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REVIEW ARTICLE

Agnès S. Kamoun-Goldrat · Martine F. Le Merrer

Animal models of osteogenesis imperfecta and related syndromes

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Introduction

Osteogenesis imperfecta (OI) is a genetic disorder of increased bone fragility and low bone mass. Severity varies widely, ranging from intrauterine fractures and perinatal lethality to very mild forms without fractures. There is variable association of typical extraskeletal manifestations with the disorder, including blue sclera, dentinogenesis imperfecta, hyperlaxity of ligaments and skin, hearing impairment, and the presence of Wormian bones on skull radiography [1]. Even though the range of clinical severity in OI is a continuum, categorization of patients into separate types can be useful to assess prognosis and to help assess the effects of therapeutic interventions. The most widely used classification of OI distinguishes four clinical types [2]. The most relevant clinical characteristic of all OI types is bone fragility, the severity of which increases in the order type I < type IV < type III < type II.

OI type I includes patients with mild disease and absence of major bone deformities. Typical features of OI type I are normal height or mild short stature, blue sclera, and no dentinogenesis imperfecta. However, vertebral fractures are typical and can lead to mild scoliosis. The typical associated mutation is a premature stop codon in the COL1A1 gene. Type II is lethal in the perinatal period, usually because of respiratory failure resulting from multiple rib fractures. Typical features of OI type II are multiple fractures at birth, pronounced deformities, broad long bones, low density of skull bones on radiography, and dark sclera. Type III is the most severe form in children surviving the neonatal period. Typical features of OI type III are very short stature, triangular face, severe scoliosis, grayish sclera, and dentinogenesis imperfecta. Deformities secondary to multiple fractures can lead to respiratory difficulties, identified as a leading cause of death in this patient group [3,4]. Patients with mild to moderate bone deformities and variable short stature are classified as OI type IV. This last group includes all individuals who are not clearly part of the first three types. Typical features of OI type IV are moderately short stature, mild to moderate scoliosis, grayish or white sclera, and dentinogenesis imperfecta. Glycine substitutions in proα1(I) or proα2(I) collagen chains are the typical mutations associated with OI types II, III and IV.

It is now widely recognized that there may be more types of OI than those classified by Sillence et al. [2]. Some forms of congenital brittle bones have been considered OI and have been added as types V, VI, and VII [5–7]. Other forms of congenital brittle bone disease have been described with either eponyms, such as Cole–Carpenter syndrome [8] or Bruck syndrome [9], or with clinical features, such as OI with denser areas in bones [10], OI with microcephaly and cataracts [11], or osteoporosis-pseudoglioma syndrome [12,13]. There is no consensus about the definition of OI. Plotkin recently proposed to define OI as syndromes resulting from mutations in either COL1A1 or COL1A2 genes and to group all other syndromes with congenital brittle bones as "syndromes resembling OI (SROI)," pending the identification of their causal mutations [14]. Table 1 shows SROI as described by Plotkin and several skeletal disorders resembling OI as described in another current review [1]. It is noteworthy that the one patient described with "congenital brittle bones with denser areas in bones" had to be classified with OI types I to IV because genetic testing showed that this patient was heterozygous for a COL1A1 mutation. Abnormal proα1(I) chains were slow to assemble into dimers and trimers, and abnormal molecules were retained intracellularly for an extended period [10]. We discuss several animal models of OI and a model of human SROI.

A.S. Kamoun-Goldrat (✉) · M.F. Le Merrer
Paris Descartes University, INSERM U781, Tour Lavoisier, Hôpital Necker, 75743 Paris Cedex 15, France
Tel. +33-1-4640-7775; Fax +33-1-4083-8771
e-mail: agnes.kamoun@yahoo.fr

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Table 1. Human syndromes resembling osteogenesis imperfecta (OI)

