberg et al [2001], Reichenberger et al [2001]
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. Since AD-CMD occurs through a gain-of-function/dominant negative mechanism and large intragenic deletion or duplication has not been reported, testing for intragenic deletions or duplication is unlikely to identify a disease-causing variant.
7. Some simplex cases of CMD did not have identifiable pathogenic variants in *ANKH*, suggesting possible locus heterogeneity.

Clinical Characteristics

Clinical Description

Autosomal dominant craniometaphyseal dysplasia (AD-CMD) is often detected within the first few weeks of life because of breathing or feeding problems resulting from choanal stenosis (narrowing of nasal sinus) [Haverkamp et al 1996, Cheung et al 1997, Taggart et al 2014].

Early stages of AD-CMD can be radiographically recognized as sclerosis of the cranial base. Hyperostosis of the cranial base, cranial vault, facial bones, and mandible occurs gradually. Overgrowth of the lower jaw (mandibular hyperostosis) and recessed midface (midface retrusion) are often seen [Hayashibara et al 2000].

Progressive thickening of craniofacial bones continues throughout life, often resulting in narrowing of the cranial foramina, including the foramen magnum. If untreated, compression of cranial nerves can lead to disabling conditions such as facial palsy, blindness, or deafness (conductive and/or sensorineural hearing loss) as cranial hyperostosis and sclerosis progress [Beighton et al 1979, Richards et al 1996]. Nasal obstruction and mandibular hyperostosis affect speech modulation.

Associated Chiari I malformation can lead to severe headaches [Tanaka et al 2013].

Development of dentition may be delayed and teeth may fail to erupt as a result of hyperostosis and sclerosis of alveolar bone [Chen et al 2014].

Malocclusion and anterior cross-bite can be caused by jaw overgrowth [Hayashibara et al 2000].

Life expectancy. Individuals with typical uncomplicated AD-CMD have normal life expectancy. Expressivity in simplex cases (i.e., single occurrence in a family) of CMD is highly variable.

Genotype-Phenotype Correlations

No genotype-phenotype correlation has been reported.

The phenotypic severity (expressivity) in AD-CMD is variable even among affected members of the same family.

Penetrance

Penetrance is 100%. Males and females are equally affected.

Nomenclature

AD-CMD was previously referred to as "craniometaphyseal dysplasia-Jackson type."

Prevalence

CMD is very rare. No epidemiology has been established.

Genetically Related (Allelic) Disorders

Table 2. *ANKH* Allelic Disorders

Disorder	MOI	Comment
Chondrocalcinosis 2 (OMIM 118600)	AD	1 family described w/cosegregating AD-CMD & chondrocalcinosis [1]
Intellectual disability, deafness, & ankylosis syndrome	AR	In 1 family, hearing loss, intellectual disability, spinal ankylosis, & periarticular calcification of small joints described in individuals w/ biallelic pathogenic variants (mild arthropathy described in individuals w/ heterozygous pathogenic variants) [2]

AD = autosomal dominant; AD-CMD = autosomal dominant craniometaphyseal dysplasia; AR = autosomal recessive; MOI = mode of inheritance

1. Baynam et al [2009]

2. Morava et al [2011]

Differential Diagnosis

Table 3. Genes of Interest in the Differential Diagnosis of Autosomal Dominant Craniometaphyseal Dysplasia

Gene	Disorder	MOI	Clinical Characteristics	Distinguishing Features
AMER1	Osteopathia striata with cranial sclerosis	XL	Longitudinal striations of sclerotic long bones in combination w/osteosclerosis of cranial & facial bones	Short stature, delayed closure of anterior fontanelle, micrognathia, linear striations in long bones of females
FLNA	Frontometaphyseal dysplasia type 1 (See Otopalatodigital Spectrum Disorders.)	XL	Skeletal findings are frontal bone hyperostosis & metaphyseal dysplasia (similar to those seen in Pyle disease).	Urogenital defects, contractures in hands, elbows, knees, & ankles
GJA1	Autosomal recessive craniometaphyseal dysplasia (AR-CMD) (OMIM 218400)	AR	Hyperostosis of cranial base & cranial vault w/ metaphyseal flaring similar to AD-CMD	Skeletal phenotype may be less severe than in typical AD-CMD.
LRP5	Autosomal dominant osteopetrosis type 1 (OMIM 607634)	AD	Cranial sclerosis & high bone mass w/o ↑ fragility	Diffuse osteosclerosis, no metaphyseal flaring
SFRP4	Pyle disease (OMIM 265900)	AR	Metaphyseal dysplasia	Little or no involvement of cranial bones in Pyle disease
SOST	Craniodiaphyseal dysplasia (CDD) (OMIM 218300)	AD	• Progressive overgrowth of craniofacial bones w/deafness, facial palsy, & visual disturbance due to nerve entrapment • Choanal stenosis is a clinically significant complication. • Radiologically, cranial & facial bones are hyperostotic while diaphyses of limb bones are expanded, w/thin cortices.	Cranial & facial thickening are generally more severe in CDD than in CMD.
	Sclerosteosis (See *SOST* Sclerosing Bone Dysplasias.)	AR	• Progressive skeletal overgrowth (most pronounced in skull & mandible) & variable syndactyly • Facial distortion due to bossing of forehead & mandibular overgrowth becomes apparent in early childhood w/ progression into adulthood. • Hyperostosis of skull → narrowing of foramina & entrapment of 7th cranial nerve (→ facial palsy) w/other, less common nerve entrapment syndromes. • Hyperostosis of calvarium ↓ intracranial volume, ↑ risk for potentially lethal elevation of intracranial pressure. • Survival into old age is unusual but not unprecedented.	Sclerosis in spine & pelvis, 2-3 finger syndactyly, nail dysplasia, no metaphyseal flaring, gigantism
	Van Buchem disease (See *SOST* Sclerosing Bone Dysplasias.)	AR	• Progressive skeletal overgrowth • Van Buchem disease is generally milder than sclerosteosis; no syndactyly. • Life span appears normal.	Osteosclerosis incl clavicles & ribs; hyperphosphatasemia.
TGFB1	Progressive diaphyseal dysplasia	AD	Hyperostosis of skull results in narrowing of foramina, causing facial palsy & deafness.	Diaphyseal hyperostosis of long bones is pronounced.

