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Caffey Disease

Synonym: Infantile Cortical Hyperostosis

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Summary

Clinical characteristics

Caffey disease is characterized by massive subperiosteal new bone formation (usually involving the diaphyses of the long bones as well as the ribs, mandible, scapulae, and clavicles) typically associated with fever, soft-tissue swelling, and pain, with onset between birth and five months and spontaneous resolution by age two years. Recurrence of bone hyperostosis, fever, soft-tissue swelling, and pain can occur later in life. Adults with a history of Caffey disease in childhood may have joint laxity, skin hyperextensibility, hernias, short stature, and an increased risk for bone fractures and/or deformities.

Diagnosis/testing

The diagnosis of Caffey disease is established in a proband with typical clinical and radiographic findings; identification of a heterozygous *COL1A1* pathogenic variant associated with Caffey disease on molecular genetic testing can confirm the diagnosis.

Management

Treatment of manifestations: Anti-inflammatory agents, antipyretics, and analgesics can be used in the short term to decrease swelling and fever and to relieve pain; standard treatments for joint hypermobility, skin hyperextensibility, and hernias.

Surveillance: Annual evaluation of stature, fracture history, joint extensibility, and hernias throughout childhood. Consider assessment of bone mineral density in adults with a history of recurrent fractures.

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Genetic counseling

Caffey disease is inherited in an autosomal dominant manner. Some individuals diagnosed with Caffey disease have a parent who had Caffey disease in childhood; others have the disorder as the result of a *de novo* pathogenic variant. The proportion of individuals with Caffey disease caused by a *de novo* pathogenic variant is unknown. Each child of an individual who had Caffey disease in childhood has a 50% chance of inheriting the pathogenic variant. Once a molecular diagnosis has been established in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for Caffey disease have been published.

Suggestive Findings

Caffey disease **should be suspected** in probands with the following clinical, radiographic, laboratory, and family history findings. Clinical and radiographic findings typically appear between birth and age five months and resolve spontaneously by age two years, although recurrence in adolescence is possible.

Clinical findings

- Irritability, fever, and/or pallor
- Soft-tissue swelling and pain adjacent to involved bones (See Figure 2.)

Radiographic findings

- Subperiosteal cortical hyperostosis of the diaphyses of the long bones (with sparing of the epiphyses)
- Subperiosteal cortical hyperostosis of the ribs, scapulae, clavicles, and mandible (See Figures 1 and 2.)

Laboratory findings

- Serum biochemical markers of inflammation (white blood cell count, erythrocyte sedimentation rate, C-reactive protein) have been elevated a few affected individuals [Gensure et al 2005].
- Alkaline phosphatase may be elevated.

Family history is consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of Caffey disease **is established** in a proband with typical clinical and radiographic findings. Identification of a heterozygous *COL1A1* pathogenic variant associated with Caffey disease (p.Arg1014Cys, p.Arg918Cys) on molecular genetic testing can confirm the diagnosis in those with atypical clinical and radiographic features (see Table 1).

