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Manifestations in a Family With Autosomal Dominant Bone Fragility and Limb-Girdle Myopathy

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We report on an unusual family with an autosomal dominant limb-girdle type of myopathy and bone fragility. This family was previously reported by Henry et al. [1958] as autosomal dominant progressive limb girdle "muscular dystrophy" with propensity to fractures and defective healing of long bones. Clinical, biochemical, and radiological aspects were evaluated in eight living relatives in this family (three males and five females) and in eight deceased individuals. The average age-of-onset of the limb-girdle myopathy was 31 years occurring in 87% of affected individuals. The average age of onset of fractures was 24 years occurring in 88% of affected individuals. Biochemical analysis showed a mean alkaline phosphatase (ALP) of 64 U/L (normal 30–120) and borderline high creatine kinase (CK) of 213 U/L (normal 4–220). Radiographs revealed coarse trabeculation, patchy sclerosis, cortical thickening, and narrowing of the medullary cavity with an appearance not considered typical of Paget disease of bone (PDB) or of fibrous dysplasia. Results of nerve conduction studies were normal, and electromyograms and muscle biopsies documented non-specific myopathic changes. There is premature graying with thin hair, thin skin, hernias and the affected individuals appear older than their chronological age, and three members had a clotting disorder. Linkage analysis for markers for the chromosome 9p22.3-q12 locus indicated that the disorder in this family does not segregate with markers in the critical region of limb-girdle/inclusion body myopathy, PDB, and frontotemporal dementia (FTD) [IBMPFD, OMIM #605382]. Sequencing of Valosin-containing protein (*VCP*), the gene associated with IBMPFD, did not identify mutations. We have excluded linkage to the known loci for limb-girdle type of myopathy and bone disease and excluded several candidate genes. Elucidation of the novel molecular basis of this disorder may provide valuable links between bone, collagen and muscle, and targeted therapeutic options. © 2006 Wiley-Liss, Inc.

Key words: Paget disease of bone (PDB); fractures; bone fragility; fibrous dysplasia; limb girdle myopathy; adult-onset myopathy; hereditary inclusion body myopathy (HIBM); myopathy; premature graying; coagulopathy; osteosarcoma

INTRODUCTION

We have previously reported on a family with an autosomal dominant adult-onset limb-girdle myopathy with apparent Paget disease of bone (PDB) associated with fractures in a few individuals during late stages of the bone disease [Kimonis et al., 2000]. A genome-wide search in this family and three additional families with limb-girdle myopathy/inclusion body myopathy (HIBM), PDB, and frontotemporal dementia (FTD) identified chromosome band 9p22.3-q12 as the disease region [Kovach et al., 2001]. Mutations in the Valosin-containing protein (*VCP*) gene were found to be associated with this disorder now called IBMPFD [Watts et al., 2004].

Fractures complicating neuromuscular disorders, such as Duchenne muscular dystrophy, are thought to reflect osteoporosis due to loss of ambulation and wheelchair dependency [Larson and Henderson,

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2000; Vestergaard et al., 2001]; however, primary bone disease causing fractures before the onset of myopathy is unusual. Henry et al. [1958] reported that six men in a Canadian family, who would develop myopathy, presented with delayed healing of fractures of long bones. The earliest radiographic changes included thickening of cortices with reduction in the width of the medullary cavity of the long bones (endosteal hyperostosis). Gross histopathology suggested an irregular osteoporotic process with coarse trabeculation suggestive of PDB. Here, we describe updated clinical, biochemical, radiological, and molecular information concerning several members of this Canadian family.

MATERIALS AND METHODS

Clinical Studies

Informed consent was obtained from each subject prior to participation in the research studies approved by Children's Hospital, Boston, MA. A diagnosis of myopathy was based on the presence of weakness on physical examination and by creatine kinase activity, and in several individuals by EMG changes or muscle biopsy findings suggestive of myopathy. Skeletal disease was identified by radiographs of skull, spine, hips, long bones, hands and feet, and measurement of serum alkaline phosphatase (ALP) activity. Bone histology was available concerning several individuals.

Molecular Studies

DNA extraction and genotyping. DNA was extracted from whole blood using the Puregene Blood Kit (Gentra Minneapolis, MN). Linkage to candidate loci was performed. DNA from the family was submitted for a genome-wide search to the National Heart, Lung and Blood Institute Mammalian Genotyping Service (Marshfield, WI). Two-point linkage analysis was carried out using the MLINK and GENEHUNTER programs.

Mutation Studies

Mutation analysis of the *VCP* gene [Watts et al., 2004], *TNFRSF11A*[Hughes et al., 2000], *TGFB1* [Janssens et al., 2000; Kinoshita et al., 2000], *TNFRSF11B* [Whyte et al., 2002a], and *SQSTM1* [Laurin et al., 2002] involved two living affected individuals (propositus plus one other) was performed using previously described methods.

