Type V Osteogenesis Imperfecta: A New Form of Brittle Bone Disease*

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ABSTRACT

Osteogenesis imperfecta (OI) is commonly subdivided into four clinical types. Among these, OI type IV clearly represents a heterogeneous group of disorders. Here we describe 7 OI patients (3 girls), who would typically be classified as having OI type IV but who can be distinguished from other type IV patients. We propose to call this disease entity OI type V. These children had a history of moderate to severe increased fragility of long bones and vertebral bodies. Four patients had experienced at least one episode of hyperplastic callus formation. The family history was positive for OI in 3 patients, with an autosomal dominant pattern of inheritance. All type V patients had limitations in the range of pronation/supination in one or both forearms, associated with a radiologically apparent calcification of the interosseous membrane. Three patients had anterior dislocation of the radial head. A radiodense metaphyseal band immediately adjacent to the growth plate was a constant feature in growing patients. Lumbar spine bone mineral density was low and similar to age-matched patients with OI type IV. None of the type V patients presented blue sclerae or dentinogenesis imperfecta, but ligamentous laxity was similar to that in patients with OI type IV. Levels of biochemical markers of bone metabolism generally were within the reference range, but serum alkaline phosphatase and urinary collagen type I N-telopeptide excretion increased markedly during periods of active hyperplastic callus formation. Qualitative histology of iliac biopsy specimens showed that lamellae were arranged in an irregular fashion or had a meshlike appearance. Quantitative histomorphometry revealed decreased amounts of cortical and cancellous bone, like in OI type IV. However, in contrast to OI type IV, parameters that reflect remodeling activation on cancellous bone were mostly normal in OI type V, while parameters reflecting bone formation processes in individual remodeling sites were clearly decreased. Mutation screening of the coding regions and exon/intron boundaries of both collagen type I genes did not reveal any mutations affecting glycine codons or splice sites. In conclusion, OI type V is a new form of autosomal dominant OI, which does not appear to be associated with collagen type I mutations. The genetic defect underlying this disease remains to be elucidated. (J Bone Miner Res 2000;15:1650–1658)

Key words: autosomal dominant, bone fragility, children, hyperplastic callus, interosseous membrane, osteogenesis imperfecta

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**INTRODUCTION**

OSTEOGENESIS IMPERFECTA (OI) is a heritable disorder characterized by increased bone fragility. Four different types are commonly distinguished on the basis of clinical features.\(^{(1)}\) Type I comprises patients with a mild presentation and often normal height, whereas type II is usually lethal in the perinatal period. Type III is the most severe form in children surviving the neonatal period. These patients have a well-defined phenotype including short stature, growth plate abnormalities, and progressive limb and spine deformities secondary to multiple fractures. Patients with a moderate to severe phenotype who do not fit into one of the above categories are classified as type IV. This is clearly a heterogeneous group of disorders, and some patients with OI type IV have features that are inconsistent with the Sillence classification.

One of these features is hyperplastic callus, which can appear after fractures or corrective surgery.\(^{(5,15)}\) Typically, hyperplastic callus presents as a hard, painful, and warm swelling over the affected bone and initially may suggest inflammation or sarcoma. Microscopically there is exuberant production of poorly organized, partly mineralized extracellular matrix.\(^{(5,4)}\) After a rapid growth period, the size and shape of the callus may remain stable for many years.\(^{(5)}\)

Hyperplastic callus formation in OI was first described more than 90 years ago.\(^{(6)}\) Although generally believed to be rare,\(^{(7)}\) a number of case reports can be found in the literature.\(^{(5,8–13)}\) The incidence of hyperplastic callus among OI patients is unknown, but in a series of 60 type IV patients, 10 (17%) had developed at least one hyperplastic callus before the age of 20 years.\(^{(14)}\) Familial occurrence of hyperplastic callus formation in OI with an autosomal dominant pattern of inheritance has been described.\(^{(2,13)}\) In some cases additional features, such as calcified interosseous membrane and irregular collagen fibril diameter, were noted to be associated with hyperplastic callus formation.\(^{(5,15)}\) It has been suggested that patients who form hyperplastic callus may constitute a specific subgroup of OI,\(^{(14,15)}\) but no attempt has been made to characterize this phenotype in more detail.

