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CAFFEY DISEASE: NEW PERSPECTIVES ON OLD QUESTIONS

Harikiran Nistala, Ph.D¹, Outi Mäkitie, M.D^{2,3}, and Harald Jüppner, M.D⁴

¹Department of Oral Medicine, Infection and Immunity, Harvard School of Dental Medicine, Boston MA ²Division of Pediatric Endocrinology and Metabolic Bone Diseases, Helsinki University Central Hospital and University of Helsinki, Helsinki, Finland ³Folkhälsan Institute of Genetics, Helsinki, Finland ⁴Pediatric Nephrology Unit and Endocrine Unit, Massachusetts General Hospital and Harvard Medical School, Boston MA

Abstract

The autosomal dominant form of Caffey disease is a largely self-limiting infantile bone disorder characterized by acute inflammation of soft tissues and localized thickening of the underlying bone cortex. It is caused by a recurrent arginine-to-cysteine substitution (R836C) in the $\alpha 1(I)$ chain of type I collagen. However, the functional link between this mutation and the underlying pathogenetic mechanisms still remains elusive. First, it remains to be established as to how a point-mutation in type I collagen leads to a cascade of inflammatory events and spatio-temporally limited hyperostotic bone lesions, and second, the contribution of the structural and inflammatory components to the different organ-specific manifestations in Caffey disease. In this review we attempt to shed light on these questions based on the current understanding of other mutations in type I collagen, their role in perturbing collagen biogenesis, and consequent effects on cell-cell and cell-matrix interactions.

Keywords

Caffey disease; Collagen; Extracellular matrix; COX-2; PGE2; TGF β

CAFFEY DISEASE OVERVIEW

Caffey disease or infantile cortical hyperostosis (OMIM 114000) is a rare disease affecting various skeletal elements and contiguous connective tissue. First reported by Roske in 1930, the congenital and regressive aspects of the disease were described by Toni in 1943 [1, 2]. In 1945, based on radiographic observations in a large kindred with several affected members,

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Correspondence: Harald Jüppner, Pediatric Nephrology Unit and Endocrine Unit, Massachusetts General Hospital, Thier 1051, 50 Blossom St. Boston MA 02114. hjueppner@partners.org.

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Caffey and Silverman formally defined it as an infantile inherited disease, with a mean age at onset of 9 weeks [3]. Bennett et al., and later Lecolier et al. also described a lethal prenatal form of Caffey disease with distinct bone lesions that are recognized radiographically on average by 27 weeks of gestation [4, 5]. The infantile form of the disease is usually self-limiting, with spontaneous regression by two years; however, several well documented cases of recurrence of cortical hyperostosis during adolescence have also been reported [6, 7].

The infantile form of the disease is characterized by fever, soft tissue swelling and hyperirritability. Radiographic evaluation is used to establish the diagnosis. The disease is variably penetrant involving a single or multiple bones. Periosteal new bone formation leads to cortical thickening (hyperostosis) of the affected bone(s) and swelling of the overlying soft tissue (Fig. 1) [8]. The bone lesions are often asymmetric with a characteristic involvement of the mandible, clavicle, scapula, skull, ilium and long bones. The mandible is most frequently involved (70–90% of the cases) and is often used as a defining diagnostic criterion [9, 10]. In half the cases the clavicle is affected, whereas the ribs and the scapulae are affected in 20–30% of the cases. In the long bones, primary bone lesions are localized to the diaphysis resulting in grossly deformed spindle shaped bones. The epiphysis and metaphysis are typically not involved; however cortical hyperostosis frequently extends to these areas. Episodes of hyperostosis may also lead to the formation of bony bridges between adjacent bones [8, 11].

Laboratory findings in affected patients include elevated erythrocyte sedimentation rates and alkaline phosphatase levels along with increased C-reactive protein and immunoglobulin levels suggesting a concurrent inflammatory distress [12–15]. Eversole et al. were the first to provide a detailed histological analysis of the affected bones with evidence for local inflammation along with subperiosteal new lamellar bone formation. Foci of acute inflammation were confined to the periosteum early on but progressively disrupted the adjacent soft tissue. As the disease resolves the periosteum reestablishes as a fibrous layer under which new subperiosteal bone is formed. Subsequently, the inflammation disappears and excess peripheral bone is eliminated through remodeling [16].

