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A New Osteogenesis Imperfecta With Improvement Over Time Maps to 11q

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Osteogenesis imperfecta (OI) is basically divided into four clinical types, I–IV. Type IV clearly represents a heterogeneous group of disorders. Here we describe two OI patients in the same family. They would typically be classified as having type IV, but are distinguishable from other OI type IV patients by the improving and resolving course of their disease. Mutation screening did not identify mutations affecting glycine codons or splice sites in the coding regions of the two collagen I genes. Genome-wide screening of DNA samples from the two homozygous patients identified one region of high concordance of homozygosity on chromosome 11 on the long arm (11q23.3–11q24.1).

Key words: bone; collagen; metabolic bone disease; osteogenesis imperfecta; osteoporosis

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INTRODUCTION

Osteogenesis imperfecta (OI) is a congenital disorder characterized by low bone mass and fragile bones. Four types are commonly recognized, based on clinical features and disease severity [Sillence et al., 1979]. Patients with OI type I have a mild phenotype with normal or near-normal height and typically have blue sclerae. OI type II is usually lethal in the perinatal period. OI type III, known as progressive deforming OI, is the most severe form in children surviving the neonatal period. Patients with a moderate-to-severe form of the disease who do not fit one of these descriptions have been classified with OI type IV. Mutations in either *COL1A1* and *COL1A2*, respectively encoding the pro-α1 and pro-α2 chains of type I collagen, lead to bone fragility, blue sclerae, dentinogenesis imperfecta, ligament laxity and deafness [Byers and Steiner, 1992]. Various OI phenotypes arise from lethal to mild disease depending on the location and the nature of the mutation. DNA linkage studies have suggested that more than 90% of probands with OI have a mutation in *COL1A1* or *COL1A2* [Sykes et al., 1990]. OI is usually an autosomal dominant disorder, resulting from inheritance of a mutant gene or from a de novo mutation. However, autosomal recessive cases of OI have been reported, with altered *COL1A2* only [Nicholls et al., 1984; Piihlajaniemi et al., 1984; Spotila et al., 1992; De Paepe et al., 1997]. Moreover, 6% of sporadic OI cases are due to mosaicism in one parent. In addition recent proposed classifications have added types V–VIII (vide infra).

OI with autosomal recessive inheritance has been reported in various ethnic groups with high rates of consanguinity: the black population of South Africa [Beighton and Versfeld, 1985], an Irish family [Williams et al., 1989] and the American Indian population [Ward et al., 2002]. *COL1A1* and *COL1A2* have been excluded as the OI-causing genes in these populations. Various autosomal recessive cases of atypical OI associated with specific clinical signs have also been described [Viljoen et al., 1989; Bank et al., 1999; Gong et al., 2001; Morello et al., 2006; Cabral et al., 2007]. Here, we report on another inbred family with an improving OI in which DNA studies have excluded the involvement of the type I collagen genes.

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CLINICAL REPORTS

The propositus was born at term after a normal pregnancy (birth weight (BW) = 3,230 g, birth length (BL) = 49 cm, occipito-frontal head circumference (OFC) = 34 cm). OI was suspected at birth because of metaphyseal fractures in the tibias, the femora, the radius and the ribs. Radiographs at birth showed wide sutures with wormian bones (Fig. 1A), enlarged and rounded metaphyses with fractures and mild bowing of the tibias (Fig. 1B). Vertebrae seemed to be normal, with cupped anterior rib ends and fragmentation (Fig. 1C). The distal end of the radius was fractured when the boy was two months old (Fig. 1D). He suffered pain at four months of age; spinal radiographs showed flattened biconcave vertebral bodies and severe osteoporosis (Fig. 2A). The long bones were wide, large and short with external periosteal thickening and enlarged, sclerotic metaphyses (Fig. 2B). Poor mineralization of the long bones with enlarged metaphyses, but thinner diaphyses were observed at 3 years of age: the tibia and the femora were bowed, the fibula was very slender and a coxa vara had improved (Fig. 3). He had a limited extension of the hips and the knees and could not walk until the age of three. No treatment (bisphosphonates or surgical treatment) was administered. At this age, his height was 81 cm (−3 SD). Along with modifications of his vertebral bodies, no other fracture of the long bones occurred.