In our experience hyperplastic callus formation is only one feature of a syndrome, which can be distinguished from other forms of OI on the basis of clinical, histological, and molecular findings. Although hyperplastic callus is the clinically most conspicuous symptom of this syndrome, it may not be present at the time of diagnosis. Here, we give a comprehensive description of this disorder. We propose to call this disease entity OI type V.

**MATERIALS AND METHODS**

*Patient and control groups*

The phenotype described in this report was found in 7 children (Table 1). Originally, these patients were classified among a group of 26 patients with type IV OI according to the Sillence classification.\(^{(1)}\) Some radiological findings in one of these patients were described previously.\(^{(11)}\)

The control population for histomorphometric analyses consisted of 12 age-matched children (age 3.0–13.7 years), who had undergone bone biopsy with the aim to establish reference data.\(^{(16)}\) In these individuals iliac bone biopsy specimens were obtained during various orthopedic procedures for conditions such as lower limb deformities, scoliosis, clubfoot, and other problems that required corrective surgery. All subjects were ambulatory, had normal renal function as assessed by serum creatinine, and had no evidence of metabolic bone disease. None were immobilized before surgery or received medications known to affect bone metabolism.

Clinical and histomorphometric results in patients with the type V phenotype were also compared with those in 8 age-matched children with OI type IV (aged 5–13.5 years at the time of evaluation), who did not have any of the features specific for OI type V.

**Clinical follow-up**

All OI patients were seen at least once per year in our department. Clinical examination, biochemical measurements, and bone mineral density analyses were performed at each visit. The birth and fracture histories were obtained directly from the parents. For consistency, anthropometric measures and bone density results are given at the time of biopsy. Results for height and weight were transformed to gestational or chronological age and sex-specific Z scores using standard growth curves.\(^{(17,18)}\) 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 pharmacologic treatment other than vitamin and calcium supplementation in the 6 months preceding the 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, U.S.A.). Serum parathyroid hormone levels were determined by radioimmunoassay.\textsuperscript{(19)} Osteocalcin was quantified with an immunoradiometric assay (N-tact Osteo SP; DiaSorin, Stillwater, MN, U.S.A.). 25-Hydroxyvitamin D [25(OH)D] and 1,25-dihydroxyvitamin D [1,25(OH)\textsubscript{2}D] were measured with radioimmunoassays (Osteo SP; DiaSorin). Urine creatinine and calcium were measured colorimetrically and urinary cross-linked N-telopeptides of type I collagen (NTx) were measured by enzyme-linked immunosorbent assay (Osteomark; Ostex, Seattle, WA, U.S.A.) on the second void sample of the morning. Patients were fasting at the time of blood and urine sampling.

**Bone mineral density**

Areal bone mineral density and coronal area in the anteroposterior direction were determined at the lumbar spine (L1–L4) using a Hologic QDR 2000W device (Hologic, Inc., Waltham, MA, U.S.A.; entrance radiation dose less than 5 mrem). Results for bone mineral density were transformed to age-specific Z scores using data provided by the densitometer manufacturer.