The role of prostaglandin E (PGE1 and 2) received strong support when Ueda et al. reported induction of cortical hyperostosis in infants with ductus-dependent cyanotic heart diseases receiving prophylactic PGE1 administration to prevent duct closure [17]. This PGE-induced side effect has considerable prevalence with radiologic changes evident in 62% of all infants receiving PGE1 infusion for more than 60 days [18]. Heyman et al. subsequently reported elevated PGE levels in five patients with cortical hyperostosis, whose symptoms resolved upon abrogation of PGE synthesis via indomethacin administration or other anti-inflammatory drugs, such as glucocorticoids [19]. However, the mechanistic context of PGE elevation and consequent immunoregulatory effects on disease onset and progression remain unresolved.

The pathophysiology of Caffey disease presents a unique clinical conundrum, as it is a spatio-temporally limited state of acute bone and soft tissue inflammation that is transmitted as an autosomal dominant trait with incomplete penetrance. Moreover, incidence of non-

familial cases attributed to PGE therapy further complicates matters and indicates that there could be several distinct subtypes of the disease. In an attempt to identify the genetic defect responsible for the infantile form of Caffey disease, Gensure et al. undertook genetic linkage studies in one large kindred with the autosomal dominant form of the disease. These studies revealed that affected individuals (including patients with severe prenatal cortical hyperostosis) and obligate carriers are heterozygous for a missense mutation (3040C→T) in the *COL1A1* gene. This mutation results in an Arg to Cys (R836C/p.R1014C) substitution within the helical domain of $\alpha 1(I)$ chain of type I collagen (COL1A1) [12, 20]. Furthermore, Gensure et al. identified the same mutation in several unrelated kindred and revealed previously unknown features of the disease in adults, namely hyperextensible skin and joint hypermobility. Subsequently, other groups identified the R836C mutation in Thai, Korean, Indian and Australian kindreds with the classical familial form of the disease and in sporadic cases of the infantile and prenatal forms of disease. Taken together these studies validated the pathogenetic role of this particular amino acid substitution in Caffey disease [21–24].

Ultrastructural analyses of mutant dermal collagen fibrils revealed variability in diameter and aberrant disulfide bonded $\alpha 1(I)$ homodimers[20]. These structural defects in type I collagen may explain the skin and joint manifestations in adults, however their role in pathogenesis of the self-limiting bone lesions during infancy remains unresolved.

TYPE I COLLAGEN MUTATIONS AND PATHOPHYSIOLOGY

The structural building blocks of connective tissues, including the skeleton, involve collagens, proteoglycans, non-collagenous proteins along with enzymes capable of matrix assembly and degradation. The relative differences in molecular composition define the structural and functional topology of the matrix at various anatomical sites. Collagens are the most abundant extracellular matrix (ECM) components in the skeleton, with ~90% of the bone matrix consisting of type I collagen fibrils [25]. Apart from providing multidimensional strength, they serve as the primary substrate for mineralization. In addition, type I collagen fibrils within bone participate in the formation of supramolecular assemblies in conjunction with small leucine-rich proteoglycans and other non-collagenous proteins to produce an architecturally precise ECM that facilitates cell adhesion, migration and function [26]. Therefore, mutations in genes encoding different ECM components often result in similar phenotypes. A corollary is that in cases where the molecules are composed of multiple domains with different functional properties, different mutations in the same gene can result in different clinical manifestations. Cases in point are the various collagenopathies including osteogenesis imperfecta (OI), Ehlers-Danlos syndrome (EDS) and Caffey disease (Table.1).

