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Osteogenesis Imperfecta Type VII: An Autosomal Recessive Form of Brittle Bone Disease

L. M. WARD,[1] F. RAUCH,[1,3,4] R. TRAVERS,[1] G. CHABOT,[1] E. M. AZOUZ,[2] L. LALIC,[1] P. J. ROUGHLEY,[1,4] and F. H. GLORIEUX[1,3,4]

[1]*Genetics Unit, Shriners Hospital for Children, Montréal, Québec, Canada*
[2]*Department of Radiology, Montréal Children's Hospital and Shriners Hospital for Children, McGill University, Montréal, Québec, Canada*
Departments of [3]*Pediatrics and* [4]*Surgery, McGill University, Montréal, Québec, Canada*

Osteogenesis imperfecta (OI) is a heritable disease of bone with low bone mass and bone fragility. The disease is generally classified into four types based on clinical features and disease severity, although recently fifth and sixth forms have also been reported. Most forms of OI are autosomal dominant. Rarely, autosomal recessive disease has been described. We report the clinical, radiological, and histological features of four children (age 3.9–8.6 years at last follow-up; all girls) and four adults (age 28–33 years; two women) with a novel form of autosomal recessive OI living in an isolated First Nations community in northern Quebec. In keeping with the established numeric classification for OI forms, we have called this form of the disease OI type VII. The phenotype is moderate to severe, characterized by fractures at birth, bluish sclerae, early deformity of the lower extremities, coxa vara, and osteopenia. Rhizomelia is a prominent clinical feature. Histomorphometric analyses of iliac crest bone samples revealed findings similar to OI type I, with decreased cortical width and trabecular number, increased bone turnover, and preservation of the birefringent pattern of lamellar bone. The disease has subsequently been localized to chromosome 3p22-24.1, which is outside the loci for type I collagen genes. The underlying genetic basis for the disease remains to be determined. (Bone 31:12–18; 2002)

Key Words: Autosomal recessive; Bone fragility; Osteogenesis imperfecta (OI).

Introduction

Osteogenesis imperfecta (OI) is a congenital disorder characterized by low bone mass and increased bone fragility. Four different types are commonly distinguished on the basis of clinical features and disease severity.[24] Patients with OI type I have a mild phenotype with normal or near-normal height and typically blue sclerae, whereas 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 the aforementioned descriptions are classified with OI type IV.

This latter group is heterogeneous and likely comprises patients suffering from a variety of different OI forms. Among these, we have recently described a disease entity that we have named OI type V.[12] This is a moderate-to-severe form of OI with an autosomal dominant inheritance, which is characterized by hypertrophic callus formation, calcification of the interosseous membrane of the forearm, and a mesh-like appearance of the bone matrix on histological sections. Another novel phenotype that has emerged from the OI IV group, named OI type VI, features osteopenia and bone fragility due to a mineralization defect, in the absence of any abnormality in mineral metabolism.[14] The inheritance of this form of OI is not yet known.

In the majority of families with OI, the disease is associated with mutations in one of the two genes that encode collagen type I α chains, COL1A1 and COL1A2, and heritability follows an autosomal dominant mode of transmission.[5,22,25] However, autosomal recessive transmission has been described in rare kindreds.[1,3,5,8,9,26–28] In this study we describe a new form of recessively inherited OI with unique phenotypic characteristics, which is evident in a small, consanguineous First Nations community. We report the clinical, radiological, and histological features of the disease in eight affected family members. We propose the term "OI type VII" for this disorder, in keeping with the numeric classification for OI forms.[12,14] Linkage and protein studies, with localization of the disease to chromosome 3p22-24.1,[11] outside the loci for COL1A1 and COL1A2, are described in detail elsewhere.[16]

Subjects and Methods

Patient and Control Groups

Eight affected members were identified in a First Nations community from the province of Québec, consisting of 2500 individuals. Detailed clinical and radiological studies were performed in four girls (patients V-3, V-5, V-6, and V-7; **Figure 1**). These children first presented at our institution at between 2 weeks and 2.5 years of age and were subsequently followed at regular intervals. The aim of the present report is to describe the natural evolution of the disease when the girls were between 3.9 and 8.6 years of age. In addition to these children, we report the clinical and radiological findings in four affected adults (patients IV-3, IV-15, IV-22,