**Histomorphometry**

Full-thickness transiliac bone biopsy specimens were obtained with a Bordier trephine (5–7 mm core diameter) under general anesthesia, from a site located 2 cm below and behind the anterior superior iliac spine. In both patients and controls, biopsy specimens were collected on the fourth or fifth day after dual tetracycline labeling (Declomycin, Wyeth-Ayerst Canada Inc, Montreal, Canada; 15–20 mg/kg per day taken orally during two 2-day periods separated by a 10-day free interval). Biopsy specimens were processed and analyzed as previously described.\textsuperscript{(16)}

**Mutation and cytogenetic analyses**

Mutation analysis was performed using two methods. First, messenger RNA (mRNA) was extracted from skin fibroblasts and complementary DNA (cDNA) was obtained using reverse transcriptase. The coding regions of the COL1A1 and COL1A2 cDNAs were amplified by polymerase chain reactions (PCR), using 10 primer pairs for each cDNA, which created overlapping sequences of 510–662 base pairs (bp) in length. The primers and PCR conditions were chosen from the published sequence of the COL1A1 and COL1A2 genes and are available from the authors on request. PCR products were screened for mutations by conformation-sensitive gel electrophoresis.\textsuperscript{(20)} Those products containing heteroduplexes were sequenced using the ThermoSequenase kit (Amersham, Cleveland, OH, U.S.A.). Analysis of fibroblast mRNA was performed in all OI patients included in the present study.

In the second technique, genomic DNA from peripheral blood leukocytes was analyzed, as described by Korkko et al.\textsuperscript{(21)} All exons of the COL1A1 and COL1A2 genes and their respective exon-intron boundaries, with the exception of the six exons encoding the N-propeptides, were amplified by PCR. This was followed by heteroduplex mutation screening and sequencing of positive PCR products, as described above. Analysis of genomic DNA was only performed in type V patients.

Karyotype analyses from lymphocytes of OI type V patients (except patients 3 and 5) were performed according to standard procedures by direct visualization of G-banded chromosomes.

**Statistical analysis**

Differences between type V patients and controls or the type IV group were tested for significance using Student’s unpaired \(t\)-test. All tests were two-tailed. Throughout, a \(p < 0.05\) was considered significant. These calculations were performed using the SPSS software, version 6.0 for Windows (SPSS Inc, Chicago, IL, U.S.A.)

**RESULTS**

**Demographic data and clinical evaluation**

Demographic data and clinical findings in patients with OI type V are summarized in Tables 1 and 2. The family history was positive for OI in three of these children. Heritability followed a dominant pattern with documented father-to-son transmission in two families, suggesting autosomal inheritance. Both the type V and the type IV patients had a history of frequent fractures with similar fracture rates (3.2 ± 2.3 fractures/year in type V vs. 2.3 ± 1.3 fractures/year in type IV; \(p = 0.34\)). All type V patients experienced fractures in the first year of life, compared with 5 of 8 patients in the type IV group. Hyperplastic callus formation was observed only in the type V group, but the majority of fractures in these patients healed without clinically apparent formation of a hyperplastic callus.

Birth length and weight were mostly appropriate for gestational age, similar to type IV OI (Table 2). However, at the time the bone biopsy was taken, 4 patients with the type V OI had a height of more than 2 SD below the mean (Table 2). No difference in height and weight was found between OI types V and IV.

None of the type V patients presented blue sclerae or dentinogenesis imperfecta. Ligamentous laxity and the tendency to easy bruising were similar between types V and IV. A symptom found only in type V OI was the severely limited range of movement in pronation/supination of the forearm. In all 7 patients there was a restriction of both active and passive movements in at least one forearm. As to mobility, patient 3 required a wheelchair at the age when the bone biopsy was performed. The remainder of the patients were ambulatory, although patient 1 required the use of a walker. Of the affected family members reported in this study (Table 1), two out of six of these adults were wheelchair bound because of the severity of their disease.

**Radiological studies**

Hyperplastic callus of at least one bone was present in 4 patients (Table 3; Figs. 1a and 1b). All 7 patients showed radiological signs of calcification of the interosseous membrane of the forearm, corresponding to the limited range of pronation/supination (Table 3; Figs. 1b and 1c). One girl
callus formation. Serum concentrations of osteocalcin did
in phases of quiescence, but increased markedly at times of
levels of alkaline phosphatase (Fig. 2) and urinary excretion
on the activity of hyperplastic callus formation. Serum
Biochemical studies
similar to OI type IV.