Clinical Description

Fifteen living individuals (affected and unaffected) representing two generations consented to participate (Fig. 1). Clinical and molecular data were available on eight living affected persons (three males and five females) as well as further information on the six deceased affected individuals who were reported by Henry et al. [1958]. Clinical data based on medical records, physical examination, biochemical, and radiological studies of the affected individuals are summarized in Table I.

In this family, a distinctly unusual manifestation is that fractures precede myopathy. Fractures are primarily of the long bones of the lower limbs, particularly of the femora. The bones do not heal well leading to osteomyelitis, which is resistant to treatment. Many of the relatives had multiple orthopedic procedures to correct skeletal problems with poor results leading to amputations. The myopathy is proximal and progressive leading to early death with an average age of demise of 61 years.

Individual IV-3, the propositus, age 64 years, sustained several atraumatic fractures of his right and left tibia and fibula at ages 14 and 15 years. He developed proximal muscle weakness at age 29 years. He has difficulty combing his hair, lifting food to his mouth, and getting out of low chairs. He cannot walk uphill and needs a handrail for ascending stairs. Fine hand movements are difficult. He has a myopathic waddle, complete foot drop, and exertional dyspnea not explained by his echocardiographic findings of mild pulmonary stenosis, or by his pulmonary function results, which were normal. He has soft thin skin, has had three inguinal hernias, and his hair turned gray in his early 20s. Weakness and wasting of his paraspinal muscles, quadriceps, tibialis anterior, and gastrocnemius muscles was noted. He has wasted triceps, biceps muscles, and thenar eminences. Skin biopsy for collagen studies yielded normal results (courtesy Dr. Byers). He bruises easily, with a von Willebrand like picture. Muscle biopsy of the left deltoid at age 41 years showed no necrotic or regenerating fibers, no inflammatory infiltrates or structural abnormalities, and results of special immunohistological studies were normal. An EMG showed two quite different populations of motor units, some of which appeared myopathic and others normal. There was no evidence of denervation anywhere. Muscle fiber recruitment was increased except in the paraspinal muscles where there was very little muscle left. The biceps was certainly myopathic with short duration small potentials. The first dorsal interosseus muscle was also rather short duration; vastus medialis, although it was wasted, showed only mild change. Tibialis posterior also showed mild change. Results of immunological studies were normal. Skeletal survey shows patchy sclerotic changes in the ilia and femora. There were fractures of the femoral shafts that appeared to be fatigue fractures. The increase in cortical bone thickness, pronounced primary bone trabeculae, some modeling defects, and overtubulation for a male were not typical of