Address for correspondence and reprints: Dr. Francis H. Glorieux, Genetics Unit, Shriners Hospital for Children, 1529 Cedar Avenue, Montréal, Québec H3G 1A6 Canada. E-mail: glorieux@shriners.mcgill.ca

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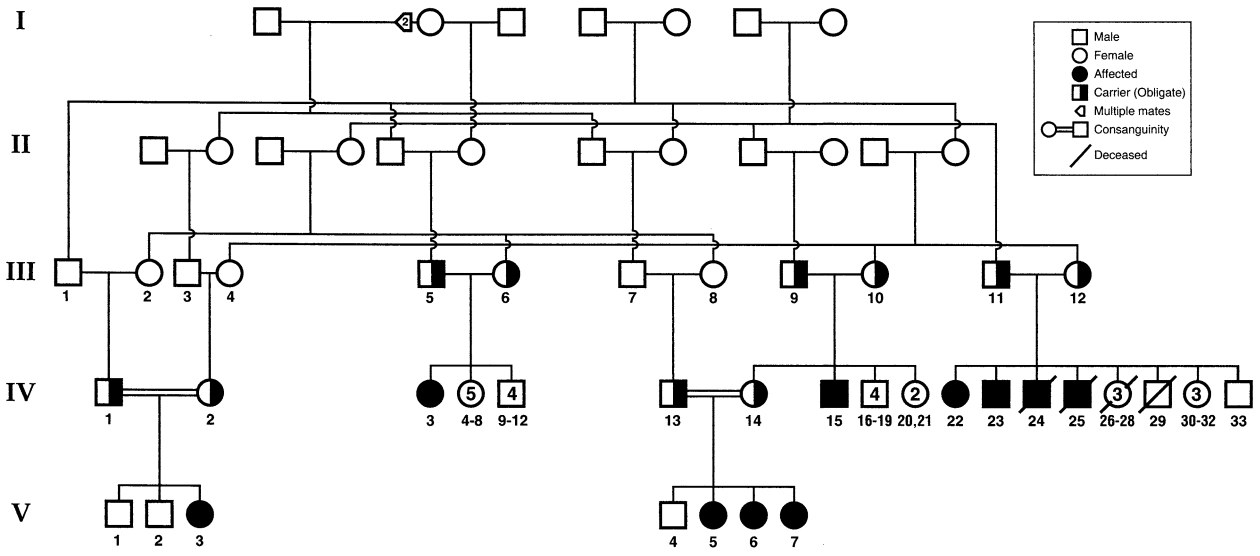

Figure 1. Pedigree of the First Nations community from Quebec with OI type VII. All affected individuals (patients V-3, V-5, V-6, V-7, IV-3, IV-15, IV-22, and IV-23) described were born in the last two generations.

and IV-23; Figure 1), who were seen only once. The adults' ages ranged from 28 to 33 years at the time of evaluation.

The control population for histomorphometric analyses consisted of six age-matched children (age 2.1–4.5 years; 2 girls), who were part of a group that has previously been described in detail.[13] Anthropometric, densitometric, and histomorphometric findings in the four girls described here were also compared with those in nine age-matched children with OI type I (aged 2.6–4.9 years; 2 girls). Histomorphometric results in these children were published previously.[20] To compare limb length measurements with unaffected members of the community, three healthy adult women from the same community were also investigated radiologically.

Clinical Evaluation

The four affected children were seen at least once a year in our hospital department. Clinical examination, biochemical measurements, and areal bone mineral density (aBMD) analyses were performed at each visit. Birth and fracture histories were obtained from the parents. For consistency, anthropometric measures and aBMD results are given at the time of biopsy. Results for height and weight were transformed to chronological age- and gender-specific *z* scores using growth curves for Canadians of white ethnic extraction.[4,15] Normative growth curves for this First Nations population were not available. X-ray surveys of the entire skeleton were obtained at the time of first presentation. Thereafter, radiological imaging studies were performed when required for clinical management. None of the participants in the present study had received pharmacological treatment other than vitamin and calcium supplementation in the 6 months preceding the bone biopsy. Informed consent was obtained in each instance from the subject and/or a legal guardian, as appropriate. The study protocol was approved by the ethics committee of the Shriners Hospital.