The size of the vertebrae was also
the lumbar spine was low in all patients, with values similar
were found in 5 patients (Table 3). Bone mineral density of
were evident in all patients, and wormian bones in the skull
relative to the growth plate. Signs of spine involvement
thickness during development; and maintained its position
proximal tibias, and distal radii; did not appear to alter its
most clearly visible in the metaphyses of distal femora,
feature in growing type V patients (Fig. 1c). This band was
immediately adjacent to the growth plate was a constant
membrane of the forearms. A radiodense metaphyseal band
the radial head in association with the calcified interosseous
lower extremities. Three patients had anterior dislocation of
the radial head bilaterally

Patient
1
2
3
4
5
6
7
Mean ± SD
Type IV (n = 8)

Hyperplastic callus
Both forearms
Both forearms
Both forearms
Both forearms
Left forearm
Right forearm
Left forearm

Age at
biopsy
12.8
6.1
12.6
5.1
12.5
8.4

Bone
mineral
density
2.6
3.0
1.5
5.3
1.3
3.5

Vertebral
area
36.6
22.5
27.0
23.0
38.5
22.4
29.0

Values are individual results or mean ± SD.

p, Significance of difference between OI type V and IV patients by unpaired t-test; vertebral area, coronal area on anteroposterior
projection, as determined by dual X-ray absorptiometry; f excluding 1 patient with OI type IV—data not available.

At time of biopsy.

additionally had an ossified interosseous membrane in the
lower extremities. Three patients had anterior dislocation of
the radial head in association with the calcified interosseous
membrane of the forearms. A radiodense metaphyseal band
immediately adjacent to the growth plate was a constant
feature in growing type V patients (Fig. 1c). This band was
most clearly visible in the metaphyses of distal femora,
proximal tibias, and distal radii; did not appear to alter its
thickenss during development; and maintained its position
relative to the growth plate. Signs of spine involvement
were evident in all patients, and wormian bones in the skull
were found in 5 patients (Table 3). Bone mineral density of
the lumbar spine was low in all patients, with values similar
to OI type IV (Table 2). The size of the vertebrae was also
similar to OI type IV.

Biochemical studies
Systemic indicators of bone turnover appeared to depend
on the activity of hyperplastic callus formation. Serum
levels of alkaline phosphatase (Fig. 2) and urinary excretion
of NTx (not shown) were mostly within the reference ranges
in phases of quiescence, but increased markedly at times of
callus formation. Serum concentrations of osteocalcin did
not follow these variations, remaining within the reference
range. There were no abnormalities in serum levels of
calcium, inorganic phosphorus, parathyroid hormone, creatinine, 25(OH)D, 1,25(OH)2D, or the urinary excretion of
calcium.

Histology and histomorphometry
Sections of iliac crest bone biopsy specimens revealed a
smaller than normal biopsy specimen size, and a decreased
amount of both cancellous and cortical bone were evident
(Fig. 3). Lamellae were arranged in a somewhat irregular
fashion and had a coarsened or even meshlike appearance
under polarized light. In OI type IV lamellae were thinner
than in controls, but the pattern generally was better pre-
served. Tetracycline labels often displayed abrupt width
to changes in OI type V.

Results of the quantitative histomorphometric evaluation
are shown in Table 4. The width of the entire biopsy
specimen core was decreased in type V patients, similar to
Type V OI. Cortical width also was diminished but tended
to be better preserved than in type IV patients. Cancellous
bone volume was similarly low in type V and IV OI.
As to indicators of bone formation, type V patients had much thinner osteoid seams than healthy controls, but higher relative osteoid surface. These patients also had a lower mineral apposition rate, adjusted apposition rate, and mineralizing surface related to osteoid surface. Compared with OI type IV patients, all bone surface–based indices of bone formation were lower in type V. Osteoblast surface and mineralizing surface remained lower in the type V group when these values were related to osteoid surface. Adjusted apposition rate also tended to be lower in type V than in type IV disease.