The triple helical domain within the collagen chains enables self-assembly into highly organized collagen fibrils with high tensile strength that are then integrated into the bone matrix. Formation of type I collagen fibers involves C-propeptide-mediated intracellular assembly of two $\alpha 1(I)$ and one $\alpha 2(I)$ pro-collagen chains followed by extracellular cleavage of the N- and C-termini of procollagen monomer by specific proteinases resulting in the higher order assembly into fibrils and fibers [26] (Fig. 2). Tandem Gly-X-Y sequences

within the triple helical domain are critical for this self-assembly and triple helical conformation. Consequently, Gly substitutions result in structural or quantitative defects of type I collagen leading to bone fragility and fractures characteristic of OI types II-IV. Rare mutations affecting type I procollagen processing sites or involving X/Y residues result in distinct variants of OI [27]. Mutations resulting in delayed N-propeptide processing cause a phenotype that overlaps OI and EDS, whereas mutations in C-propeptide cleavage site result in mild OI with increases in bone mineralization (29). Substitutions of X or Y residues cause clinically similar disorders, including mild OI, classical EDS, and Caffey disease, but only Caffey disease is characterized by increased cortical bone formation [20, 28, 29]. The overlapping clinical manifestations of these diseases are thought to result from delayed propeptide processing or impaired ligand interactions with COL1 fibrils, however precise mechanism(s) leading to bone fragility or increased cortical bone formation in these cases remains unclear.

The mature triple helical collagen molecules contain multiple sites for interactions with other structural and signaling components leading to the formation of the heterotypic fibril that is then incorporated into a higher order structure within the extracellular matrix [30, 31]. *In silico* analyses by the San Antonio group of putative ligand binding sites along with the distribution of known type I collagen mutations resulted in a domain model that mapped various cell, signaling and matrix interactions to the type I collagen fibril. These studies identified three ligand-binding hotspots defined as major ligand binding regions (MLBR 1-3). MLBR 2 and 3 (helix positions 680-830 and 920-1012) within type I collagen fibril have been shown to be crucial for intermolecular crosslinking and self-assembly, binding to integrins $\alpha 1\beta 1/\alpha 2\beta 1$, and interactions with an array of non-collagenous proteins (fibronectin, cartilage oligomeric matrix protein, discoidin domain receptors, decorin and heparin) (Table 2). Clustering of lethal collagen mutations to MLBR 2 and 3 underscores the importance of these sites for maintaining matrix homeostasis. The Arg836 residue that causes Caffey disease when mutated, maps to a gap region between MLBR 2 and 3 (Fig. 2). Arg-to-Cys substitutions within the triple helical domain of type I collagen are thought to influence both structure and function of type I collagen fibrils. In fact, presence of cysteine residues results in aberrant disulfide bonded $\alpha 1(I)$ dimers leading to abnormal fibril diameter often noticed in ultrastructural analyses of patient-derived dermis [20, 29]. Importantly, local unwinding surrounding the R-to-C substitutions is thought to interrupt ligand interactions [29]. Broadly, these mutations (i.e. R134C, R836C, and R888C) are characterized by hyperextensible skin and joint hypermobility. However, each mutation can also be recognized by specific phenotype during early childhood. For example, periosteal new bone formation and cortical hyperostosis associated with soft tissue inflammation are only observed in Caffey disease. Furthermore, these phenotypes are not replicated by other R-to-C substitutions, suggesting that the R836C mutation may disrupt specific type I collagen-ligand interaction(s), resulting in impaired resident cell function. Several lines of evidence support such a hypothesis: 1) R836C is localized within the region that was shown to interact with interleukin-2 (IL-2), and is in close vicinity of the site known to interact with fibronectin (FN) (Fig. 2) 2. Neonates have a hyporesponsive immune system with blunted inflammatory cytokine production[32]. Thus, suggesting inflammation in Caffey disease to be a local matrix-driven process. 3. Upregulation of COX2/PGE axis and transforming

growth factor (TGF β) signaling have been shown to cause cortical hyperostosis in humans [17, 33]. Taken together, these observations argue for a pathogenesis driven not necessarily by gross structural or quantitative defects in type I collagen fibrils, but by a subtle alteration in ECM composition that may affect cell signaling as a result of impaired collagen interactions.