AD = autosomal dominant; AD-CMD = autosomal dominant craniometaphyseal dysplasia; AR = autosomal recessive; CMD = craniometaphyseal dysplasia; MOI = mode of inheritance; XL = X-linked

Braun-Tinschert type of metaphyseal dysplasia (OMIM 605946) is inherited in an autosomal dominant manner. The gene(s) in which mutation is causative are unknown [Braun et al 2001].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with autosomal dominant craniometaphyseal dysplasia (AD-CMD), the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Autosomal Dominant Craniometaphyseal Dysplasia

System/Concern	Evaluation	Comment
Respiratory & feeding problems in infancy	Referral for craniofacial team eval incl otolaryngologic eval	Incl eval for choanal stenosis
Skeletal hyperostosis	• X-rays of skull, hands, knees • CT to evaluate involvement of foramina & foramen magnum	
Cranial nerve compression	Neurologic exam	
	Otolaryngologic eval	To evaluate auditory system
	Audiologic assessment	To evaluate for hearing loss
	Ophthalmologic exam	To evaluate for vision loss
Endocrine / Bone metabolism	• Alkaline phosphatase • P1NP • CTX	To evaluate bone turnover
Speech	Eval by speech therapist	In early childhood; progressive hearing loss, facial palsy, & hyperostosis can → speech issues.
Delayed eruption & malocclusion	Eval by dentist	From the time of primary tooth eruption to identify tooth impaction or delay in tooth eruption
Genetic counseling	By genetics professionals [1]	To inform affected persons & families re nature, MOI, & implications of AD-CMD to facilitate medical & personal decision making

AD-CMD = autosomal dominant craniometaphyseal dysplasia; CTX = carboxy-terminal collagen crosslinks; MOI = mode of inheritance; P1NP = procollagen type 1 N-terminal propeptide
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 5. Treatment of Manifestations in Individuals with Autosomal Dominant Craniometaphyseal Dysplasia

Manifestation/Concern	Treatment	Considerations/Other
Feeding & respiratory issues in newborns & infants	Per craniofacial team	
Cranial nerve compression	Surgical intervention	To relieve severe symptoms caused by cranial nerve compression
Narrowed foramen magnum	Surgical intervention	To relieve headaches & risks assoc w/Chiari malformation

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Hyperostosis of facial bones	Severe bony overgrowth of facial bones & nasal, forehead, & cranial regions can be contoured.	• Surgical procedures can be technically difficult & bone regrowth is common. • As severe complications have occurred, surgery is considered for conservative purposes to relieve severe symptoms caused by cranial nerve compression.
Hearing loss	Hearing aids	Cochlear implant may be possible.
Vison loss	• Surgery for optic nerve impaction • Vision aids	In anticipation of progressive vision loss, children may learn Braille.
Speech issues	Consider speech therapy.	
Malocclusion	Surgical intervention for severe malocclusion	Delayed tooth eruption should be considered when planning orthodontic treatment [Chen et al 2014].

Surveillance

Table 6. Recommended Surveillance for Individuals with Autosomal Dominant Craniometaphyseal Dysplasia

System/Concern	Evaluation	Frequency
Feeding & respiratory issues in newborns & infants	Craniofacial team	Annually, or more frequently if needed
Narrowing cranial foramina, incl foramen magnum	Neurologic eval	
Hearing loss	Hearing assessment	
Vision loss	Ophthalmologic exam	

Evaluation of Relatives at Risk

It is appropriate to evaluate relatives at risk in order to identify as early as possible those who would benefit from initiation of treatment and preventive measures. Early diagnosis of at-risk relatives may be beneficial for management of complications from progressive hyperostosis.

