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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, joint swelling, and pain in children, with onset between birth and five months and spontaneous resolution by age two years. Episodes of recurrence of the manifestations of Caffey disease have been reported multiple times in individuals with the classic infantile presentation. Limited follow-up information suggests that adults who had Caffey disease in childhood may manifest 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 and a c.3040C>T heterozygous pathogenic variant in *COL1A1* identified by molecular genetic testing.

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.

Surveillance: Given that Caffey disease is a collagenopathy, evaluation of stature, joint extensibility, hernias, fracture history, and dental health is recommended. Assessment of bone mineral density may be prudent in adults with a history of Caffey disease in childhood.

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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 cases 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. Prenatal and preimplantation genetic testing are possible if the pathogenic variant has been identified in the proband.

Diagnosis

Suggestive Findings

Caffey disease **should be suspected** in probands with the following:

- Clinical findings of irritability, fever, and/or pallor accompanied by soft-tissue swelling and pain adjacent to involved bones
- Radiologic findings of subperiosteal cortical hyperostosis of the diaphyses of the long bones (with sparing of the epiphyses), as well as the ribs, scapulae, clavicles, and mandible
- Findings typically appearing between birth and age five months and resolving spontaneously by age two years, although recurrence in adolescence is possible

See Figure 1 and Figure 2.

Establishing the Diagnosis

The diagnosis of Caffey disease **is established** in a proband with typical clinical and radiographic findings and a c.3040C>T heterozygous pathogenic variant in *COL1A1* identified by molecular genetic testing (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) 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 Caffey disease has a limited differential diagnosis, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of Caffey disease has not been considered are more likely to be diagnosed using genomic testing (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**:

- **Single-gene testing.** Sequence analysis of *COL1A1* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. All published cases in which molecular testing has been done involve heterozygosity for the single known c.3040C>T pathogenic variant.

  Perform sequence analysis first. If the single known pathogenic variant is not found, gene-targeted deletion/duplication analysis can be performed to detect intragenic deletions or duplications. However, no large multiexon gene deletions or duplications have been identified to date in individuals with Caffey disease