Regarding resorption parameters, no significant differences between type V OI and healthy controls were found. Compared with OI type IV patients, both relative eroded surface and osteoclast surface were lower in type V, but the difference achieved statistical significance only for eroded surface.

### Molecular and cytogenetic studies

Heteroduplex analysis of fibroblast cDNA as well as genomic DNA revealed several sequence polymorphisms in the COL1A1 and COL1A2 genes of the type V patients. However, sequence analysis did not detect any mutations affecting glycine residues or splice sites in these individuals. Five sequence polymorphisms were observed in the OI type V patients, three in exons and two in introns. The exon polymorphisms were (1) COL1A1 3453T > C (Gly973 → Gly), (2) COL1A1 3223G > A (Ala897 → Thr), and (3) COL1A2 1446G > C (Ala459 → Pro). The first of these does not affect amino acid sequence, whereas the other two are common polymorphisms in the general population. The intron polymorphisms were (1) COL1A1 IVS7 +33T > C and (2) COL1A2 IVS19–12A > G. The first of these is a common polymorphism that has been observed in normal individuals, and the second is a rare polymorphism that has been observed in individuals without the type V OI phenotype.

In type IV patients, analysis of cDNA derived from fibroblast mRNA revealed collagen type I mutations in 5 of 8 individuals (COL1A1 in 3 patients and COL1A2 in 2 patients). This difference in mutation frequency between type V and IV patients was statistically significant ($p = 0.02$ by $\chi^2$ test).

Cytogenetic analysis was carried out in all but two of the type V patients. Direct observation of G-banded chromosomes to a resolution of 500–550 bands showed no evidence of chromosomal abnormality.
DISCUSSION

Clinical aspects

In this study we describe a disease entity, which we propose to call OI type V. Like other forms of OI, type V is a hereditary disease with increased bone fragility. However, there are distinctive clinical, histological, and molecular characteristics, which allow type V OI to be separated clearly from the other forms. These are calcifications of the interosseous membrane at the forearm, hyperdense metaphyseal bands, a coarsened pattern of matrix lamellae, and lack of collagen type I mutations. Patients with OI type V have a predisposition to develop hyperplastic callus. However, a hyperplastic callus may not be evident at the time of presentation and therefore the lack of hyperplastic callus does not exclude OI type V.

Type V is a moderate to severe form of OI. The patients suffer frequent fractures, often causing deformity and short stature. In the traditional Sillence system, such patients usually are classified as having type IV OI. However, some of the cases with hyperplastic callus formation reported in the literature were labeled as type I or type III OI. This may reflect the fact that many patients are difficult to classify with certainty in the current system, so that there is a degree of subjectivity. In our experience, all patients with hyperplastic callus formation present the typical features of OI type V, but we cannot exclude that exceptions may exist.

Biochemical aspects

In OI, biochemical indices of bone turnover are typically normal. However, in type V disease serum levels of alkaline phosphatase and urinary excretion of NTx were frequently increased at times of active hyperplastic callus formation, as noted in earlier studies. This corresponds

FIG. 3. Histological appearance of iliac crest bone from a healthy control subject (girl, 12 years old), a patient with OI type IV (boy, 13 years old), and a patient with OI type V (patient 1; boy, 12.8 years old). For description see text.
to the observation that cells derived from the periphery of hyperplastic callus tissue produce 10 times more alkaline phosphatase than cells from normal bone.14 Callus cells produce only small amounts of osteocalcin in culture25 and accordingly, serum levels of osteocalcin were not influenced by hyperplastic callus formation in our study. Alkaline phosphatase is an early marker of the osteoblast lineage, whereas osteocalcin arises late in osteoblast differentiation. Therefore, the discordant behavior of these two bone formation parameters may be indicative of a defect in osteoblast differentiation. Therefore, the discordant behavior of these two bone formation parameters may be indicative of a defect in osteoblast differentiation within the callus tissue.14 Hyperplastic callus also is characterized by a high rate of collagen turnover.13 This may explain the increased urinary excretion of collagen type I telopeptide during hyperplastic callus formation.