Consistent with such a hypothesis, Somasundaram et al., demonstrated binding of IL-2 to native type I collagen and a carboxy-terminal peptide spanning Arg836 [34]. Although first isolated as a T-cell derived growth factor, IL-2 is expressed in the skin and gut of neonatal mice suggesting a role that is distinct from adult immunological responses to an antigen [35]. IL-2 has been shown to have dual and contrasting roles leading to induction and termination of inflammatory immune responses, by regulating T-cell proliferation and CD4⁺ T-helper 1 (T_H1) and T_H2 effector T-cell differentiation and inhibiting development of inflammatory T_H17 cells respectively [36]. Moreover, CD4⁺ T-helper cells predominantly mediate neonatal adaptive immunity [37]. Thus, in the context of Caffey disease, it is conceivable that pre-existing immunological memory along with CD4⁺ T-helper mediated immunological response could possibly result in the acute inflammatory phase that regresses as the immune system matures. Given the central role of IL-2 in immunity and inflammation, it would be crucial to understand how the local bioavailability of this key cytokine is altered in Caffey disease and to evaluate its effects on resident cell function.

Cellular interactions with abnormal matrix lead to aberrant tissue development that in turn influences signaling between resident cells ultimately resulting in impaired tissue homeostasis. In the context of OI, aberrant signaling between osteoblasts and osteoclasts is thought to lead to enhanced bone remodeling exacerbating the bone fragility caused by the primary collagen defect [27]. Moreover, inter-chain cross-links and collagen fibril maturity have been shown to have instructive roles in osteoblast differentiation [38]. Binding of α 2 β 1 integrins on the preosteoblast surface to type I collagen within the bone matrix has been shown to activate Runx2, a key regulator of osteoblast differentiation that drives expression of downstream genes such as osteocalcin, bone sialoprotein, alkaline phosphatase, and parathyroid hormone/parathyroid hormone-related protein receptor [39]. Furthermore, interaction of type I collagen with α 2 β 1 integrin has been shown to enable osteoblast differentiation through the down-regulation of TGF β receptor expression in osteoblastic cells. The down-regulation of TGF β receptor complexes enables these cells to evade the inhibitory effects of TGF β signaling on terminal osteoblast differentiation [40]. Moreover, FN has been shown to orchestrate type I collagen assembly and matrix sequestration of latent TGF β in conjunction with latent transforming growth factor binding protein-1 [41]. Impaired FN matrix results in promiscuous TGF β activation in both *in vitro* and *in vivo* experimental models [42, 43]. Consistent with the crucial role of TGF β signaling in bone formation, cortical hyperostosis in Camurati-Engelmann disease results from constitutively active TGF β signaling due to mutations within the latency-associated peptide of TGF β 1 [33, 44].

Taken together, these observations in rare human diseases are highly significant for the understanding of normal osteoblastogenesis and how collagen mutations lead to distinct bone phenotypes. For example, some of the type I collagen mutations identified in dominant

OI are associated with impaired osteoblast maturation and increased osteoclast recruitment, whereas mutant collagen fibrils in Caffey disease lead to enhanced lamellar bone formation along the periosteal surface. Understanding the role of the two integrin-binding RGD domains (helix residues 567-569 and 915-917) juxtaposed to Arg 836, along with fine mapping of the protein-protein interacting domains within this region may provide important clues to further our understanding of type I collagen in the bone formation process (Fig. 2).

Spatiotemporal and quantitative coupling between bone forming osteoblasts and bone resorbing osteoclasts is crucial for the maintenance of adult bone mass. However, during embryogenesis and early postnatal development these activities remain uncoupled to facilitate rapid bone matrix synthesis and growth. This is called bone modeling, a process that helps in fine tuning the spatial distribution of accumulating tissue to evolving mechanical demands [45]. The endoplasmic reticulum (ER) plays a critical role in the synthesis, folding and processing of type I collagen, the predominant protein synthesized by metabolically active osteoblasts during this phase [26, 46]. To enable the increased metabolic demands of the cell, the ER undergoes active membrane expansion thus greatly increasing its surface area. However, expression of mutant proteins results in increased levels of unfolded or misfolded proteins within the ER lumen leading to a state of chronic ER stress. This triggers the activation of the unfolded protein response (UPR), a quality control mechanism designed to maintain the protein-folding equilibrium within the ER. Type I procollagen chains harboring mutations in the C-terminal propeptide or triple helical domain (G349C in COL1A1 and G904C in COL2A1) have been shown to trigger the UPR [47]. Importantly, ER stress has been shown to induce of COX-2 (cyclooxygenase-2) expression, a key enzyme necessary for the synthesis of PGE [48]. Furthermore, numerous murine studies have demonstrated the bone anabolic effects of PGE2 resulting from increased proliferation of periosteal osteoblasts [49–51].