Biochemical Measurements

Serum calcium, inorganic phosphorus, creatinine, and alkaline phosphatase levels were measured using colorimetric methods (Monarch, Instrumentation Laboratory, Inc., Lexington, MA). Serum parathyroid hormone levels were determined by radioimmunoassay.[6] Osteocalcin was quantified with an immunoradiometric assay (N-tact Osteo SP; DiaSorin, Stillwater, MN). 25-Hydroxyvitamin D (25-OHD) and 1,25-dihydroxyvitamin D [$1,25(OH)_2D$] were measured with radioimmunoassays (Osteo SP; DiaSorin). Urinary creatinine and calcium levels were measured colorimetrically and urinary cross-linked N-telopeptides of type I collagen concentrations were assessed by enzyme-linked immunoabsorbent assay (Osteomark, Ostex, Seattle, WA) on the second void sample in the morning. Patients were fasting at the time of blood and urine sampling.

Radiological Studies

Areal BMD and coronal area in the anteroposterior direction were determined at the lumbar spine (L1–4) using a Hologic QDR 2000W device (Hologic, Inc., Waltham, MA; entrance radiation dose <5 mRem). Results for aBMD were transformed to age-specific *z* scores combining reference data provided by the densitometer manufacturer and from Salle et al.[23]

Measurement of long bone lengths (humeri, radii, tibiae, and femora) was performed according to the guidelines set forth by Maresh.[18] For the children, the measurements were made between the epiphyseal plates. For the adults, measurements were taken from the most proximal edge of the upper epiphysis to the most distal edge of the lower epiphysis. Two modifications to the measurement guidelines outlined by Maresh[18] were made. First, the bowing deformity was taken into account by including the length of the curvature, instead of measuring along a vertical axis from the proximal-to-distal ends of the long bones. Second, due to the coxa vara, the lengths of the femora were measured from the proximal edge of the upper epiphysis, along the long axis of the femoral neck and femoral diaphysis, to the distal edge of the lower epiphysis. The measurements were compared with normative data based on information from white children living in the United States.[18,21] There were no such data available for this First Nations community. The lengths of long bones from three unaffected members of this

Table 1. Fracture history and clinical characteristics

Patient	Age (years)[a]	Number of fractures[b]	Long bone deformity	Rodding	Ambulation
Children					
V-3	5.3	3	Femora at birth, tibiae at 7 months	Femora, tibiae	Walking since age 5 years, 3 months
V-5	8.5	7	Femora, tibiae at birth	Femora	Walking since age 25 months
V-6	8.6	7	Femora, tibiae, humeri at birth	Femora, tibiae	Walking since age 30 months
V-7	3.9	8	Femora, tibiae, left humerus at birth	Femora, tibiae	Walking since age 36 months
Adults					
IV-3	28	NA[c]	Right femur, humeri, tibiae	Pinning femora	Walks with assistance of a cane
IV-15	29	20	Tibiae, humeri	Femora (left tibia in past)	Walks unassisted
IV-22	33	40	Left femur, tibiae, humeri	Right femur	Wheelchair
IV-23	31	40	Femora, tibiae, humeri	Femora (tibiae in past)	Wheelchair

[a]At last follow-up prior to medical treatment.
[b]Excluding fractures present at birth.
[c]Not available.

First Nations community were also performed for comparison. Two of these unaffected subjects are obligate carriers for the trait (subjects IV-2 and IV-14; Figure 1).

Bone Histomorphometry

Bone histomorphometry was performed as described in detail previously.[13] Full-thickness transiliac bone biopsies were obtained with a Bordier trephine (5 or 7 mm core diameter) needle under general anesthesia, from a site located 2 cm below and behind the anterior superior iliac spine. Biopsies were collected on the fourth or fifth day after dual-tetracycline labeling (Declomycin, 15–20 mg/kg per day, Wyeth-Ayerst Canada, Inc., Montréal, Canada).

Statistical Analysis

Differences between the patients with OI type VII and controls or the OI type I group were tested for significance using Student's unpaired *t*-test. All tests were two-tailed, and throughout the study $p < 0.05$ was considered statistically significant. These calculations were performed using SPSS software, version 6.0 for Windows (SPSS, Inc., Chicago, IL).