Now 7 years old, no other fractures have occurred and the child had a normal life, with no bone deformation and no restriction of physical activities. The radiographs showed improvement of the eversion of the femoral neck; the vertebral bodies are quite normal in height but still osteopenia (Fig. 4). He has blue sclerae, but no dentinogenesis imperfecta. Calcium and phosphorus metabolism was investigated at birth and 1 and 2 years later. Serum calcium, inorganic phosphorus, creatinine, and alkaline phosphatase levels were measured by classic colorimetric methods and were normal. Serum parathyroid hormone (Bio-Intact PTH 1-84 Nichols Advantage), hydroxyvitamin D (25-OH D), 1, 25-dihydroxyvitamin D (Liaison 25-OH vitamin D Diasorin), and osteocalcin (N-MID osteocalcin, Modular Analytics, Roche) levels were also normal, as determined by radioimmunoassays.

The second patient, the 44-year-old father of the propositus, had multiple fractures during his first years of life, difficulty acquiring walking skills and a long stay in the hospital. These clinical features gradually disappeared (no radiographs from this period are available). However, he had blue sclerae and dentinogenesis imperfect and was short in stature (160 cm). He did not develop deafness. Radiographs showed mild osteopenia, deformities of the right femora secondary to childhood fractures and a short right femoral neck.

The 38-year-old mother of the propositus had normal height (159 cm). She had no fractures, dental defect or deafness. Radiographs of her long bones and her skull were normal (no wormian bones were present). The propositus has two healthy brothers without any clinical abnormalities, without wormian bones and with normal vertebral radiographs. The family originated from Algeria and has three consanguinity loops (Fig. 5).

The propositus and his father are considered to be affected by the same form of OI with an improving course: severe modification of the long bones with complete improvement during growth. The consanguinity prompted us to consider an autosomal recessive inheritance. Thus, we hypothesized that the propositus and his father are homozygous for a genetic defect and the propositus' mother is heterozygous for this defect.

MATERIALS AND METHODS

Genomic DNA was extracted from peripheral blood leukocytes by standard methods. Fibroblasts were derived by outgrowth culture from skin biopsy obtained from the proband. Total RNA from these fibroblasts was extracted with the RNeasy Midi Kit (Qiagen, Valencia, CA). *COL1A1* and *COL1A2* cDNAs were synthesized by priming with random hexamers in the presence of MutV reverse transcriptase according to the manufacturer's protocol (GenAmp RNA PCR Core Kit, Roche GmbH, Mannheim, Germany). Amplification cycles consisted of an initial denaturation at 94°C for 5 min, followed by 30 cycles (94° for 30 sec, temperature of annealing for 30 sec, 72° for 30 sec) and a final extension step at 72°C for 7 min.

Denaturing high performance liquid chromatography (DHPLC) was used to search for *COL1A1* and *COL1A2* mutations. PCR fragments with abnormal DHPLC profiles were sequenced with the Big Dye Terminator Cycle Sequencing kit V2 (AB1 Prism, Applied Biosystems, Foster City, CA) on a 3100 automated sequencer.

CRTAP sequencing was performed using genomicDNA on a 3100 automated sequencer according to the same protocol.

Microsatellite analyses were carried out as described previously [Belin et al., 1998] and primers for chromosome regions 7q22.1 and 17q21.3-q22.1 were chosen from the Genethon map [Dib et al., 1996]. Linkage to the disease loci in the family was tested with microsatellites at flanking loci D17S806, D17S1827, D17S1795, D17S943 (*COL1A1*), and D7S2410, D7S657, D7S479 (*COL1A2*), and D1S2861, D1S2713, D1S2797 (LEPRE1).

Northern blot analysis of RNA from the two patients was carried out.