Based on radiographic findings, Gensure et al., suggested that periosteal detachment from underlying bone could be the key pathological process driving hyperostosis in Caffey disease [20]. In such a scenario, the periosteal injury might elicit an inflammatory response that triggers a local positive feedback loop involving COX-2/PGE signaling driving new bone formation by periosteal osteoblasts. It would therefore be important to investigate signaling events downstream of COX-2/PGE axis and their potential contribution to Caffey disease pathogenesis (Fig. 3).

CONCLUSION

Characterization of the various collagenopathies has yielded new insights into the pathophysiology of connective tissue disorders. These findings have revised the notion that the molecular basis underlying the spectrum of clinical phenotypes is solely due to structural defects of the ECM. The emerging paradigm postulates metabolic dysfunction of the matrix and the consequent effects on resident cell function as concomitant causative drivers of disease progression. In light of these findings, a reevaluation of the pathogenetic mechanisms underlying Caffey disease may provide novel insights into bone biology and potentially offer therapeutic approaches for the clinical management of both the prenatal and infantile forms of the disease. Further investigations into the functional roles of the type I

collagen fibril could also provide clues as to how the R836C mutation leads to periosteal new bone formation that is spatially and temporally limited. Apart from unraveling novel matrix-derived signals that drive bone anabolic responses, this understanding of the interplay between type I collagen integrity and bone formation may be relevant to the management of common disorders such as osteoporosis and conditions characterized by ectopic calcifications in skin, kidney, tendons and the cardiovascular tissues.

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HIGHLIGHTS

- Caffey disease is caused by an Arg to Cys substitution (R836C) in the $\alpha 1(I)$ chain of type I collagen.
- The structural change caused by the R836C mutation may trigger collagen-dependent metabolic dysfunction of the matrix.
- Abnormal COX2/PGE signaling is likely to play role in periosteal new bone formation in Caffey disease.
- Altered interplay between collagen matrix and bone formation in Caffey could provide novel insights into common disorders affecting bone.

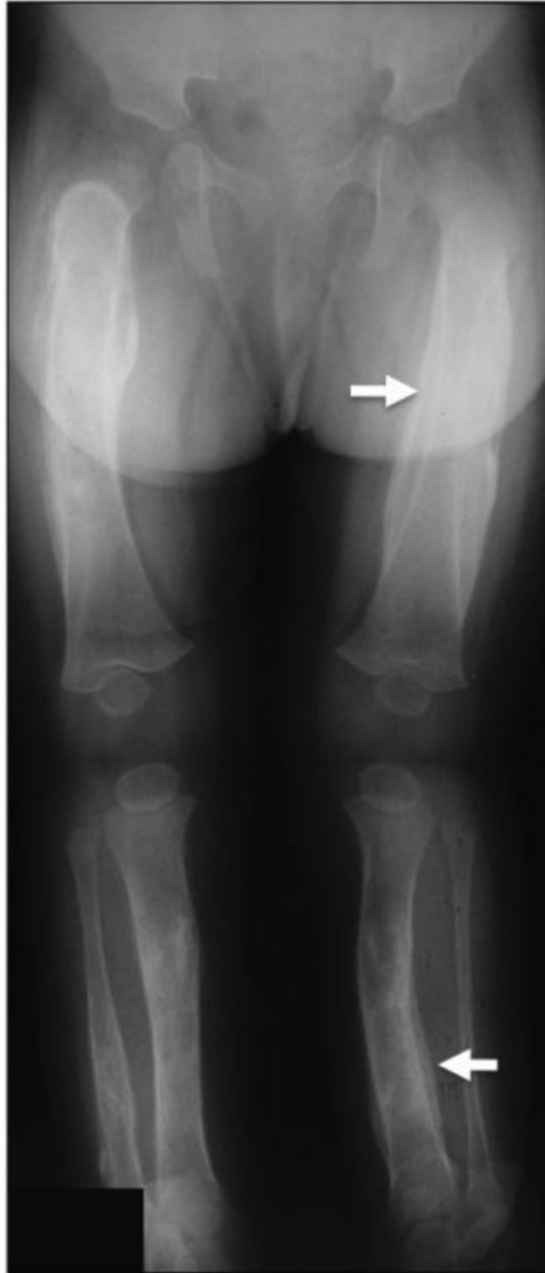


Figure 1. Radiographic features of Caffey disease

Representative radiograph of an affected individual showing periosteal thickening of the femur and the tibia (white arrow). Adapted from Gensure et al., 2005 [20].