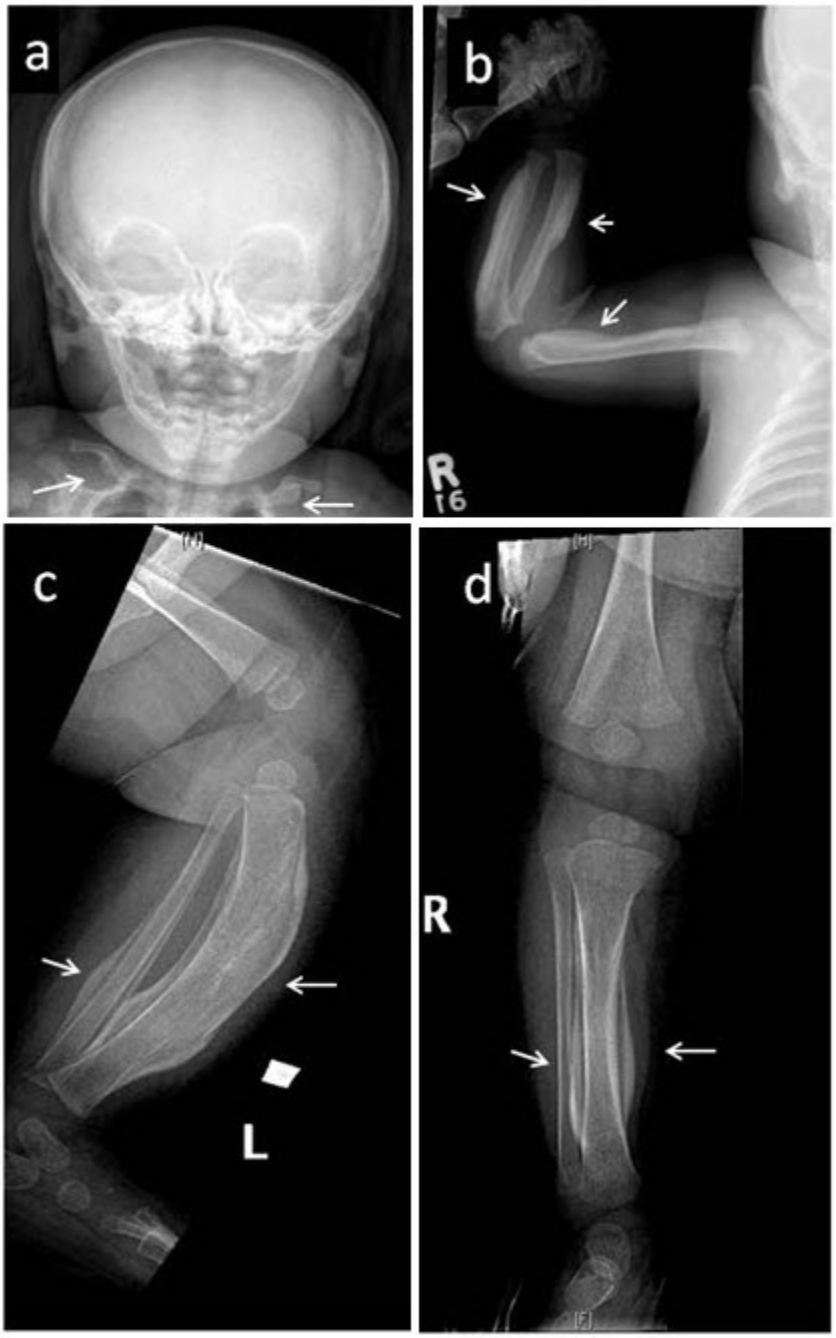

Figure 1. Skeletal survey in a female age five weeks with the defining *COL1A1* p.Arg1014Cys pathogenic variant who presented with painful swelling over the right tibia

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, femurs, tibias, and left fibula were also noted (not shown). Symptoms resolved within a month of onset.

- **A multigene panel** that includes *COL1A1* and other genes of interest (see Differential Diagnosis) is most likely 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

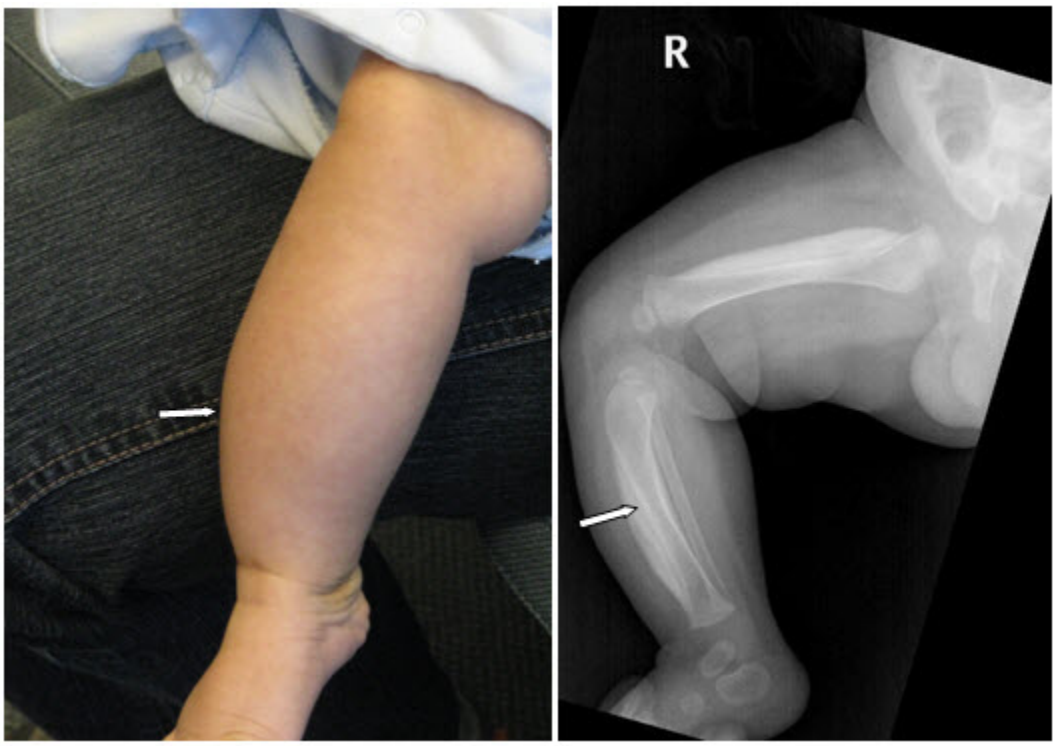

Figure 2. Clinical photograph and x-ray of male age two months with the defining *COL1A1* p.Arg1014Cys pathogenic variant who presented with irritability and swelling over the right tibia

Arrows denote the area of swelling on clinical examination and the subperiosteal reaction of the right tibia observed on x-ray. 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 remodeled over a period of one year.

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** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is the most commonly used genomic testing method; **genome sequencing** is also possible.

If exome sequencing is not diagnostic, **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 Caffey disease.