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Option 1

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

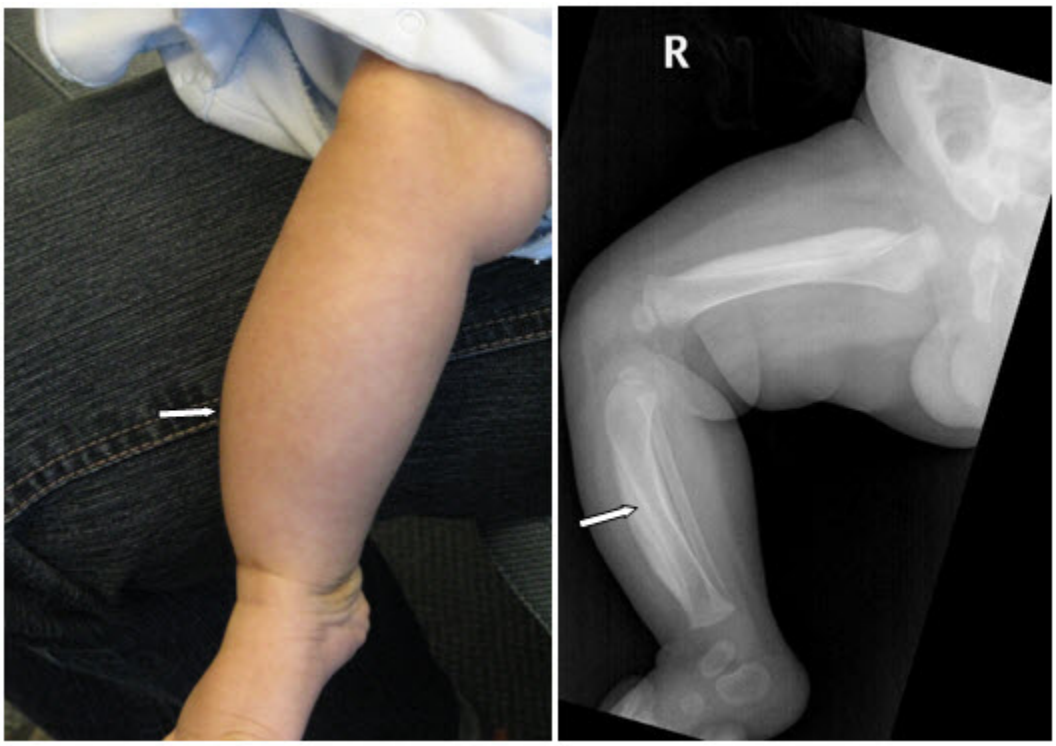

Figure 2. Clinical photograph and radiograph of male age two months with *COL1A1* pathogenic variant p.Arg1014Cys who presented with irritability and swelling over the right tibia

Arrows denote the area of swelling on clinical examination and the subperiosteal reaction of the right tibia observed on lower extremity radiograph. Skeletal survey at presentation also revealed bilateral involvement of the clavicles, radii, and ulnae. Clinical symptoms resolved within a month of onset and periosteal changes remodelled over a period of one year.

- **Single-gene testing.** Sequence analysis of *COL1A1* to detect the only reported pathogenic variants associated with Caffey disease to date, p.Arg1014Cys or p.Arg918Cys

  Note: To date, no large multiexon *COL1A1* deletions or duplications have been identified in individuals with Caffey disease.

- **A multigene panel** that includes *COL1A1* and other genes of interest (see Differential Diagnosis) may be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the diagnosis of Caffey disease is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. To date, all *COL1A1*