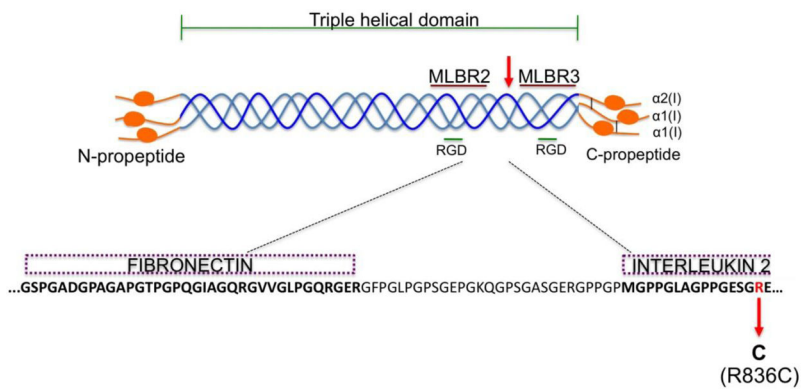


Figure 2. Schematic representation of type I collagen fibril

The R836C mutation (red arrow) is localized to a gap region between the major ligand binding regions 2 and 3 (MLBR2 and MLBR3, maroon lines) and flanked by integrin-binding RGD motifs (green line) within the C-terminus. The R836C mutation is located within the interleukin-2 binding site and juxtaposed to a fibronectin binding site (dashed purple boxes).

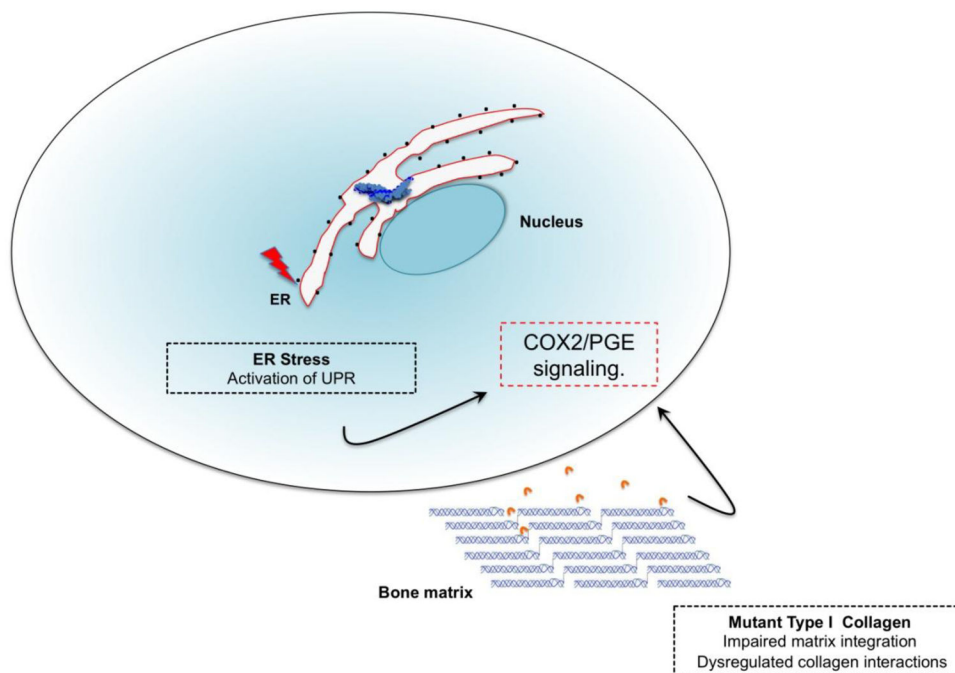


Figure 3. Hypothetical model representing pathogenetic mechanisms underlying Caffey Disease
 The R836C mutant pro α 1(I) chains may induce ER stress triggering an unfolded protein response leading to an upregulation of the COX2/PGE axis. Alternatively, the R836C mutant type I collagen fibrils may disrupt ligand interactions within the ECM resulting in signaling events that either directly or indirectly lead to elevated COX2/PGE signaling and altered resident cell function.