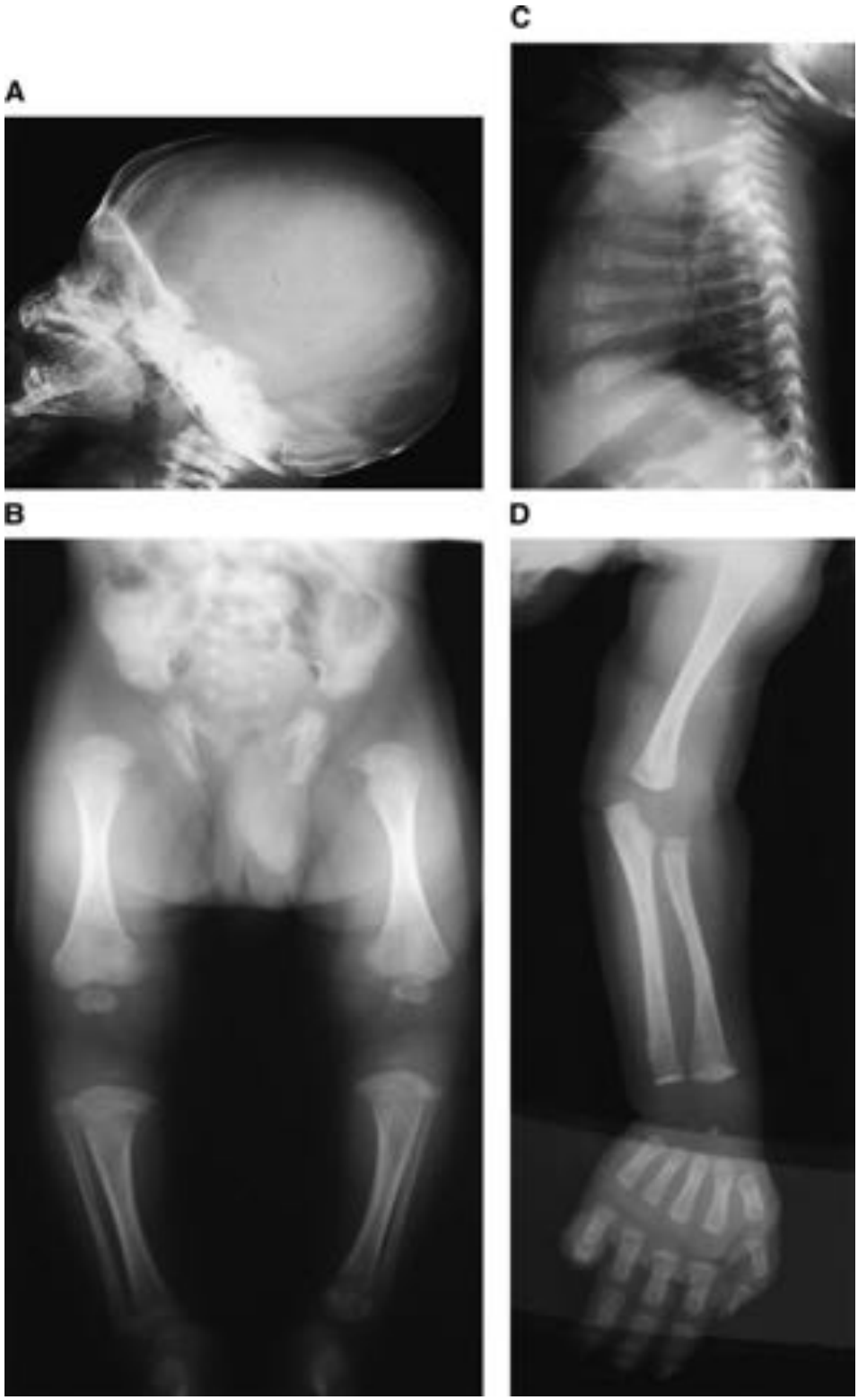

FIG. 1. Radiograph examination of the propositus at birth and 2 months old. **A**: Skull radiograph showing wide sutures and wormian bones. **B**: Lower limb radiograph showing mild bowing of the tibias, enlarged and round metaphyses, normal cortical thickness. **C**: Spinal radiograph with multiple vertebral collapses in the lumbar spine with osteoporosis. **D**: Upper limb radiograph with distal end of the radius fractured.