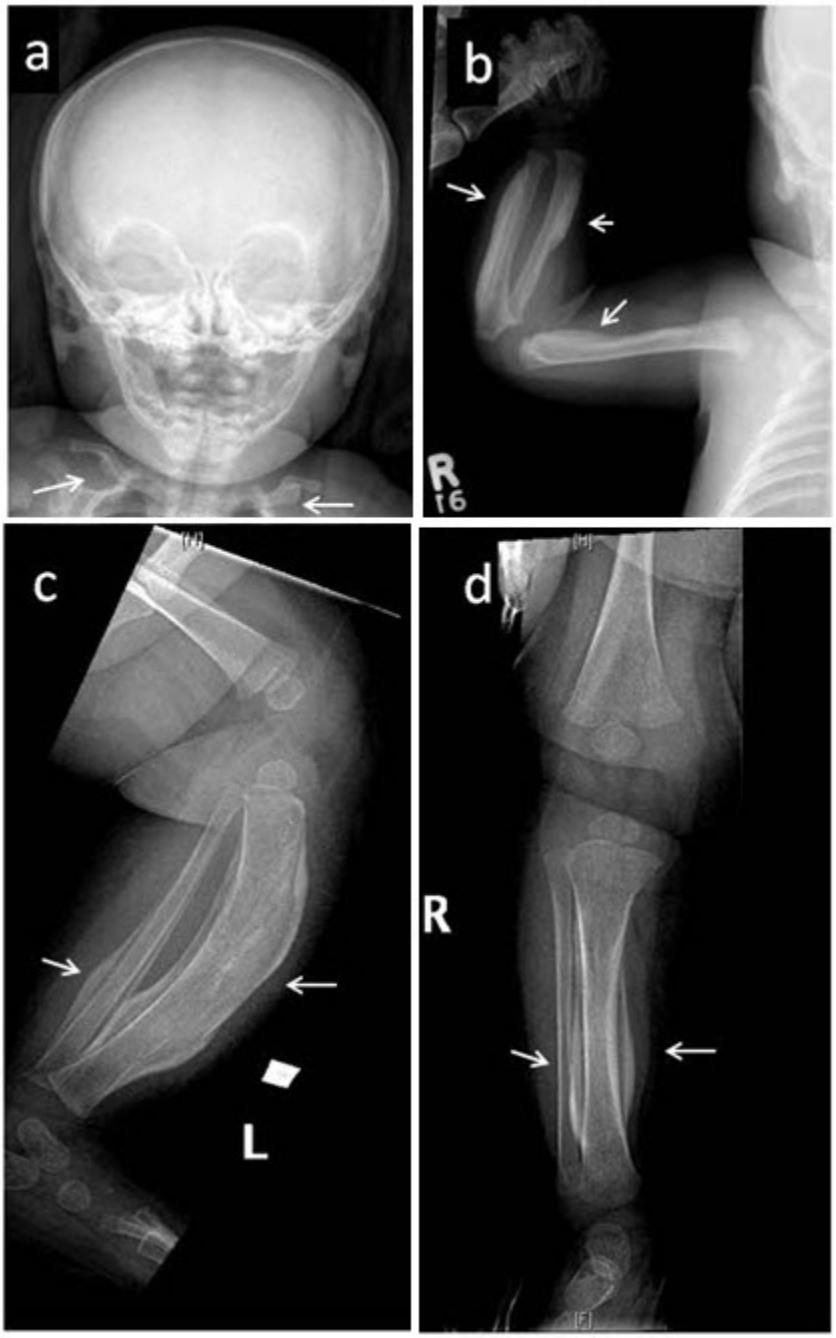

Figure 1. Skeletal survey in a female age five weeks with *COL1A1* pathogenic variant p.Arg1014Cys who presented with painful swelling over the right tibia

Note widespread involvement with (a) symmetric bilateral periosteal reaction involving the mandible and clavicles; and asymmetric involvement of (b) the humerus, proximal shaft of the radius, and distal shaft of the ulna; and of (c, d) the tibia and fibula.

Arrows point to significant subperiosteal thickening and bowing. Asymmetric reactions of the iliac bones, femora, tibiae, and left fibula were also noted (not shown). Symptoms resolved within a month of onset.

pathogenic variants associated with Caffey disease are within the coding region and are likely to be identified on exome sequencing.

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 Caffey Disease

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
COL1A1	Sequence analysis [3]	~99% [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [6]
Unknown [7]	NA	

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on 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 missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. COL1A1 variants p.Arg1014Cys and p.Arg918Cys are the only variants reported to date in individuals with Caffey disease [Gensure et al 2005, Suphapeetiporn et al 2007, Cho et al 2008, Kamoun-Goldrat et al 2008, Ranganath et al 2011, Dhooge et al 2021].
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. To date, no large intragenic deletions/duplications have been reported in individuals with Caffey disease.
7. One individual with clinical and radiographic features of Caffey disease did not have an identified *COL1A1* pathogenic variant [A Guerin, unpublished observation]. Also, one individual with clinical and radiographic features of Caffey disease had a homozygous *AHSG* pathogenic variant in the context of consanguinity [Merdler-Rabinowicz et al 2019]. To date, there are no additional reports of *AHSG*-related Caffey disease.

Clinical Characteristics

Clinical Description

Caffey disease is characterized by massive subperiosteal new bone formation (hyperostosis) usually involving the diaphyses of the long bones, as well as the ribs, mandible, scapulae, and clavicles [Caffey & Silverman 1945, Caffey 1957].

Onset. The clinical findings most often appear at age two months (typically between birth and age five months). Rarely, hyperostosis can be detected by ultrasound examination late in the third trimester of pregnancy [Schweiger et al 2003]. One report describes prenatal periosteal inflammation in a fetus with heterozygous *COL1A1* pathogenic variant p.Arg1014Cys [Kamoun-Goldrat et al 2008].

Skeletal manifestations. Typically the skeletal manifestations of Caffey disease first appear with soft-tissue swelling and pain over the affected bones between birth and age five months. Massive subperiosteal new bone formation usually involving the diaphyses of the long bones can be seen on imaging. Hyperostosis of the long bones is typically asymmetric, although symmetric hyperostosis has been reported [Tilva et al 2023].

Hyperostosis can also involve the ribs, mandible, scapulae, and clavicles. The hyperostosis resolves before age two years [Kamoun-Goldrat & le Merrer 2008, Cerruti-Mainardi et al 2011, Ranganath et al 2011].

Constitutional manifestations. Skeletal manifestations are accompanied by fever and elevated serum biochemical markers of inflammation (e.g., white blood cell count, erythrocyte sedimentation rate, C-reactive protein) [Gensure et al 2005].