Results

Description of Pedigree

Eight affected subjects from three interrelated families were identified in a First Nations community of about 2500 individuals living in the province of Québec (Figure 1). Only four patronyms were present in the pedigree, suggesting a high degree of consanguinity, and the inheritance was in keeping with an autosomal recessive pattern. All eight patients presented here were born in the last two generations (generations IV and V) as indicated in the pedigree.

Clinical Evaluation

Birth history could be obtained from the four pediatric patients only. All children were born at term. Birth was by spontaneous vaginal deliveries from the vertex position for patients V-3 and V-6. Patients V-5 and V-7 presented in the breech position, for which patient V-7 was delivered by cesarean section. Birth weight ranged from 2990 to 4005 g, and birth length was 53 cm and 52.5 cm in patients V-3 and V-6, respectively, but was not available for the other girls. Multiple fractures were present at birth in all children. None developed respiratory insufficiency in the postnatal period.

Fracture history and clinical findings are summarized in **Table 1**. Recurrent fractures occurred in all patients, but the adult patients reported that fractures had been rare after puberty. Fractures and bowing deformity led to intramedullary rodding or pinning in all eight patients. All of the children, but only one of the four adults, were ambulatory without assistance. None of the patients had dentinogenesis imperfecta or ligamentous laxity. The skin and hearing were normal, and the sclerae were minimally bluish. None had been diagnosed with cardiac or other anomalies. There was no facial dysmorphism. Two brothers with the phenotype (patients IV-24 and IV-25) died in early childhood. Precise details regarding the causes of death were unavailable.

Table 2. Radiological features

Patient	Coxa vara	Vertebral compression fractures	Scoliosis
V-3	Left	Th[a]-2–10	No
V-5	Bilateral	Th-6, Th-7, Th-9	Minimal
V-6	Right	None	Mid-lower thoracic, convex right (24°)
V-7	Bilateral	Th-3, Th-6, Th-8, Th-12	Minimal
IV-3	Left with protrusio acetabula	None	Mid-lower thoracic, convex right (39°)
IV-15	Bilateral with protrusio acetabulae	Multiple middle and lower thoracic	NA[b]
IV-22	Bilateral with protrusio acetabulae	None	NA
IV-23	Bilateral with protrusio acetabulae	Th-11, Th-12, lumbar	NA

[a]Thoracic.
[b]Not available.

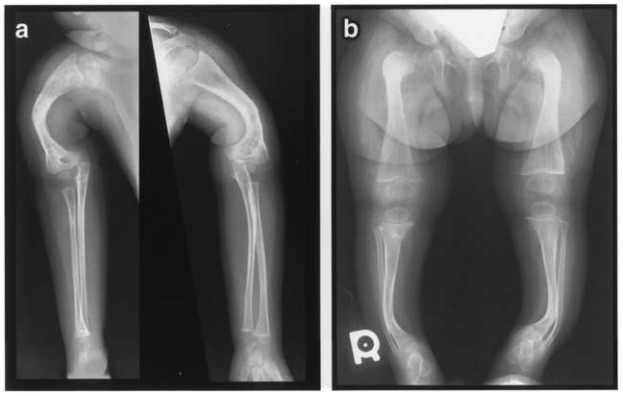

Figure 2. (a) Patient V-3, age 3 years 5 months, showing selective shortening of the humeri (rhizomelia). (b) Patient V-6, age 4 months, showing bilateral coxa vara. Bowing deformity of the lower extremities is also evident.