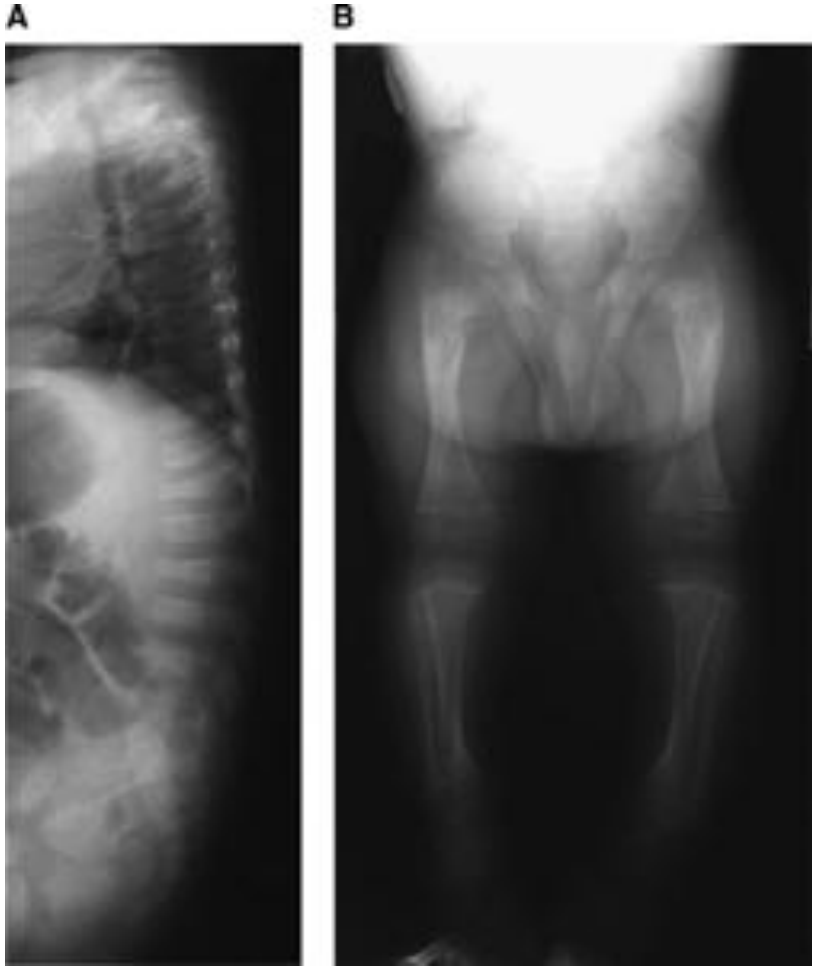

FIG. 2. Radiograph examination of the propositus at 4 months old. **A**: Spinal radiograph showing flattened biconcave vertebral bodies and severe osteoporosis. **B**: Lower limb radiograph showing the stubby long bones with external periosteal thickening, thin cortices, sclerotic metaphyses, and coxa vara.

A genome-wide screen in the two patients was conducted with 1,095 markers (average spacing = 4 cM; average heterozygosity = 0.75) from the deCODE protocol (deCODE, Reykjavic, Iceland) [Nievergelt et al., 2004; Aslam et al., 2005] to determine whether the two patients were homozygous for the same marker alleles. Twenty-seven additional markers were used in chromosome 11.

RESULTS

Microsatellite analyses did not detect linkage of the disease gene to chromosome regions 7q22.1 and 17q21.3-q22.1. The affected child and one healthy brother inherited the same paternal and maternal chromosome in these regions (Fig. 6). DHPLC analysis and cDNA sequencing showed no evidence of sequence alterations in *COL1A1* and *COL1A2* cDNAs. There were no quantitative or qualitative alterations of *COL1A1* or *COL1A2* mRNAs identified by Northern blot analysis.