Disorder	Severity of bone fragility/deformity	Characteristics	Inheritance	Genetic defect
Cole–Carpenter syndrome OMIM 112240	Severe	Craniosynostosis; Ocular proptosis	Unknown	Unknown
Bruck syndrome 1 OMIM 259450	Moderate to severe	Congenital joint contractures	Autosomal recessive	On short arm of chr.17 (17p12)
Bruck syndrome 2 OMIM 609220	Moderate to severe	Congenital joint contractures	Autosomal recessive	Telopeptide lysylhydroxylase (PLOD2) deficiency
OI with microcephaly and cataracts OMIM 259410	Severe	Prenatal bone fractures; bilateral cataracts; small brain; blue sclerae	Unknown	Unknown
Osteoporosis-pseudoglioma syndrome OMIM 259770	Mild to severe	Blindness	Autosomal recessive	Low-density lipoprotein receptor-related protein 5 (LRP5) deficiency
Idiopathic hyperphosphatasia OMIM 239000	Severe	Raised alkaline phosphatase activity; wide diaphyses; thick calvarium	Autosomal recessive	TNFRSF11B (osteoprotegerin) deficiency
Hypophosphatasia OMIM 241500	Mild to severe	Low alkaline phosphatase activity	Autosomal (recessive or dominant)	ALPL (alkaline phosphatase liver) deficiency
Congenital brittle bones with redundant callus formation (type V OI)	Severe	Hyperplastic calluses; white sclera and no dentinogenesis imperfecta	Autosomal recessive	Unknown
Congenital brittle bones with mineralization defect (type VI OI)	Severe	No dentinogenesis imperfecta; no Wormian bones	Autosomal recessive	Unknown
Congenital brittle bones with rhizomelia (type VII OI)	Moderate to severe	Rhizomelia	Autosomal recessive	CRTAP deficiency
Panostotic fibrous dysplasia	Severe	Cystic or ground-glass lesions in all bones	None (somatic mutation)	αS G-protein subunit

Animal models of OI

Mov-13 mouse: a model of OI type I

In Mov-13 mice, transcription of the proα1(I) gene is completely blocked as a result of Moloney leukemia virus integration at the 5′-end of the gene [15]. Transcription of the proα2(I) gene is not affected by viral integration [16]. However, no functional α2(I) chains were detected in embryos by immunostaining [17], nor were they synthesized in cell lines from homozygous embryos. This failure was probably the result of rapid degradation of the proα2(I) procollagen chains, which are unable to form stable triple helices in the absence of proα1(I) chains [18]. Mice homozygous for the null mutation produced no type I collagen and died at midgestation whereas heterozygotes survived to young adulthood [19]. Dermal fibroblasts from heterozygote mice produced about 50% less type I collagen than normal littermates. The partial deficiency in gene expression resulted in a 50% decrease in tissue collagen content, progressive hearing loss, and alterations in the mechanical properties of long bones [20]. The heterozygous Mov-13 mouse therefore serves as a model of human OI type I.

Tooth rudiments from embryos of homozygous Mov-13 mice produced a dentin layer containing normal amounts of type I collagen when grown as transplants either in the anterior chamber of the eye or under the kidney capsule of syngenic hosts. There is evidence that odontoblasts can efficiently produce α1(I) mRNA despite stable integration of the retrovirus within the first intron of the α1(I) collagen gene [21]. The authors stated that perhaps as many as 5% of osteoblasts from long bones could produce normal amounts of type I collagen, thus implying that a small subset of osteoblasts also did not express the mutant phenotype. Bone tissue mosaïcism for expression of the mutant allele may explain why Mov-13 heterozygotes do not display an obvious bone fragility mutant phenotype. Introduction of the human proα1(I) collagen gene into Mov-13 mouse cells led to formation of functional mouse–human hybrid type I collagen [22]. Functional expression of the inserted proα1(I) gene rescued the proα2(I) gene products from rapid degradation and allowed secretion of normal levels of collagen proα2(I) chains. Bonadio et al. [23] have identified an adaptation of Mov-13 skeletal tissue that significantly improved the bending strength of long bones. The adaptative response occurred over a 2-month period, during which time a small number of newly proliferated osteogenic cells produced a significant amount of matrix components and thus generated new bone along periostal surfaces.

Brittle II mouse: a model of OI type II

The cre/lox recombination system was used to develop a lethal knock-in murine model of OI type II [24]. A 3.2-kilobase-pair transcription/translation stop cassette was introduced in intron 22 and flanked by directly repeating lox recombination sites. After homologous recombination in ES cells, two male chimeras were obtained. A knock-in mouse carrying an "intronic" inclusion was generated by mating chimeras with wild-type females. Alternative splicing involving the stop cassette resulted in retention of noncollagenous sequences. This mouse had the lethal phenotype of similar human mutations and was designated BrtlII. Skeletal staining showed rib fractures, poor skeletal mineralization, and shorter vertebral bodies. The mice died a few hours after birth, from apparent respiratory distress.