Radiological Studies

Qualitative radiological features are presented in **Table 2** and in **Figure 2**. The most striking findings were the presence of rhizomelia (selective shortening of proximal limb segments, Figure 2a) and coxa vara (Figure 2b) in all affected patients. The coxa vara was bilateral in five patients, and it was present as early as 4 months of age for patient V-7. Patients V-5 and V-7 underwent bilateral hip valgus osteotomies for this reason. Bowing of the upper and lower extremities was detectable at an early age; the presence of scoliosis and vertebral compression was variable. Skull radiographs (performed only in the children) revealed Wormian bones in patients V-3 and V-5. To obtain a quantitative measure of rhizomelia, the lengths of the radii, humeri, tibiae, and femora were measured on X-rays. Results were compared with age-specific reference ranges for whites.[18,21] Humeral and femoral lengths were markedly below the tenth percentile in all patients. Because radial length was within or close to the reference range, the radius/humerus length ratio was clearly abnormal in all patients (**Figure 3**). Tibial length was normal in all children during the first year of life, but was decreased in the adult patients. The lengths of the tibiae were also found to be decreased for patient V-3, when she underwent a second evaluation at the age of 4.3 years. Tibia/femur length ratios were increased in all children and in half of the adults' legs (Figure 3). In three unaffected members from the same community, the length of all measured bones was within or slightly above the reference range (Figure 3), showing that the findings in the OI patients were not just the result of population-specific differences in limb development.

In three of the four children, lumbar spine aBMD was within the normal range early on, but fell below the lower limit of normal over time (**Figure 4**). The lumbar spine aBMD in one patient (patient V-3) was low initially and did not increase as expected with age. Body height, aBMD, and vertebral size were comparable to patients with OI type I (**Table 3**). Lumbar spine aBMD (L1–4) was normal in the parents of these children (subjects IV-1, IV-2, IV-13, and IV-14). These findings, combined with the normal long bone lengths for unaffected family members, indicate that obligate heterozygotes are not clinically affected.

Biochemical Studies

There were no abnormalities in the serum levels of calcium, inorganic phosphorus, alkaline phosphatase, parathyroid hormone, osteocalcin, creatinine, 25-OHD, and $1,25(OH)_2D$. Similarly, the urinary excretion of calcium and cross-linked N-telopeptides of type I collagen was normal.[2]

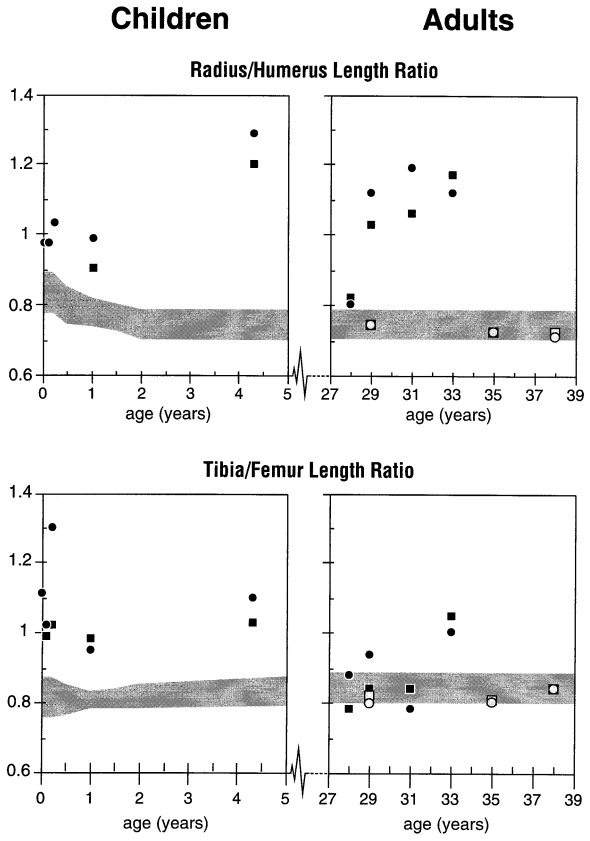

Figure 3. Radius/humerus and tibia/femur lengths. Filled circles: affected patient, left side; filled squares: affected patient, right side; open circles: normal control from same community, left side; open squares: normal control from same community, right side. The normal range for age is shown in the shaded region (5th–95th percentile).

Bone Histology and Histomorphometry

Inspection of sections from iliac crest bone samples revealed a decreased amount of both cancellous and cortical bone (**Figure**

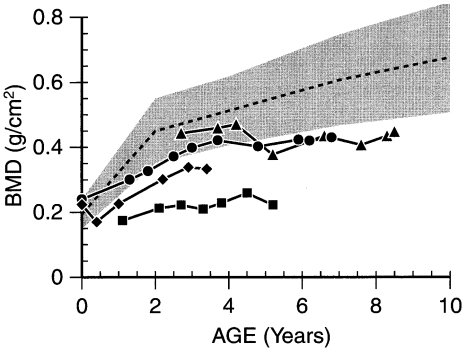

Figure 4. Bone mineral density values for the four affected girls. Squares: patient V-3; triangles: patient V-5; circles: patient V-6; diamonds: patient V-7. The normal range for age is shown in the shaded region.