Sequencing showed no evidence of sequence alterations in *CRTAP* genomic DNA. The propositus and his father were heterozygous for markers surrounding *LEPRE1*.

Homozygosity mapping was suitable for localizing the gene underlying this disorder because there were two affected inbred patients. This mapping approach is based on the inheritance of two identical copies of the disease locus by the affected inbred subjects from a common ancestor, that is, homozygosity by descent [Lander and Botstein, 1987]. The genome-wide screen showed homozygosity for 130 of 1,095 markers in the propositus and his father. We identified these homozygous markers on 21 autosomes. There were clusters of adjacent homozygous markers in chromosome 11, in one candidate region.

The region is between D11S4127 and D11S4094 (11q23.3–11q24.1). It includes 5.7 megabases (Mb) containing 48 genes and 30 pseudogenes. Seven consecutive markers in this region are homozygous in the propositus and his father. No two consecutive

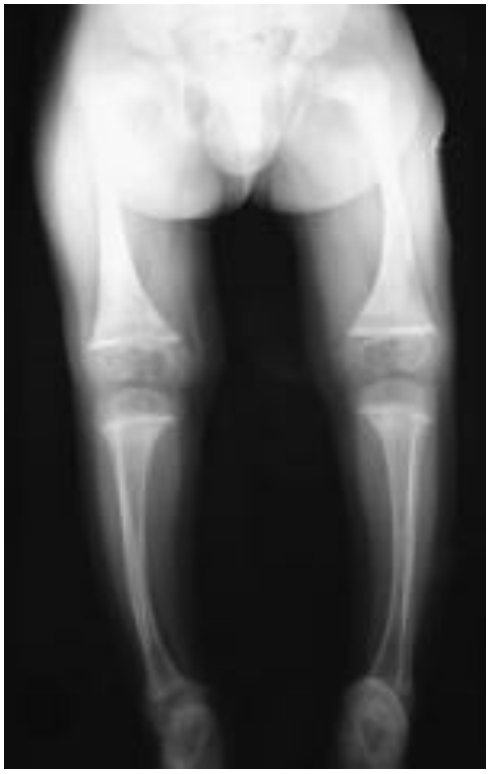

FIG. 3. Lower limb radiograph examination of the propositus at 3 years old showing enlarged metaphyses, but thinner diaphyses, bowed tibia and femora and an improved coxa vara.

markers were homozygous in other regions of the genomes of these two patients.

DISCUSSION

Our two patients had fragile bones, wormian bones, dental abnormalities, and blue sclerae. They were short in stature and had delayed acquisition of walking skills. These characteristics are consistent with OI, but radiographs of the long bones were not typical. Indeed, stubby shaft with metaphyseal breakage and irregularities and severe early onset platyspondyly with codfish vertebral bodies are uncommon features of OI. A diagnosis of OI type IV was considered for the propositus at birth; however, the outcome of the disease with an improving course does not fit typical OI type IV.

Most individuals with OI are heterozygous for mutations in *COL1A1* and *COL1A2*. However, *COL1A1* and *COL1A2* failed to segregate with the disease in the patients reported here. There was no mutation in *COL1A1* and *COL1A2*, as determined by DHPLC analysis and cDNA sequencing. Moreover, Northern blot analysis did not indicate quantitative or qualitative abnormalities in collagen I mRNAs. Thus, these patients do not have an autosomal dominant *COL1A1* or *COL1A2* mutation, either homogenous or arising due to mosaicism.