Recurrence of hyperostosis, joint swelling, pain, and fever have been reported multiple times, until late adolescence in individuals with the typical infantile presentation [Borochowitz et al 1991; Navarre et al 2013; ALBagshi & ALZoayed 2015; A Guerin, unpublished data]. Etiology and precipitating factors for recurrence remain unclear [Navarre et al 2013].

Additional findings reported. In one reported family, an individual with *COL1A1* pathogenic variant p.Arg1014Cys had a history of Caffey disease as a child and developed joint laxity, skin hyperextensibility, hernias, and multiple fractures in adulthood [Gensure et al 2005]. Additional individuals in the family with the *COL1A1* pathogenic variant p.Arg1014Cys had varying degrees of joint laxity and skin hyperextensibility. Skin biopsy of affected individuals showed collagen fibrils that were larger, more variable in shape, and less densely packed than age- and sex-matched controls. Granulofilamentous material was also visible in the matrix along the collagen fibrils. Cultured fibroblasts showed a mix of normal type I collagen and abnormal disulfide crosslinking, either within or between abnormal collagen fibrils. These findings have not been identified in other individuals/families with the same *COL1A1* pathogenic variant [Cho et al 2008, Cerruti-Mainardi et al 2011, Ranganath et al 2011].

Other

- Tumoral calcinosis (1 individual); thought to be due to constant remodeling after repeated inflammatory events [Issa El Khoury et al 2012]
- Anemia (1 individual) [Restrepo et al 2004]
- Thrombocytosis (1 individual) [Krishnamurthy & Srinivasan 2012].

Prognosis. In many individuals, the manifestations of Caffey disease resolve spontaneously by age two years and do not predispose to long-term bone abnormalities. Affected individuals from one family had short stature in adulthood and residual bone deformities [Suphapeetiporn et al 2007]. Fractures have been reported in some individuals [Gensure et al 2005, Suphapeetiporn et al 2007].

Histopathology. Bone and muscle biopsy of affected sites in a few individuals have demonstrated an inflammatory reaction [Katz et al 1981].

Genotype-Phenotype Correlations

There are no known genotype-phenotype correlations.

Penetrance

Reduced penetrance based on family history or molecular genetic testing has been reported [Cho et al 2008, Kutty et al 2010, Prior et al 2012, Kitaoka et al 2014, Dhooge et al 2021].

Nomenclature

In the 2023 revision of the Nosology of Genetic Skeletal Disorders [Unger et al 2023], Caffey disease known to be caused by a heterozygous *COL1A1* pathogenic variant is referred to as *COL1A1*-related Caffey disease and included in the osteosclerotic disorders group.

"Prenatal lethal forms of hyperostosis," also referred to as "prenatal Caffey disease" or "Caffey dysplasia" [Nemec et al 2012], are distinct from Caffey disease (also known as infantile cortical hyperostosis) (see Differential Diagnosis).

Prevalence

The number of clinical reports of Caffey disease described to date is no more than a few hundred; however, given the spontaneous resolution of this condition in early childhood, it is likely underdiagnosed.

Genetically Related (Allelic) Disorders

Other phenotypes known to be associated with germline pathogenic variants in *COL1A1* are summarized in Table 2.

Table 2. *COL1A1* Allelic Disorders

Disorder	Comment
Osteogenesis imperfecta	The majority of pathogenic variants in *COL1A1* are assoc w/osteogenesis imperfecta.
Arthrochalasia Ehlers-Danlos syndrome (OMIM 130060)	Phenotype is characterized by extreme joint laxity & congenital hip dislocation but minimal skin involvement.
Classic Ehlers-Danlos syndrome	Three percent of classic EDS is attributed to pathogenic variants in *COL1A1*.
EDS/OI overlap phenotypes (OMIM 619115)	Three arginine-to-cysteine changes (Arg134Cys, Arg915Cys, & Arg396Cys) in *COL1A1* have been reported in an EDS phenotype w/a propensity to arterial rupture in early adulthood [Malfait et al 2007].

EDS = Ehlers-Danlos syndrome; OI = osteogenesis imperfecta

Differential Diagnosis

Other genetic and acquired conditions may manifest as joint swelling and hyperostosis and thus need to be distinguished from Caffey disease.