Table 3. Anthropometric and densitometric results (results in children are compared with those in age-matched osteogenesis imperfecta (OI) type I patients at the time when bone biopsy was performed)

Patient	Age (years)	Height (*z* score)	Weight (*z* score)	aBMD (*z* score)	BMC (g)	Vertebral area (cm^2)
Children						
V-3	4.2	−2.7	−0.5	−4.8	6.1	23.4
V-5	2.7	−1.3	0.0	−1.3	8.1	18.2
V-6	3.4	−1.5	−0.9	−1.6	7.6	19.0
V-7	3.9	−2.8	−0.7	−3.1	8.2	24.7
Mean ± SD	3.6 ± 0.7	−2.1 ± 0.8	−0.5 ± 0.4	−2.7 ± 1.6	7.5 ± 1.0	21.3 ± 3.2
OI type I (n = 9)	3.8 ± 0.8	−1.1 ± 1.5	−0.8 ± 1.0	−3.1 ± 0.9	6.7 ± 1.8	19.7 ± 4.7
Adults						
IV-3	28.4	NA	NA	−2.8	33.2	40.5
IV-15	28.2	−4.7	−0.03	−3.6	40.7	58.4
IV-22	33.2	−4.7	0.0	−2.8	33.4	45.1
IV-23	31.6	−4.4	+1.2	−3.7	29.7	43.2

Values expressed as mean ± SD.
Differences between results in children and age-matched OI type I patients not significant ($p > 0.10$) for any parameter.
Key: aBMD, areal bone mineral density; BMC, bone mineral content; NA, not available.

5). Quantitative histomorphometric results are shown in **Table 4**. Compared with healthy controls, the size of the biopsy core tended to be smaller, and cortical width was about half the value seen in controls. Relative cancellous bone volume was decreased by 53%. This was due entirely to the decreased number of trabeculae, whereas trabecular thickness was preserved. All bone surface-based parameters of bone formation were markedly increased, but mineral apposition rate was decreased. The yearly turnover of bone tissue was almost twice as high as in controls. Similar to formation parameters, bone surface-based indicators of bone resorption were increased.

The histological appearance of the biopsies in OI type VII was similar to that of OI type I, although lamellation appeared to be better preserved in OI type VII (Figure 5). No significant histomorphometric differences were found between the two forms of OI (Table 4).

Discussion

Herein we have described a moderate-to-severe form of OI with autosomal recessive inheritance in an isolated First Nations community. Autosomal recessive OI has been evaluated previ-