Three new types of OI with normal collagen type I have been described in recent years. The first newly identified type is type V which was described in seven OI patients [Glorieux et al., 2000] who would typically be classified as having OI type IV, but which can be distinguished from other type IV patients. This type is characterized by moderate-to-severe bone fragility. Inheritance seems to follow an autosomal dominant pattern, but there is no evidence of collagen type I abnormality. The interosseous membrane at the forearm becomes calcified early in life, severely limiting hand movement. These patients are predisposed to develop a hyperplastic callus after fractures and surgical procedures. Between four and five percent of OI patients have type V. The second newly identified type is type VI, also a moderate-to-severe form of OI [Glorieux et al., 2002]. This type was defined by specific histological findings: a higher than usual amount of osteoid and an abnormal lamellation pattern, suggesting abnormal mineralization of bone tissue. It is estimated that between four and eight percent of clinically diagnosed OI patients have type VI [Glorieux et al., 2002]. The mode of inheritance of OI type VI has not been established [Rauch and Glorieux, 2004]. The third newly identified type is type VII. This is a recessive disorder which has been reported only in a community of Native Americans in Northern Quebec [Ward et al., 2002]. Rhizomelia is a prominent clinical feature of this type and coxa vara can be present even in infancy. The 3p22-24.1 region of chromosome 3 has been implicated in this disease [Labuda et al., 2002] which is associated with a homozygous defect in *CRTAP* (cartilage-associated protein gene) [Morello et al., 2006]. A form of autosomal recessive OI was recently described and designed as OI type VIII [Cabral et al., 2007]. This form is characterized by white sclerae, severe growth deficiency, extreme skeletal undermineralization and bulbous metaphyses. This bone dysplasia is caused by mutation in the *LEPRE1* gene. Prolyl 3-hydroxylase, the product of the *LEPRE1* gene forms a complex with cartilage associated protein and cyclophilin B and hydroxylates a single proline of the Col1a1 chain.

We describe here a new disease entity including wormian bones, blue sclerae, increased bone fragility early in childhood and an improving course in homozygous patients. However, this new OI can be distinguished from other forms by distinctive clinical and molecular characteristics. Such patients could be classified as having OI type IV by the Sillence system. This may reflect the fact that many patients are difficult to classify with certainty within the current system. Whether the phenotype we describe here should be considered a novel form of OI, as proposed in this report, or a new syndrome