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 Probands with a Pathogenic Variant [2] Detectable by Method
COL1A1	Sequence analysis [3]	100% [4]
	Gene-targeted deletion/duplication analysis [5]	Unknown [6]
Unknown [7]	NA	

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. All individuals with Caffey disease have had the c.3040C>T pathogenic variant [Gensure et al 2005, Suphapeetiporn et al 2007, Cho et al 2008, Kamoun-Goldrat et al 2008, Ranganath et al 2011].
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. No data on detection rate of gene-targeted deletion/duplication analysis are available.
7. All published cases of Caffey disease in which molecular testing has been done have identified heterozygosity for the single known c.3040C>T pathogenic variant. However, one individual who met clinical criteria did not have this variant, suggesting allelic or genetic heterogeneity [Author, unpublished observation].

Clinical Characteristics

Clinical Description

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 [Caffey & Silverman 1945, Caffey 1957].

Presentation. Typically the skeletal manifestations of Caffey disease first appear with fever, joint swelling, and pain between birth and age five months, and resolve before age two years [Kamoun-Goldrat & le Merrer 2008, Cerruti-Mainardi et al 2011, Ranganath et al 2011].

- The clinical findings most often appear at age two months.
- On rare occasion, the 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 heterozygous for the defining *COL1A1* pathogenic variant [Kamoun-Goldrat et al 2008].

Recurrence. Episodes of recurrence of the manifestations of Caffey disease have been reported multiple times, in individuals with the classic infantile presentation [Navarre et al 2013]. Etiology and precipitating factors for recurrence remain unclear [Navarre et al 2013].

Other findings. In a family described by Gensure et al [2005], an individual with the defining *COL1A1* pathogenic variant had a history of Caffey disease as a child and joint laxity and skin hyperextensibility with a history of hernias and multiple fractures in adulthood. Subsequent clinical examination of other individuals in that family who also had the defining *COL1A1* pathogenic variant revealed varying degrees of joint laxity and 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 mutated collagen fibrils. The findings reported by Gensure et al [2005] have not been found in other families with the same pathogenic variant [Cho et al 2008, Cerruti-Mainardi et al 2011, Ranganath et al 2011]

Long-term outcome. Although anecdotal evidence suggests that the manifestations of Caffey disease resolve spontaneously by age two years and do not predispose to long-term bone abnormalities, the literature on Caffey disease does not directly address long-term outcomes. The study of a single family suggested that individuals who have the defining pathogenic variant may be prone to short stature and residual bone deformities [Suphapeetiporn et al 2007]. In addition, it has been suggested that fractures (possibly related to decreased bone mineral density) may be more common in these individuals [Gensure et al 2005, Suphapeetiporn et al 2007].

Other bone-related complications may potentially occur: in one case report a child with Caffey disease developed tumoral calcinosis (thought to be due to constant remodeling) after repeated inflammatory events [Issa El Khoury et al 2012].

Laboratory findings observed in a few affected individuals:

- Serum biochemical markers of inflammation (white blood cell count, erythrocyte sedimentation rate, C-reactive protein) have been elevated [Gensure et al 2005].
- Anemia and thrombocytosis have been described in single case reports [Restrepo et al 2004, Krishnamurthy & Srinivasan 2012].
- Bone and muscle biopsy of affected sites in a few individuals have demonstrated an inflammatory reaction [Katz et al 1981].

Genotype-Phenotype Correlations

Within the range of *COL1A1* pathogenic variants responsible for different phenotypes, c.3040C>T is the defining variant responsible for the Caffey disease phenotype. See Molecular Pathogenesis.

Penetrance

Incomplete penetrance based on family history or molecular genetic testing has been noted [Cho et al 2008, Kutty et al 2010, Prior et al 2012, Kitaoka et al 2014]. In a family studied by Gensure et al [2005], 19 of 24 individuals with the defining *COL1A1* pathogenic variant had a clinical history of an episode consistent with Caffey disease.

Nomenclature

"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.

The defining *COL1A1* c.3040C>T pathogenic variant does not appear to be more prevalent in one particular population; it has been described in individuals of northern European [Gensure et al 2005, Cerruti-Mainardi et al 2011], Indian [Ranganath et al 2011], Thai [Suphapeetiporn et al 2007], Korean [Cho et al 2008], and Japanese [Hasegawa et al 2004] ancestry.

Genetically Related (Allelic) Disorders

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

Table 2. Allelic Disorders

Gene	Disorder
COL1A1	Osteogenesis imperfecta (See *COL1A1/2*-Related Osteogenesis Imperfecta.)
	Ehlers-Danlos syndrome, arthrochalasia type (OMIM 130060)
	Rarely, an Ehlers-Danlos syndrome phenotype that resembles the classic type (See Classic Ehlers-Danlos Syndrome.)
	The association of 3 arginine-to-cysteine changes (Arg134Cys, Arg915Cys, & Arg396Cys) reported in an Ehlers-Danlos syndrome phenotype w/a propensity to arterial rupture in early adulthood [Malfait et al 2007]