Oim/oim mice: a model of OI type III

Chipman et al. [25] described a strain of mice with a nonlethal recessively inherited mutation that resulted in phenotypic and biochemical features that simulate moderate to severe human OI. Oim/oim mice have a normal lifespan. The phenotype of homozygous oim mice includes skeletal fractures, limb deformities, generalized osteopenia, and small body size. Their femurs are smaller and demonstrate marked cortical thinning and fewer medullary trabeculae than those of wild-type mice. Heterozygote oim/+ mice have subtle skeletal fragility whereas homozygous oim/oim mice have marked skeletal fragility. The dental phenotype in oim/oim is more severe in incisors than in molars and includes changes in pulp chamber size, tooth shape, and dentin ultrastructure. Teeth in oim/oim animals are clinically fragile. Although oim/+ teeth are grossly normal, ultrastructural abnormalities such as reduction in the number and regularity of spacing of the dentinal tubules, less mineralization, and blurring of the boundary between peritubular and intertubular dentin can be found in oim/+ teeth [26].

Breeding studies showed that the oim mutation was inherited in most crosses as a single recessive gene on chromosome 6, near the murine COL1A2 gene. Biochemical analyses of skin and bone, as well as isolated dermal fibroblast cultures, demonstrated that α1(I) homotrimer collagen accumulated in these tissues and was secreted by fibroblasts. Short labeling studies in fibroblasts demonstrated an absence of proα2(I) collagen chains. Nucleotide sequencing of cDNA encoding the COOH-propeptide revealed a G deletion at proα2(I) nucleotide 3983; this results in an alteration of the sequence of the last 48 amino-acids. Normal-sized mRNA is transcribed, but no secreted protein has been identified in oim/oim fibroblasts and osteoblasts.

The unusual size and crystal alignment undoubtedly contribute to the reduced mechanical properties of oim/oim bone [27]. Collagen from the oim/oim mouse showed reduced resistance to tensile stress [28]. Neutron activation analyses demonstrated that oim/oim femurs had significant differences in magnesium, fluoride, and sodium content compared to +/+ mouse femurs, and oim/oim teeth had significant differences in magnesium content compared to +/+ teeth [29–34]. These and other studies suggest that the known decreased biochemical properties of oim/oim bone reflect both altered mineral composition and decreased bone mineral density, which further suggests that the presence of α2(I) chains plays an important role in bone mineralization. Bone structure was determined as a function of animal age by small-angle X-ray scattering. We found anomalies in the arrangement of bone mineral crystals in both homozygous and heterozygous mice that were 1–14 months old [27]. The organization of cortical bone is deficient in heterozygotes (oim/+), exhibiting a morphology intermediate to specimens from homozygotes and wild-type mice [35,36]. The amount and structure of oim/oim type I collagen affects the mechanics of ventricular myocardium [37] and induces an abnormal glomerular collagen deposition [38]. Oim/oim mice have altered biochemical integrity, collagen content, and collagen cross-linking of their thoracic aorta [39].

Bisphosphonates reduce fracture incidence and improve bone density in children with OI [1]. Alendronate, a third-generation bisphosphonate drug, acts directly on the osteoclast, inhibiting its resorption capability. Its effects on linear bone growth were studied in oim/oim mice. High doses of alendronate inhibit long bone length in oim/oim mice through alteration of the growth plate, and these high doses may possibly reduce resorption of the chondro-osseous junction [40]. Bone density increased significantly in the femur and the spine with treatment [41]. Positive treatment effects include a reduction in the number of fractures sustained by the alendronate-treated oim/oim mice compared with untreated oim/oim mice [42]. Growth hormone injections improve bone quality in oim/oim mice, as measured by significant increases in bone stiffness, maximum load, the energy absorbed by the femurs to the point of maximum load, and the energy to actual fracture. These results support expanded clinical testing of growth hormone injections in children with OI [43].

Retrovirally transduced bone marrow stromal cells isolated from oim/oim mouse persisted in bone and retained the ability to form cartilage and bone after extended passaging [44]. Murine proα2(I) cDNA was inserted into an adenovirus vector and transferred into bone marrow stromal cells isolated from oim/oim femurs. Murine cDNA under the control of the cytomegalovirus early promoter was expressed by the transduced cells [45]. Analysis of the collagens synthesized by the transduced cells demonstrated that the cells synthesized stable type I collagen composed of α1(I) and α2(I) heterotrimers in the correct ratio of 2:1. These data encourage further studies in gene replacement for some forms of OI.