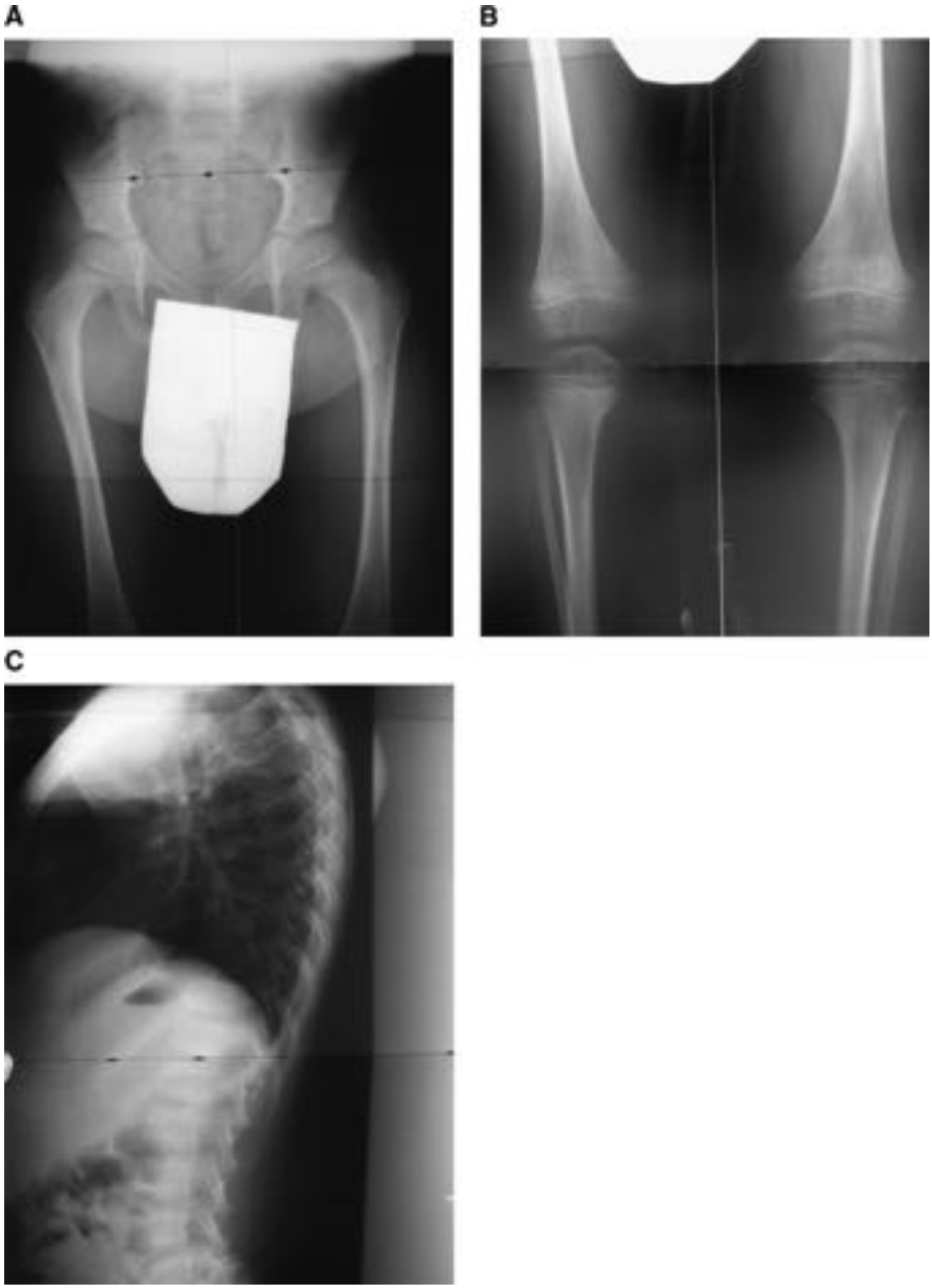

FIG. 4. Radiograph examination of the homozygous patient at 7 years old. **A**: Hips: see mild eversion of the femoral neck with striation. **B**: Knee with osteoporosis and mild flaring of the metaphyses. **C**: Lateral spine showing improvement of the platyspondyly; the vertebral bodies are quite normal in height but still osteoporotic.

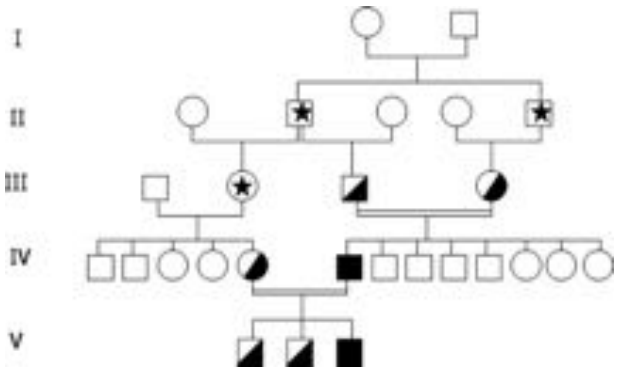

FIG. 5. Pedigree of the family. The black stars indicate possible heterozygosity of these family members, according to autosomal recessive inheritance.