Differential Diagnosis

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

- 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, Hall 2005, 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].
- 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 conditions [Al Kaissi et al 2009, Lo et al 2010].
- Hypervitaminosis A, which 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].
- Hyperphosphatemic familial tumoral calcinosis (HFTC). A rare autosomal recessive disorder caused by pathogenic variants in *FGF23*, *GALNT3*, or *KL*, HFTC is characterized by hyperphosphatemia, normal or elevated 1,25-dihydroxyvitamin D_3 concentrations, and cortical hyperostosis [Olauson et al 2008].
- Storage diseases presenting in early infancy (including I-cell disease [mucolipidosis II] and GM1 gangliosidosis type I), which may be characterized by periosteal cloaking; however, the involvement of the metaphysis and generalized findings of these conditions differentiate them from Caffey disease [Hall 2005].
- Bone malignancies, which may also be suspected initially; biopsies have been performed in the past to rule out this diagnosis [Katz et al 1981].
- Osteomyelitis, which may be mistakenly diagnosed as joint swelling. Febrile episodes can be common to both conditions; however, the finding of hyperostosis on x-ray helps distinguish between these two entities [Behbehani et al 1997].

Management

Evaluations Following Initial Diagnosis

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

- Evaluation for joint range of motion, tissue hyperlaxity, and hernias
- Radiographs of long bones, ribs, scapulae, clavicles, and mandible to assess the extent of disease and stage of hyperostosis
- Consultation with a clinical geneticist and/or genetic counselor

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 [Thometz & DiRaimondo 1996, Parnell & Parisi 2010].

No recommendations for the prevention of recurrence of hyperostosis currently exist.

Surveillance

Currently, no standard surveillance protocols exist. However, given that Caffey disease is a collagenopathy, yearly evaluation of stature, joint extensibility, hernias, fracture history, and dental health is recommended.

Although no systematic reviews of bone mineral density in adults with the defining pathogenic variant have been performed, reports of fractures and short stature in adults with other *COL1A1* pathogenic variants suggest that assessment of bone mineral density may be prudent in adults with a history of Caffey disease in childhood.

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.
- A proband with Caffey disease may have the disorder as the result of a *de novo* pathogenic variant. The proportion of cases caused by a *de novo* pathogenic variant is unknown.
- Recommendations for the evaluation of the parents of a proband with an apparent *de novo* pathogenic variant include molecular testing for *COL1A1* c.3040C>T and a detailed medical history focusing on symptoms of hyperostosis in infancy and current bone health.
- 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 germline mosaicism have been reported.
- 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 molecular genetic testing has been performed on the parents of 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 the *COL1A1* c.3040C>T pathogenic variant, the risk to the sibs is 50%.
- If the *COL1A1* c.3040C>T pathogenic variant 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 parents have not been tested for the *COL1A1* c.3040C>T pathogenic variant but are known not 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 the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual who had Caffey disease in childhood has a 50% chance of inheriting the 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, the parent's family members may be at risk.

Related Genetic Counseling Issues

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

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who 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 the *COL1A1* pathogenic variant has been identified in an affected family member, prenatal testing 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.

Ultrasound evaluation. A diagnosis of the typical infantile form of Caffey disease presenting with hyperostosis was made on the basis of ultrasound examination after 35 weeks' gestation [Schweiger et al 2003].

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 α1 chains and one α2 chain (encoded by *COL1A2*), which is a fibril-forming collagen found in most connective tissues and is abundant in bone, cornea, dermis, and tendon.

Mechanism of disease causation. The mechanism of p.Arg1014Cys (formerly known as p.Arg836Cys) pathogenesis is unknown. Possibilities as to why p.Arg1014Cys causes the Caffey disease phenotype include the following:

- Disruption of protein-protein interaction since p.Arg1014 is located in the carboxy-terminal cyanogen bromide terminus 6 (CB6) of the α1(I) chain, which has been shown to interact with both IL-2 and the amyloid protein precursor (APP) [Somasundaram et al 2000, Di Lullo et al 2002].
- Reduced thermal stability of the collagen triple helix [Gensure et al 2005].

Table 3. Notable *COL1A1* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change (Alias [1])	Comment [Reference]
NM_000088.3 NP_000079.2	c.3040C>T	p.Arg1014Cys (Arg836Cys)	Defining pathogenic variant responsible for Caffey disease phenotype [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

Author Notes

Dr Guerin, Ms Dupuis, and Dr Mendoza are currently conducting a research study for individuals with a clinical or molecular diagnosis of Caffey disease. The goals of the study are to better describe the natural history, pathogenesis, and complications in order to enhance the management and counseling of Caffey disease.

Revision History

- 13 June 2019 (ha) Comprehensive update posted live
- 29 November 2012 (cd) Revision: prenatal testing available
- 2 August 2012 (me) Review posted live
- 17 February 2012 (ag) Original submission

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