Table 3. Genes of Interest in the Differential Diagnosis of Caffey Disease

Gene(s)	Disorder	MOI	Features of Disorder	
			Overlapping w/ Caffey Disease	Distinguishing from Caffey Disease
ANTXR2	Hyaline fibromatosis syndrome	AR	Presents w/irritability, poor feeding, fever, & soft-tissue swelling	Progressive joint contractures, & often severe motor disability, thickened skin, & hyperpigmented macules/patches over bony prominences of joints
FGF23 *GALNT3* *KL*	Hyperphosphatemic familial tumoral calcinosis (HFTC)	AR	Cortical hyperostosis	Hyperphosphatemia
GLB1 *GNPTAB*	Mucolipidosis II (*GNPTAB*-Related Disorders) & type I (infantile) GM1 gangliosidosis (*GLB1*-Related Disorders)	AR	Mucolipidosis II, type I GM1 gangliosidosis, & other storage diseases presenting in early infancy may be characterized by periosteal cloaking.	The involvement of the metaphysis & generalized findings of storage disorders differentiate these disorders from Caffey disease.
TGFB1	Camurati-Engelmann disease	AD	Bone pain, hyperostosis of diaphyses of long bones	Proximal muscle weakness, limb pain, a wide-based, waddling gait, & joint contractures; facial features such as macrocephaly, frontal bossing, enlargement of mandible, proptosis, & cranial nerve impingement resulting in facial palsy

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance

Lethal prenatal Caffey disease (prenatal Caffey disease / Caffey dysplasia). This condition typically presents before 35 weeks' gestation and is characterized by cortical hyperostosis as well as bowing or angulation of the long bones and the presence of polyhydramnios and fetal lung disease [Langer & Kaufmann 1986, Lécolier et al 1992, Drinkwater et al 1997, Dahlstrom et al 2001, Savarirayan et al 2002, Hochwald & Osiovich 2011, Nemec et al 2012]. Autosomal recessive inheritance involving genes other than *COL1A1* has been proposed [de Jong & Muller 1995, Drinkwater et al 1997, Schweiger et al 2003, Gensure et al 2005].

Acquired conditions

- **Hypervitaminosis A** can result in bone pain and swelling similar to that seen in Caffey disease. In addition, hyperostosis has been documented in adults with hypervitaminosis A [Wendling et al 2009].
- **Prostaglandin E_1 (PGE1) exposure.** Reversible hyperostosis and long bone swelling has been noted in neonates on PGE1 therapy for several weeks for maintenance of ductus arteriosus patency in the context of congenital heart disease [de Almeida et al 2007].
- **Bone malignancies** can present similarly to Caffey disease but can be distinguished on bone biopsy.
- **Osteomyelitis** may be mistakenly diagnosed as joint swelling. Febrile episodes can be common to both conditions; however, the finding of hyperostosis on radiographs helps distinguish between these two entities.

Non-accidental childhood injury (child physical abuse / non-accidental trauma). The prevalence of physical abuse is much greater than the prevalence of Caffey disease. Often the clinical history and presence of fractures, which are not usually a presenting feature of Caffey disease, aid in distinguishing the two [Lee et al 2021].

Management

No clinical practice guidelines for Caffey disease have been published. In the absence of published guidelines, the following recommendations are based on the authors' personal experience managing individuals with this disorder.

Evaluations Following Initial Diagnosis

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

Table 4. Caffey Disease: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Skeletal manifestations	• Assess for pain & extremity swelling. • Radiographs of long bones, ribs, scapulae, clavicles, & mandible to assess extent of disease & stage of hyperostosis	
Joint & connective tissue manifestations	Eval for joint range of motion, skin hyperextensibility, & hernias	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of Caffey disease to facilitate medical & personal decision making

MOI = mode of inheritance

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

Treatment of Manifestations

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 5).

Table 5. Caffey Disease: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Skeletal manifestations	Anti-inflammatory agents, antipyretics, & analgesics can be used in the short term to ↓ swelling & fever & relieve pain.	No recommendations for the prevention of recurrence of hyperostosis currently exist.
Joint & connective tissue manifestations	Standard treatments for joint hypermobility, skin hyperextensibility, & hernias	

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 6 are recommended.