that is similar to OI is subjective. We based the diagnosis of OI on clinical findings, whether or not mutational analysis showed a collagen defect. This is consistent with OI being a hereditary disorder (or group of disorders) with osteopenia and fragile bones. However, various authors present OI as a "type I collagenopathy" [Byers and Steiner, 1992]. The idea that OI should be equated with collagen type I mutations derives its support mainly from linkage analyses, which conclude that more than 90% of typical familial OI cases were linked to collagen type 1 genes [Sykes et al., 1990]. Recently, two other genes responsible for post-translational modification (prolyl 3-hydroxylation) of collagen I were found to be implicated in OI forms [Morello et al., 2006; Cabral et al., 2007]. Indeed, our patients do not have clinical signs associated with OI types V, VI, VII, and VIII. This new entity is also different from various primary skeletal disorders that can be confused with OI. Four of these skeletal disorders are autosomal recessive disorders [Beighton et al., 1985; Mc Pherson and Clemens, 1997; Roughley et al., 2003]. In support of the clinical resemblance of these disorders and OI, Bruck syndrome has been called OI with congenital joint contractures and osteoporosis-pseudoglioma syndrome and has been called an ocular form of OI [Beighton et al., 1985; Mc Pherson and Clemens, 1997; Roughley et al., 2003]. These syndromes are associated with bone-specific telopeptide lysyl hydroxylase deficiency and LDL-receptor-related protein 5, respectively [Gong et al., 2001; Ha-Vinh et al., 2004]. Idiopathic autosomal recessive hyperphosphatasia, also known as juvenile Paget disease, is characterized by a high rate of bone turnover and by inactivating mutations of the osteoprotegerin gene [Middleton-Hardie et al., 2006]. It is usually easily distinguished from OI radiologically and on the basis of very high serum alkaline phosphatase activity. Hypophosphatasia (low serum alkaline phosphatase activity) has a wide range of clinical expressions, from stillbirth without mineralized bone through metaphyseal abnormalities in early life to pathological fractures that develop late in adulthood only. This disease is caused by mutations in the alkaline phosphatase liver-type gene [Spentchian et al., 2006]. Our patients do not have clinical, radiological or biological signs of these diseases. Moreover, the gene responsible for this novel form of OI is on long arm of chromosome 11.

We describe a consanguineous family with an improving course of bone fragility associated with blue sclerae, the most prominent features of OI. Genetic defects of *COL1A1/COL1A2*, *CRTAP*, and *LEPRE1* are not involved. The underlying molecular mechanisms are still unknown. The causal mutation in this family is unknown and may be in an extracellular matrix component gene involved in bone morphogenesis or metabolism or in genes controlling type I collagen processes and maturation, as in Bruck syndrome and OI type VII or VIII. The gene implicated in this new OI form is located on the

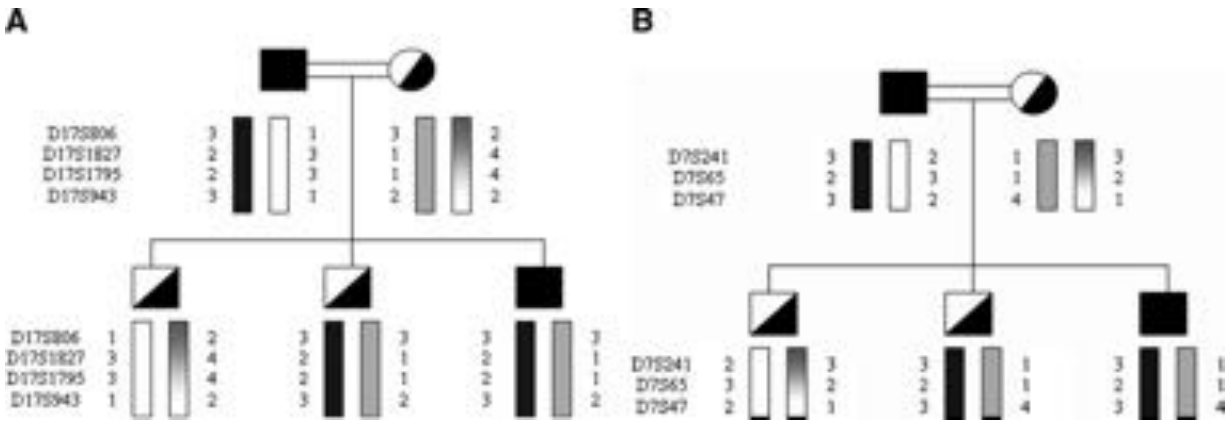

FIG. 6. Pedigree and genotypes of *COL1A1* and *COL1A2* regions. **A**: Pedigree and genotypes of *COL1A1* regions for the propositus, his two healthy brothers, and his mother and father; the propositus has similar alleles with healthy brother. **B**: Pedigree and genotypes of *COL1A2* regions for the propositus, his two healthy brothers, and his mother and father; the propositus has similar alleles with healthy brother.

long arm of chromosome 11, and 1 of 48 genes in the region identified by the genome-wide screen.

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