Brittle IV mouse: a model of OI type IV

The cre/lox recombination system was used to develop a nonlethal knock-in murine model for OI [24]. A moderately

severe OI phenotype was obtained from an α1(I) 349 Gly → Cys substitution in type I collagen, which is the same mutation in a type IV OI child. These mice, designated as Brtl IV (Brittle IV), have phenotypic variability ranging from perinatal lethality to long-term survival with reproductive success. The size of Brtl IV mice was about 50% that of normal littermates at 6 weeks of age, after which their size increased to about 80% of normal. Deformity of the rib cage was apparent. Both forelegs and hindlegs were bowed and thinner than those of control littermates. The Brtl IV mouse has the molecular, biochemical, and radiographic features of human OI type IV. Heterozygous mutant mice have the undermineralization of the skeleton, the bone fragility, and the deformity characteristic of human patients. Their growth pattern, with normal size at birth followed by growth deficiency until 4–5 weeks of age, resembles the early childhood growth pattern reported for moderately severe OI patients. No significant deformities in long bones were evident in mutant mice after puberty. Long bone fractures were also infrequent in adult mice.

Similarly, moderately severe OI patients experienced a dramatic decrease in fracture frequency following puberty. The Brtl IV mice with lethal outcomes died at birth from apparent respiratory insufficiency, a common cause of morbidity and mortality in human OI. In patients with OI, phenotypic variability has been reported in several instances of both related and unrelated probands with the same collagen mutation. Mice with variable phenotype have equivalent expression of mutant α1(I) mRNA in several tissues, including bone and skin; they also have equivalent incorporation of the mutant α1(I) chain into skin [24]. These findings support the proposal that discrete noncollagenous modifying factors are responsible for variable severity in OI. There is a postpubertal adaptation in which Brtl femoral strength and stiffness increase through a mechanism independent of changes in whole-bone geometry [46]. This finding parallels the currently unexplained clinical observation of fewer fractures in human OI after puberty. OI symptoms and phenotype variation are related to abnormal interactions of mutant collagen helices with other matrix molecules, or abnormal osteoblast function, rather than to abnormal structures, physical properties, or interactions between mutant collagen helices [47].

Other animal models of OI

Mouse

Stacey et al. [48] reported preparation of transgenic mice expressing a mutated proα1(I) gene in which a cysteine codon was replaced by a glycine codon. Four of the seven transgenic mice obtained had some of the phenotypic features of OI. However, no fractures were seen.

A minigene version of the human gene for a proα1(I) of type I procollagen was prepared that contained the promoter region and the 5′- and 3′-ends of the gene but lacked a large central region containing 41 exons [49]. This minigene was used to prepare transgenic mice. Several of the founders obtained were apparently mosaic as they produced progeny that died shortly after birth with a distinctive phenotype [50]. The phenotype included extensive fractures of ribs and long bones, similar to the fractures seen in lethal variants of OI. The shortened proα1(I) chains synthesized from the minigene became disulfide linked to proα1(I) chains synthesized from the endogenous mouse gene and caused degradation through a process called procollagen suicide. A similar mosaïcism in parents of probands with lethal variants of human OI was observed in several families.

Mice expressing relatively high levels of the transgene developed the lethal phenotype just described, but a line of mice expressing moderate levels of the internally deleted gene for the proα1(I) chain of human type I procollagen is characterized by a phenotype of fractures, a decrease in mineral and collagen content in bone, and a mechanically brittle bone matrix [51]. As seen in some variants of OI, the mice appeared to improve after birth in that there were fewer fractures and the difference in their appearance from control littermates became less apparent with age [51–54].

Dog

In a 3-month-old golden retriever puppy with dentinogenesis imperfecta and multiple pathological fractures, sequence analysis of COL1A1 identified a G to C point mutation predicting a codon change from glycine to alanine for amino acid 208 [55,56]. Some cases of human OI type III caused by substitution of glycine with alanine have also been reported. A 12-week-old female beagle puppy with a 10-week history of multiple fractures affecting almost every long bone was observed [57]. The dog has a mutation in COL1A2, involving a deletion of four nucleotides and an insertion of five nucleotides, resulting in a frameshift and premature termination of translation of the proα2(I) chain.

OI has been documented only clinically in other dogs [58–60].