Histology/histomorphometry

The hallmark of qualitative histology in OI type V is the altered pattern of lamellation. This observation is in accordance with an earlier report on iliac crest biopsy samples from patients with hyperplastic callus.15 In that study, light and electron microscopic evaluation revealed a large variation in collagen fibril diameter and irregularities in fiber delimitation. In some patients these characteristics were apparent several years before hyperplastic callus developed.13

Comparison of quantitative histomorphometric results in OI type V and controls revealed no difference in most bone surface–based indicators of bone formation and resorption. This suggests that remodeling cycles are initiated at a normal rate in OI type V.26 However, parameters reflecting bone formation activity in individual remodeling sites were clearly decreased. The rate of matrix deposition as estimated by adjusted apposition rate was less than half of the control value, and correspondingly, osteoid seams were very thin.27 The increased relative osteoid surface most likely reflects a prolonged formation period, indicating decreased osteoblast vigor. Thus, bone remodeling in type V OI is characterized by a normal rate of activation of remodeling units, but an impaired bone formation within individual remodeling units.

Histomorphometry also revealed striking differences between OI types V and IV. In type V, bone surface–based formation and resorption parameters were lower than in type IV, indicating a lower rate of remodeling activation.24 Additionally, osteoid apposition in individual remodeling sites was lower in type V than in type IV, as shown by the differences in adjusted apposition rate. These differences clearly suggest that OI types V and IV have different pathogenetic bases. However, the net effect of these abnormalities on bone mass was similar, because cancellous bone volume was similarly low in both OI types and mean lumbar bone mineral density was almost identical in both groups.

Molecular aspects

The tissue-level differences between OI types V and IV described above are probably the result of differences at the molecular level. Mutations of collagen type I were detectable in more than half of type IV patients with screening by conformation-sensitive gel electrophoresis using the rela-

| Table 4. Histomorphometric Data in OI Type V, Compared with Healthy Controls and OI Type IV |
|---|---|---|---|---|---|
| | Type V | Controls | Type IV | p (C) | p (IV) |
| n (m/f) | 7 (4/3) | 12 (7/5) | 8 (6/2) | | |
| Age (years) | 8.9 ± 3.6 | 9.0 ± 3.5 | 9.9 ± 3.4 | 0.99 | 0.60 |
| Structural parameters | | | | | |
| Core width (mm) | 3.9 ± 1.7 | 6.5 ± 1.8 | 3.1 ± 1.4 | <0.0001 | 0.77 |
| Cortical width (mm) | 0.61 ± 0.25 | 0.86 ± 0.24 | 0.44 ± 0.25 | 0.05 | 0.19 |
| Bone volume/tissue volume (%) | 8.0 ± 4.1 | 22.7 ± 5.4 | 7.3 ± 4.8 | 0.14 | 0.60 |
| Trabecular thickness (μm) | 90 ± 19 | 134 ± 34 | 97 ± 29 | 0.006 | 0.60 |
| Trabecular number (/mm) | 0.87 ± 0.42 | 1.71 ± 0.14 | 0.70 ± 0.29 | 0.01 | 0.43 |
| Formation parameters | | | | | |
| Osteoid thickness (μm) | 3.8 ± 0.5 | 6.7 ± 1.8 | 5.7 ± 1.2 | 0.001 | 0.002 |
| Osteoid surface/bone surface (%) | 39 ± 11 | 26 ± 8 | 55 ± 14 | 0.01 | 0.02 |
| Osteoid volume/bone volume (%) | 2.9 ± 0.6 | 2.8 ± 1.4 | 6.3 ± 3.0 | 0.83 | 0.02 |
| Mineralizing surface/bone surface (%) | 12 ± 5 | 14 ± 6 | 29 ± 8 | 0.49 | 0.0007 |
| Osteoblast surface/bone surface (%) | 6.1 ± 3.5 | 7.1 ± 3.9 | 27 ± 7 | 0.64 | 0.0001 |
| Mineralizing surface/osteoid surface (%) | 31 ± 16 | 52 ± 21 | 52 ± 11 | 0.05 | 0.01 |
| Osteoblast surface/osteoid surface (%) | 18 ± 11 | 28 ± 14 | 51 ± 18 | 0.19 | 0.003 |
| Mineral apposition rate (μm/day) | 0.70 ± 0.15 | 0.94 ± 0.06 | 0.74 ± 0.14 | 0.009 | 0.59 |
| Adjusted apposition rate (μm/day) | 0.23 ± 0.15 | 0.49 ± 0.18 | 0.38 ± 0.09 | 0.01 | 0.03 |
| Bone formation rate/bone surface (μm²/year) | 32 ± 21 | 47 ± 19 | 78 ± 28 | 0.14 | 0.005 |
| Resorption parameters | | | | | |
| Erosion surface/bone surface (%) | 13 ± 4 | 17 ± 7 | 23 ± 4 | 0.20 | 0.0007 |
| Osteoclast surface/bone surface (%) | 1.1 ± 0.7 | 1.2 ± 0.4 | 1.8 ± 0.6 | 0.76 | 0.06 |