Table 6. Caffey Disease: Recommended Surveillance

System/Concern	Evaluation	Frequency
Skeletal manifestations	Assess stature.	Annually throughout childhood
	Assess fracture history.	Annually
	Consider assessment of bone mineral density w/DXA scan.	As indicated in adults w/history of recurrent fractures
Joint & connective tissue manifestations	Assess joint extensibility & hernias.	Annually

DXA = dual-energy x-ray absorptiometry

Evaluation of Relatives at Risk

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

Therapies Under Investigation

Search ClinicalTrials.gov 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, 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

Caffey disease is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Some individuals diagnosed with Caffey disease have a parent who had Caffey disease in childhood.

- An individual diagnosed with Caffey disease may have the disorder as the result of a *de novo* pathogenic variant. The proportion of individuals with Caffey disease caused by a *de novo* pathogenic variant is unknown.
- If the proband appears to be the only family member with Caffey disease (i.e., a simplex case), recommendations for the evaluation of the parents of the proband include molecular genetic testing (if a molecular diagnosis has been established in the proband) and a detailed medical history focusing on features of hyperostosis in infancy and current bone health.
- If a molecular diagnosis has been established in the proband, the pathogenic variant identified in the proband is not identified in either parent, and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ (gonadal) cells only.
- The family history of some individuals diagnosed with Caffey disease may appear to be negative because of failure to recognize or remember the occurrence of the disorder in family members or because of reduced penetrance in a parent. Therefore, an apparently negative family history cannot be confirmed unless a molecular diagnosis has been established in the proband and molecular genetic testing has established that neither parent is heterozygous for the pathogenic variant identified in the proband.

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

- If a parent of the proband had Caffey disease in childhood and/or is known to have a Caffey disease-related pathogenic variant, the risk to the sibs is 50%.
- If the proband has a known Caffey disease-related 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 possibility of parental germline mosaicism [Rahbari et al 2016].
- If the genetic status of the parents has not been established but neither parent is known to have had Caffey disease in childhood, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for Caffey disease because of the possibility of reduced penetrance in a parent or parental germline mosaicism.

Offspring of a proband. Each child of an individual who had Caffey disease in childhood has a 50% chance of inheriting a Caffey disease-related pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent had Caffey disease in childhood, the parent's family members may be at risk.

Related Genetic Counseling Issues

Family planning

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

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once a molecular diagnosis has been established in an affected family member, prenatal 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.

- **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. Caffey Disease: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
COL1A1	17q21.33	Collagen alpha-1(I) chain	COL1A1 @ LOVD	COL1A1	COL1A1

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 Caffey Disease (View All in OMIM)

114000	CAFFEY DISEASE; CAFYD
120150	COLLAGEN, TYPE I, ALPHA-1; COL1A1

Molecular Pathogenesis

COL1A1 encodes collagen type I, a heterotrimer consisting of two alpha-1 chains and one alpha-2 chain (encoded by *COL1A2*), which is a fibril-forming collagen found in most connective tissues and is abundant in bone, cornea, dermis, and tendon.

Both *COL1A1* pathogenic variants associated with Caffey disease impact an Arg-to-Cys substitution in the Xaa position of the Gly-Xaa-Yaa triplet repeat of the pro-α1(I) chain and reside in regions hypothesized to interact with interleukin-2 and α1β1 integrin [Makar et al 1975, Sweeney et al 2008, Dhooge et al 2021]. Transmission electron microscopy analysis of affected probands' skin biopsies suggests that the introduction of an Arg-Cys substitution interferes with collagen fibril organization [Dhooge et al 2021].

Mechanism of disease causation. The mechanism of disease is unclear. The two *COL1A1* pathogenic variants associated with Caffey disease could impact cell signaling. The location of the variants near domains

hypothesized to interact with interleukin-2 and α1β1 integrin may play a role in temporary inflammation. Prostaglandin E (PGE) and transforming growth factor beta (TGF-β) may also play a role in pathogenesis, as both can promote cortical hyperostosis [Dhooge et al 2021].

Table 7. *COL1A1* Pathogenic Variants Referenced in This GeneReview

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change (Alias [1])	Comment [Reference]
NM_000088.3 NP_000079.2	c.2752C>T	p.Arg918Cys	Pathogenic variant assoc w/Caffey disease in ~15%-20% of reported persons [Dhooge et al 2021]
	c.3040C>T	p.Arg1014Cys (Arg836Cys)	Most common pathogenic variant assoc w/Caffey disease [Gensure et al 2005, Cho et al 2008, Cerruti-Mainardi et al 2011, Ranganath et al 2011]

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.

Chapter Notes

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Author History

Revision History

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