Zebrafish

A mutagenesis screen for skeletal dysplasias in adult zebrafish was done using radiography to detect abnormalities in skeletal anatomy and bone morphology [61]. Chihuahua, a dominant mutation causing a general defect in bone growth, was found. Heterozygous chihuahua fish have phenotypic similarities to human OI. When examined radiographically, all bones appear to be misshapen and show more irregular radiodensity than in wild-type fish. Radiographs demonstrate this phenotype as early as 1 month of age. The sequence of zebrafish COL1A1 is highly homozygous to the human gene; at the amino acid level, the two proteins are 76% identical. Both contain the uninterrupted glycine triplet repeat region characteristic of fibrillar collagens. At position 2207 of the coding sequence, the Chi/+ cDNA had both a G, which is the wild-type nucleotide, and an A, which

is predicted to change the encoded amino acid from glycine to aspartate. The Chihuahua mutant appears to be an accurate model both molecularly and phenotypically for the majority of OI cases, with the heterozygotes viable, but displaying severe disturbances in bone growth.

Miscellaneous

OI has been documented previously in cattle, sheep, domestic cats, and tigers [62–72].

Animal models of human SROI

Osteoporosis-pseudoglioma syndrome (OPPG), an autosomal recessive disorder, is characterized by juvenile-onset osteoporosis and many variable ophthalmic conditions leading to congenital or juvenile blindness. These conditions include microphthalmos, cataracts, bilateral pseudogliomatous retinal detachments, and phthisis bulbi [73]. Children with OPPG have very low bone mass and are prone to developing fractures and deformations. Obligate carriers of the OPPG mutation have been suggested to have an increased incidence of osteoporosis-related fractures. A mutation in the gene that encodes the low-density lipoprotein receptor-related protein 5 (LRP5) was discovered to be a cause of OPPG. In individuals with OPPG, nine disease-causing mutations in exons encoding the LRP5 extracellular domain have been identified, with each predicted to result in either frameshift or nonsense mutations [74]. LRP5 acts as a Wnt receptor in osteoblasts [75]. The Wnt proteins are secreted proteins that control multiple developmental processes including mesoderm induction, cell fate determination, limb patterning, and organogenesis [76–79]. LRP5 is also involved in other pathways, including cholesterol metabolism and the modulation of glucose-induced insulin secretion [80].

LRP5 –/– mice were independently generated in two laboratories [75,80]. LRP5 –/– mice of both sexes developed and appeared normal, gaining weight at a rate equal to that of LRP5 +/+ mice, and were normally fertile. Although no apparent low bone mass was observed in 3-to 6-month-old LRP5 –/– males under light microscopic examination, the femur and parietal bones were thin and fragile in LRP5 –/– females older than 6 months. Pathological fractures of lower limbs were also observed in LRP5 –/– [80]. In another laboratory, a severe low bone mass phenotype, similar to that of patients with OPPG, was observed in LRP5 –/– mice [75]. This low bone mass phenotype was observed regardless of sex and age, and a significant number of the mice died within the first month of life because of fractures [75]. This discrepancy between the two strains of LRP5 –/– mice suggests the involvment of other factors, including sex, aging, hormonal status, dietary exposure, and genetic background in the development of a low bone mass phenotype.

Prolyl hydroxylation is a critical posttranslational modification that affects structure, function, and turnover of target proteins. Prolyl 3-hydroxylation occurs at only one position in the triple helical domain of fibrillar collagen chains. Cartilage-associated protein (CRTAP) copurifies with protein fractions containing prolyl 3-hydroxylase type I activity and affects its enzymatic activity. In humans, 10% residual CRTAP results in a rhizomelic form of recessive OI (OI type VII), whereas complete loss of the protein leads to a more severe form of OI (classified as OI type II) [81]. CRTAP null mice develop progressive and severe kyphoscoliosis during the first 6 months of age. Moreover, they exhibit prenatal and postnatal growth delay that is characterized by shortening of long bone segments, affecting in particular the proximal segment of the limb. The growth plate shows slightly disorganized growth columns of proliferating chondrocytes with areas of focal cell dropout, whereas the zone of hypertrophy remains fairly intact. Skeletal radiographs and stained calcified bone sections showed striking evidence of osteoporosis. Kinetic indices of bone formation revealed a reduced bone formation rate caused by a reduction in the mineral apposition rate. The low bone mass in Crtap null mice is likely not the result of accelerated bone resorption because osteoclast numbers are normal in vivo, and ex vivo osteoclast function was also normal. Hence, Crtap null mice exhibit a severe osteoporosis characterized by low bone mass, normal osteoblast and osteoclast numbers, reduced bone formation rate and mineral apposition rate, and decreased osteoid synthesis and mineralization lag time [81].