Table 1

Type I Collagen Disorders Genotype Phenotype Relationships.

Type I Collagen Disorder	OMIM	Inheritance	Clinical Features	Gene Defect	Molecular Genetics
Osteogenesis Imperfecta, Type I	166200	Autosomal Dominant	Mild and non-deforming: Fractures with little or no limb deformity, blue sclerae, normal stature, dentinogenesis imperfecta, hearing loss.	null <i>COL1A1</i>	Frameshifts or premature termination codon in <i>COL1A1</i> .
Osteogenesis Imperfecta, Type II	166210	Autosomal Dominant	Perinatal lethal: In utero fractures and bone deformity, blue sclerae, undermineralized skull, platyspondyly	<i>COL1A1</i> or <i>COL1A2</i>	Glycine substitutions in <i>COL1A1</i> or <i>COL1A2</i> .
Osteogenesis Imperfecta, Type III	259420	Autosomal Dominant	Severely deforming: High fracture incidence with moderate bone deformity, blue/grey sclerae, very short stature, dentinogenesis imperfecta	<i>COL1A1</i> or <i>COL1A2</i>	Glycine substitutions in <i>COL1A1</i> or <i>COL1A2</i> .
Osteogenesis Imperfecta, Type IV	166220	Autosomal Dominant	Moderately deforming: Fractures with mild limb deformity, normal sclerae, variable short stature, dentinogenesis imperfecta, hearing loss.	<i>COL1A1</i> or <i>COL1A2</i>	Glycine substitutions in <i>COL1A1</i> or <i>COL1A2</i> .
Ehlers-Danlos Syndrome, Type I	130000	Autosomal Dominant	Marked skin involvement - fragile, bruisable and hyperextensible skin, joint laxity and subluxation.	<i>COL1A1</i>	Arginine to cysteine substitution (R134C) in <i>COL1A1</i>
Ehlers-Danlos Syndrome, Type VIIA	130060	Autosomal Dominant	Joint laxity and subluxations, congenital hip dislocations, minimal skin involvement	<i>COL1A1</i>	Splice-junction mutations of exon 6 in <i>COL1A1</i>
Ehlers-Danlos Syndrome VIIB	130060	Autosomal Dominant	Joint laxity and subluxations, congenital hip dislocations, minimal skin involvement	<i>COL1A2</i>	Exon 6 deletions in <i>COL1A2</i>
Ehlers-Danlos Syndrome, Cardiac Valvular	225320	Autosomal Recessive	Valvular insufficiency, joint laxity and subluxations, hyperextensible skin	null <i>COL1A2</i>	Premature termination codon in <i>COL1A2</i>
Caffey Disease	114000	Autosomal Dominant	Joint laxity and subluxation, hyperextensible skin with normal appearance, cortical hyperostosis	<i>COL1A1</i>	Arginine to cysteine substitution (R836C) in <i>COL1A1</i>

Table 2

Molecules interacting with type I collagen fibril and putative binding sites.

Interacting Molecule	Putative Interaction Site on Type I Collagen Fibril [31, 52]
Amyloid precursor protein	822–1040
Cartilage oligomeric matrix protein	582–629; 1035–1040
Type V collagen	1023–1036
Decorin	159–199; 345–387; 934–964
Dermatan sulfate proteoglycan	601–611; 622–632; 852–862; 856–866; 887–897
Fibronectin	757–790
Heparin sulfate proteoglycan	86–90
Interleukin-2	124–402; 822–1015
Keratin sulfate proteoglycan	451–461; 565–575
Matrix metalloproteinase 1, 2, 13	766–786
Phosphoryn	680–750
Secreted protein acidic and rich in cysteine	100–200; 650–800
Thrombospondin	101–200 & 651–800
von Willebrand factor	396–404