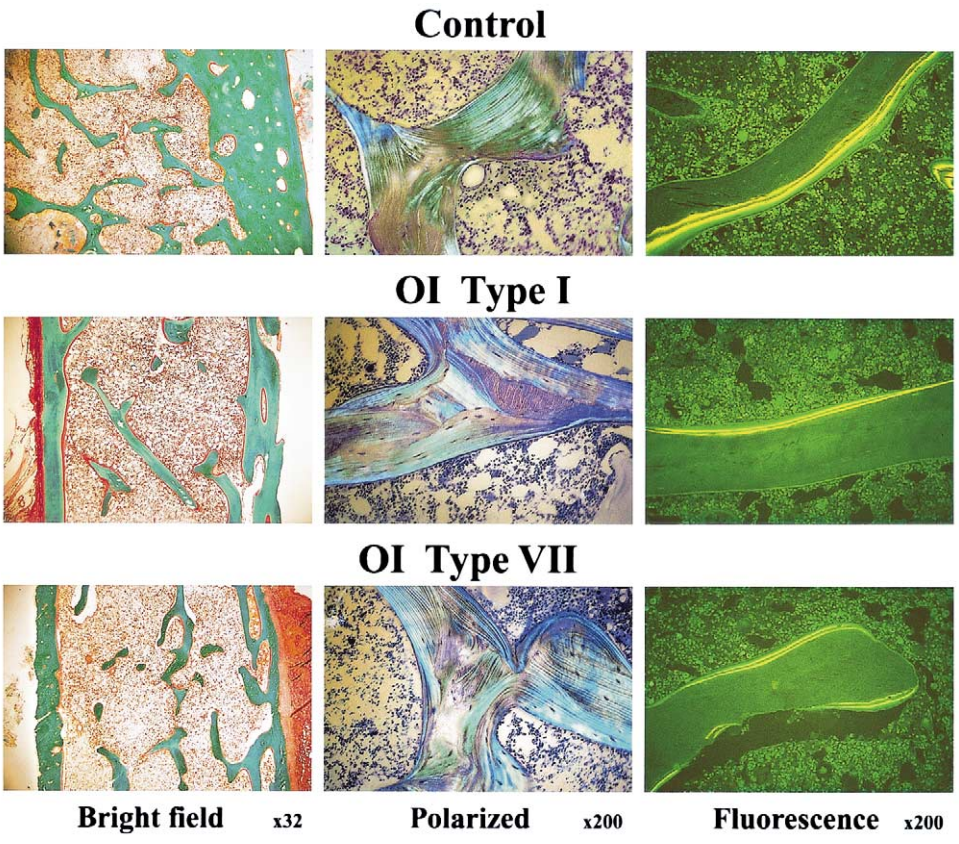

Figure 5. Bone histology from iliac crest, comparing OI type VII with normal controls and OI type I.

Table 4. Results of quantitative bone histomorphometry in four girls with osteogenesis imperfecta (OI) type VII, age-matched children without metabolic bone disease and OI type I patients

	OI type VII	Controls	OI type I	p(C)[a]	p(OI-I)[b]
n (female/male)	4 (4/0)	6 (2/4)	9 (2/7)		
Age (years)	3.6 ± 0.7	3.3 ± 0.8	3.8 ± 0.8	0.55	0.57
Structural parameters					
Core width (mm)	4.2 ± 0.3	5.7 ± 1.7	5.1 ± 1.3	0.08	0.08
Cortical width (mm)	0.38 ± 0.13	0.80 ± 0.28	0.40 ± 0.12	0.02	0.86
Bone volume/tissue volume (%)	12.3 ± 1.5	17.6 ± 3.4	10.7 ± 3.0	0.02	0.33
Trabecular thickness (μm)	101 ± 15	104 ± 12	84 ± 14	0.70	0.08
Trabecular number (/mm)	1.24 ± 0.17	1.71 ± 0.36	1.28 ± 0.34	0.04	0.81
Bone formation parameters					
Osteoid thickness (μm)	5.3 ± 0.8	5.5 ± 1.5	4.8 ± 1.5	0.80	0.64
Osteoid surface/bone surface (%)	53 ± 4	33 ± 7	48 ± 15	0.0006	0.38
Osteoid volume/bone volume (%)	5.5 ± 1.0	3.5 ± 1.1	5.7 ± 3.3	0.02	0.94
Osteoid surface/bone surface (%)	24 ± 2.3	7.4 ± 3.6	20 ± 15	<0.0001	0.49
Mineralizing surface/bone surface (%)	26 ± 5	10 ± 4	24 ± 13	0.0003	0.68
Mineralizing surface/osteoid surface (%)	50 ± 9	33 ± 13	47 ± 19	0.05	0.77
Osteoblast surface/osteoid surface (%)	45 ± 3	23 ± 12	39 ± 17	0.005	0.34
Mineral apposition rate (μm/day)	0.71 ± 0.12	0.99 ± 0.11	0.79 ± 0.23	0.006	0.54
Adjusted apposition rate (μm/day)	0.37 ± 0.12	0.33 ± 0.15	0.39 ± 0.20	0.67	0.84
Bone formation rate/bone surface ($\mu m^3/\mu m^2$/per year)	70 ± 21	38 ± 16	73 ± 47	0.02	0.90
Bone formation rate/bone volume (%/year)	135 ± 45	75 ± 35	166 ± 114	0.04	0.62
Mineralization lag time (days)	15 ± 4	19 ± 7	17 ± 12	0.35	0.83
Bone resorption parameters					
Osteoclast surface/bone surface (%)	2.3 ± 0.6	0.7 ± 0.3	1.7 ± 1.1	0.01	0.35
Erosion surface/bone surface (%)	22 ± 6	14 ± 4	20 ± 10	0.04	0.77

Values are mean ± SD; p values calculated by t-test.
[a] p(C), significance of difference between OI type VII patients and controls.
[b] p(OI-I), significance of difference between OI type VII patients and OI type I patients.

ously among pedigrees of such geo-origin as Pakistan,[1] Ireland,[28] South Africa,[27] Turkey,[3] and Australia.[24] This is the first example of autosomal recessive OI among Native Americans.