Mean ± SD; p values calculated by unpaired t-test; p(C), significance of difference between OI type V patients and controls; p(IV), significance of difference between OI type V patients and OI type IV patients.
tively insensitive method of cDNA analysis. In contrast, by examining both cDNA and genomic DNA, none of the type V patients exhibited collagen type I mutations expected to influence protein structure. Although it appears unlikely that OI type V is linked to mutations in COL1A1/COL1A2, we cannot categorically disprove that one of the type I collagen polymorphisms may in some way modulate collagen synthesis.

As such, the underlying genetic defect responsible for the disease remains in question. The disturbed pattern of lamellation and large variations in collagen fiber diameter might point to a defect in one of the enzymes that is responsible for post-translational modifications of the collagen molecule. However, genetic diseases involving loss of enzymatic function are typically recessive, whereas OI type V is a dominant disease. The overall picture of decreased osteoblast function in remodeling sites but exuberant formation of disorganized osseous tissue at sites of hyperplastic callus formation appears to be more consistent with a defect in the regulation of coordinated osteoblast differentiation and function.

As a myriad of growth factors, cytokines, and other signaling molecules have been proposed to play a role in “osteoblast regulation,” a genome wide search appears to be the only feasible strategy to narrow the number of likely candidate genes implicated in the pathogenesis of OI type V.

Nomenclature

Whether the phenotype we describe here should be considered a novel form of OI, as proposed in this report, or rather should be classified as a new syndrome revolves around the definition of OI. In the present study, we based the diagnosis of OI on clinical findings, whether or not mutational analysis showed a collagen defect. This is in accordance with a definition of OI as a hereditary disorder with osteopenia and increased bone fragility. However, recent reviews present OI as a “type I collagenopathy.”[17,28] The two definitions are not superimposable, as highlighted in the present report. The idea that OI should be equated with collagen type I mutations derives its support mainly from linkage analyses, which concluded that more than 90% of typical familial OI cases were linked to collagen type I genes.[29] However, linkage analyses are limited to familial cases, which appear to constitute a minority among severe OI cases. The prevalence of collagen type I mutations in nonfamilial OI patients is currently unknown, because methods for the detection of mutations until recently had a high rate of false negative results. Therefore, we consider it premature to change the criteria for diagnosing OI from a clinical to a molecular basis. Following these considerations, we tentatively classify the phenotype described in this report as OI type V.

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