Evaluations can include:

- Molecular genetic testing if the pathogenic variant in the family is known;
- Clinical evaluation and cranial and long bone radiographs if the pathogenic variant in the family is not known.

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

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Calcitonin has been thought to be effective because of its inhibitory effect on bone turnover. However, previous case reports found calcitonin therapy to be ineffective in treating hyperplasia of craniofacial bones in persons with CMD [Fanconi et al 1988, Haverkamp et al 1996].

Calcitriol with a low-calcium diet to stimulate bone resorption by promoting osteoclast formation had been reported to improve facial paralysis but has no effect on metaphyseal deformity [Key et al 1988, Wu et al 2016].

Acetazolamide has been suggested for treatment of disorders with increased bone mineral density. González-Rodríguez et al [2016] reported acetazolamide use in an individual with a phenotype similar to CMD, but diagnosis of AD-CMD was not confirmed.

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

By definition, autosomal dominant craniometaphyseal dysplasia (AD-CMD) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with AD-CMD have an affected parent.
- Some individuals diagnosed with AD-CMD have the disorder as the result of a *de novo* pathogenic variant. The proportion of individuals with AD-CMD caused by a *de novo* pathogenic variant is thought to be very low; however statistical data are not available.
- If the proband appears to be the only affected family member (i.e., a simplex case) and has a known *ANKH* pathogenic variant, molecular genetic testing is recommended for the parents of a proband.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent.* Though theoretically possible, no instances of a proband inheriting a pathogenic variant from a parent with germline mosaicism have been reported.

  * Misattributed parentage can also be explored as an alternative explanation for an apparent *de novo* pathogenic variant.
- The family history of some individuals diagnosed with AD-CMD may appear to be negative because of failure to recognize the disorder in affected family members. Therefore, an apparently negative family history cannot be confirmed without appropriate clinical evaluation 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 clinical/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%. Because penetrance of AD-CMD is 100%, sibs who inherit a pathogenic variant will develop the phenotype although the severity of the phenotype may vary.

- If the proband has a known *ANKH* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the genetic status of the parents is unknown but they are clinically unaffected, the risk to the sibs of a proband appears to be low but still increased over that of the general population because of the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with AD-CMD has a 50% chance of inheriting the causative pathogenic variant.

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

Related Genetic Counseling Issues

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

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.

Prenatal Testing and Preimplantation Genetic Testing

Once the AD-CMD-causing pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

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.

- **American Society for Deaf Children**
  Phone: 800-942-2732 (ASDC)
  Email: info@deafchildren.org
  deafchildren.org
- **Children's Craniofacial Association**
  Phone: 800-535-3643
  Email: contactCCA@ccakids.com
  www.ccakids.org
- **Face Equality International**
  United Kingdom
  faceequalityinternational.org

- **National Association of the Deaf**
  Phone: 301-587-1788 (Purple/ZVRS); 301-328-1443 (Sorenson); 301-338-6380 (Convo)
  Fax: 301-587-1791
  Email: nad.info@nad.org
  nad.org
- **UCLA International Skeletal Dysplasia Registry (ISDR)**
  Phone: 310-825-8998
  International Skeletal Dysplasia Registry

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Craniometaphyseal Dysplasia, Autosomal Dominant: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ANKH	5p15.2	Mineralization regulator ANKH	ANKH @ LOVD	ANKH	ANKH

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 Craniometaphyseal Dysplasia, Autosomal Dominant (View All in OMIM)

123000	CRANIOMETAPHYSEAL DYSPLASIA, AUTOSOMAL DOMINANT; CMDD
605145	ANKH INORGANIC PYROPHOSPHATE TRANSPORT REGULATOR; ANKH

Molecular Pathogenesis

ANKH encodes the progressive ankylosis protein homolog, a multispan transmembrane protein located at the outer cell membrane that transports intracellular pyrophosphate into the extracellular matrix. Pyrophosphate is a regulator of matrix (bone) mineralization. The protein sequence of the progressive ankylosis protein homolog is highly conserved among vertebrate animals.

Progressive ankylosis protein homolog expressing a craniometaphyseal dysplasia-associated variant most likely has a reduced ability to transport intracellular pyrophosphate from osteoblasts to the bone matrix [Ho et al 2000].

Mechanism of disease causation. Most common pathogenic variants result in one-amino acid deletions, while others are missense or small in-frame deletions and insertions [Nürnberg et al 2001, Reichenberger et al 2001, Kornak et al 2010, Zajac et al 2010, Dutra et al 2012]. Most pathogenic variants occur in the nucleotide region encoding presumed intracellular domains of the transmembrane loop structure. Based on findings in knockout and knock-in mice studies, *ANKH* pathogenic variants are thought to result in a dominant negative gain of function as well as loss of function of pyrophosphate transport. The shared phenotype between these murine models is explained by the rapid degradation of pathogenic ANK protein [Kanaujiya et al 2018]. To date, no other information on mechanism is available.

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Chapter Notes

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