The phenotype described here is characterized by numerous fractures at birth, early deformities of the lower extremities, impaired growth, bluish sclerae, and absence of hearing loss or dentinogenesis imperfecta. This is a moderate-to-severe form of OI, because progressive deformity led to short stature and severe ambulatory restriction in two of the four adult patients.

There are two striking features of this novel phenotype, which were present in all patients: coxa vara and shortening of the humeri and femora. Coxa vara has been reported in OI,[17] but it has not previously been considered pathognomonic of one form of OI over another. The fact that bilateral coxa vara was present as early as 4 months of age for patient V-7 demonstrates that weight-bearing is not a prerequisite for the development of this deformity. Rather, there appears to be an intrinsic skeletal defect, which affects the morphogenesis of the cartilaginous template at the stage of skeletal patterning,[10] or which interferes with the growth of the proximal femoral epiphysis.

The second distinguishing feature of OI type VII is shortening of the proximal limb segments. Rhizomelia is the result of abnormally slow growth of humeri and femora, which, like congenital coxa vara, points toward a defect in patterning or growth of the proximal limb segment. The other skeletal elements appeared to grow normally in utero, as evidenced by normal birth weight and length. Postnatal growth of the tibiae also appeared to be affected, but this may have been the effect of applying load to a bone with decreased mechanical resistance rather than an intrinsic defect. This interpretation is also suggested by the fact that forearm growth appeared to proceed normally.

The constellation of phenotypic features detailed in this First Nations pedigree appear to be unique, in comparison with the three reported autosomal forms where linkage to the type I collagen genes has been absent.[1,27,28] The Irish pedigree with three lethally affected children, as described by Williams et al.,[28] demonstrated coxa vara and blue sclerae, but in this kindred hyperextensible skin and join laxity were also noted. These clinical findings are in keeping with the overhydroxylation of type I collagen components that was found[28] despite absence of linkage to the COL1A1/COL1A2 genes.[7] Aitchison et al.[1] described a Pakistani child, born to consanguineous parents, with shortening and deformity of all four limbs, although selective shortening of the proximal limb segments was not mentioned. Flattening of the facies appeared to be a unique feature. Finally, South African autosomal recessive pedigrees,[27] wherein type I collagen protein studies were normal, demonstrated white sclerae and variable dentinogenesis imperfecta. These features are in contrast with our patients, in whom dentinogenesis imperfecta was absent and the sclerae were slightly bluish.

At the bone tissue level, OI type VII is characterized by decreased trabecular number, increased bone turnover, and preservation of the normal birefringent pattern of lamellar bone. The increase in bone surface-based parameters of both bone formation and resorption is indicative of an increased recruitment of remodeling teams.[19,20] Although the percentage of osteoid covered by osteoblasts was twice as high in OI type VII patients than in controls, mineral apposition rate was decreased. This could be explained by a diminished performance of the individual osteo-

blast, which is only partially compensated by an increase in osteoblast number. The small number of biopsies did not allow a more detailed analysis, but it is clear that bone remodeling is disturbed in OI type VII.

The histomorphometric findings were similar in OI type VII and in OI type I,[20] even though collagen type I mutations have been ruled out in OI type VII,[11,16] whereas such mutations are typically present in OI type I.[29] These observations demonstrate that the tissue-level manifestations of OI are not specific for defects in type I collagen, but may result from mutations in other genes.

In summary, OI type VII is an autosomal recessive form of brittle bone disease discovered in an isolated First Nations community from northern Quebec. There is evidence of both bone and growth plate involvement. The defect at the growth plates is most marked for the proximal limb segments, whereas bone tissue involvement is generalized. The gene defect responsible for this phenotype remains to be elucidated.

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