Syndromes resembling OI in animals

Fragilitas ossium, fro, is an often lethal recessive mutation that was discovered in a random-bred stock of mice after treatment with a chemical mutagen [82–84]. The fro/fro mutation has clinical, radiographic, and morphological manifestations similar to those that arise in autosomal recessive forms of OI in humans. Approximately 90% of mutant offspring were perinatally lethal, with clinical and radiographic findings similar to those of OI type II subgroup A in humans. The 10% of mutant mice that survived followed a course very similar to severe progressively deforming OI type III. In surviving mice, there is progressive forelimb and hindlimb bowing in the absence of a high fracture frequency. A defect in type I collagen could not be detected in the fro/fro mouse. Positional cloning of the locus identified a deletion in the gene encoding neutral sphingomyelin phosphodiesterase 3 (Smpd3) that led to complete loss of enzymatic activity [85]. Neutral sphingomyelinases are ubiquitously expressed enzymes with elevated expression in the brain and in the embryonic growth plate of bone. They cleave sphingomyelin into ceramide, which is in turn a substrate for ceramidase, resulting in the production of sphingosine. Sphingosine is then modified by a specific kinase and converted into sphingosine 1-phosphate (S1P). S1P has mitogenic activity on osteoblasts, the bone-forming cells [86]. A defective ceramide pathway could affect bone development and remodeling, leading

to excessive bone resorption. Increased bone resorption is commonly associated with bone fragility. The precise relationship between impairment of the gene encoding Smpd3 and bone fragility is not understood, but sphingomyelinases are clearly involved in bone and dentine mineralization.

Zmpste-24 is an integral membrane zinc metalloproteinase of the endoplasmic reticulum. Zmpste-24 knock-out mice weigh slightly less than littermates at weaning and gain weight very slowly. The mice also manifest muscle weakness. By 6–8 weeks of age, they develop kyphosis of the spine, lose hair, and have spontaneous bone fractures [87]. By 24–30 weeks of age, nearly every rib in Zmpste 24 –/– mice was broken in the vicinity of the costovertebral junction with hypertrophic calluses at the fracture sites. Heterozygotes (Zmpste 24 –/+) appear normal for the first 12 months of life, but by 15 months of age, most heterozygotes were smaller than wild-type littermates, appeared weak, and had lost hair. Zmpste-24 acts as a CAAX endoprotease, clipping off the C-terminal three amino acids from the protein (i.e., the –AAX of the CAAX motif). Prelamin A (a precursor to lamin A, a component of the nuclear lamina) is a Zmpste-24 substrate. After removal of the C-terminal-AAX, an additional 15 residues are removed from the C-terminus of the protein, generating mature lamin A [87,88]. The deficit in prelamin A processing induces prelamin A accumulation in the nuclear envelope of Zmpste 24 –/– mice; this could indirectly affect the amount or quality of type I procollagen secretion, accounting for the bone phenotype in Zmpste-24 –/–.

OI was described in two litters of dachshunds [89]. Clinical signs consisted of pain, spontaneous bone and teeth fractures, joint hyperlaxity, and reduced bone density on radiography. Primary teeth were extremely thin walled and brittle. The hallmark of the disease was severe osteopenia characterized by impairment of lamellar bone formation in the long bones, skull, and vertebral column. Molecular analyses of the collagen type I-encoding genes revealed several nucleotide differences compared with published canine sequences, but these were not significant for OI. A specific defect in one collagen processing enzyme has not yet been found.

Conclusion

Osteogenesis imperfecta (OI) is characterized by fragile bones, skeletal deformity, and growth retardation. This heritable disorder of connective tissue is most often the result of mutations affecting the COL1A1 or the COL1A2 genes of type I collagen. Categorization of patients into four separate types (Sillence's classification; OI types I, II, III, and IV) is useful to assess prognosis and to help assess the effect of therapeutic interventions.

Many animal models of OI have been described, and some are available for research in cellular, molecular, or pharmacological therapy. There is often no parallelism between clinical signs observed in humans and rodents suffering from the same genetic defect. In spite of this observation, the mouse models of OI are of interest: we have now a model for each type of human OI. The Mov-13 mouse is a useful animal model for OI type I, the Brittle II mouse for OI type II, the oim/oim mouse for OI type III, and the Brittle IV mouse for OI type IV. Among the 11 syndromes resembling OI (SROI) in humans, only osteoporosis-pseudoglioma syndrome has a mouse counterpart. The need for additional models, specially for syndromes resembling OI, is apparent because they can provide a way to determine the genetic defects responsible for these various syndromes.

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