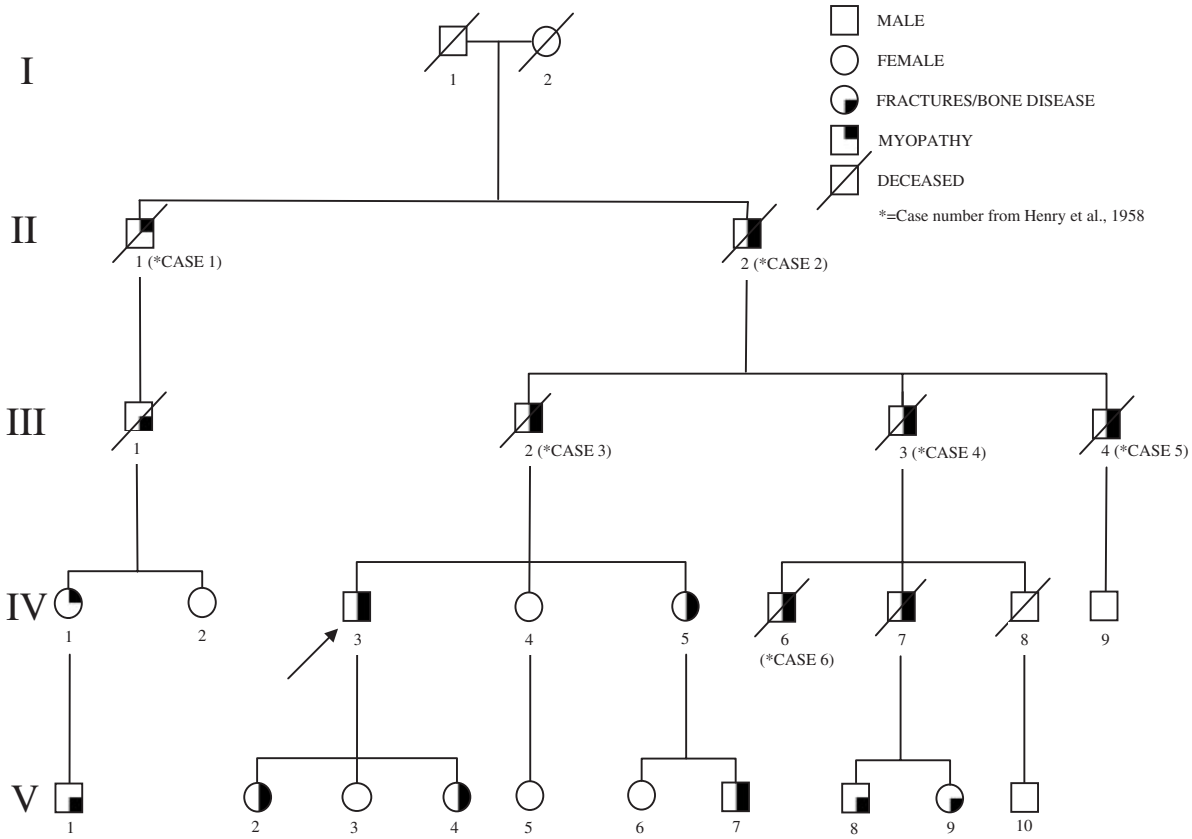

FIG. 1. Pedigree of five-generation family. The proband is indicated by the arrow.

Paget disease, osteogenesis imperfecta tarda, osteopetrosis, or fibrous dysplasia. Osteomalacia-like changes were present in addition to infarction-within-bone changes. The spine was not affected except for the presence of spondylolisthesis at L3. Histology of bone fragments taken from a fracture repair procedure showed abnormal cortical bone with irregularly shaped spaces filled with fibrous tissue, some lined by osteoid, and osteocytes within the bone were distributed unevenly. No large Pagetic osteoclasts or cement (reversal) lines were present in this specimen to indicate classical Paget disease (Fig. 2).

Individual V-2, a 43-year-old woman, the eldest daughter of individual IV-3 developed proximal limb girdle muscle weakness of her thighs at 33 years. She needs support ascending stairs, complains of poor balance, and is unable to run. Back and leg pain since her late 20s has been attributed to a herniated disc. Von Willebrand disease was diagnosed at age 18 years on the basis of easy bruising, vessel fragility, and abnormal von Willebrand factor. She also has diabetes. She developed gray hair at age 30 years. Muscle biopsy from the right quadriceps at age 35 years showed normal variability in muscle fibers with no regenerating or degenerating fibers seen. ATPase stains showed normal fiber types, and results of special immunohistological studies were normal. Bone densitometry studies of her lumbar spine and femoral neck were normal. She has recently fractured her right femur.

Individual V-4 aged 38 years, the youngest daughter of IV-3 fractured her left femur at age 15 years while roller-skating. It was originally planned that she have femoral rodding surgery for spontaneous stress fractures in both femora, but she seemed successfully managed with bisphosphonates with some initial clinical and radiographic improvement. She has difficulty walking upstairs, but there are no other reported problems. She too has a clotting disorder with platelet aggregation studies showing a possible storage pool disorder. She does not have von Willebrand disease. Bone densitometry measurements of the lumbar spine and femoral neck showed evidence of "osteopenia" without evidence of "osteoporosis". Radiographs were similar to those of her father.

Individual IV-1 is a 50-year-old woman with proximal muscular weakness of her legs for 10 years. She requires a handrail to climb stairs and has difficulty walking up an incline. For the past five years, she has had fatigue lifting her arms. Muscle

TABLE I. Summary of Clinical Studies in Affected Individuals

Case	Age (year)	Date of death	Sex	Fractures	Age of onset fractures (year)	Myopathy	Age of onset myopathy (year)	Alkaline phosphatase (30-130 U/L)	Creatine phosphokinase (20-220 U/L)	Additional features
II-1	70	1952	M	−	−	+	−	−	−	Blindness
II-2	69	1957	M	+	18	+	−	−	−	Cataracts bilaterally
III-1	60	1984	M	+	13	−	−	−	−	Fibrosarcoma
III-2	46	1958	M	+	41	+	25	−	−	
III-3	66	1980	M	No fractures but bone disease	−	+	−	−	−	
III-4	69	1985	M	+	30	+	30	−	−	
IV-1	50		F	−	−	+	38	40	201	
IV-3	64		M	+	14	+	29	62	171	Premature graying, clotting disorder
IV-5	60		F	+	24	+	40	84	107	Premature graying
IV-6	53	1986	M	+	16	+	30	−	−	Premature graying
IV-7	51	1987	M	+	39	+	36	−	−	
V-1	21		M	+	10	−	−	86	74	
V-2	43		F	+	43	+	33	41	209	Von Willebrand disease Premature graying
V-4	38		F	+	15	+	28	52	233	Clotting disorder Premature graying
V-7	39		M	+	12	+	22	80	498	Premature graying
V-9	44		F	+	37	−	−	−	−	
Mean or ratio	53	61	11M; 5F	88%	24	87%	31	64	213	
Mean or ratio (IBMPFD families)	51		46M: 51F	51% (PDB)	42 (PDB)	88%	40	508	141	Frontotemporal dementia

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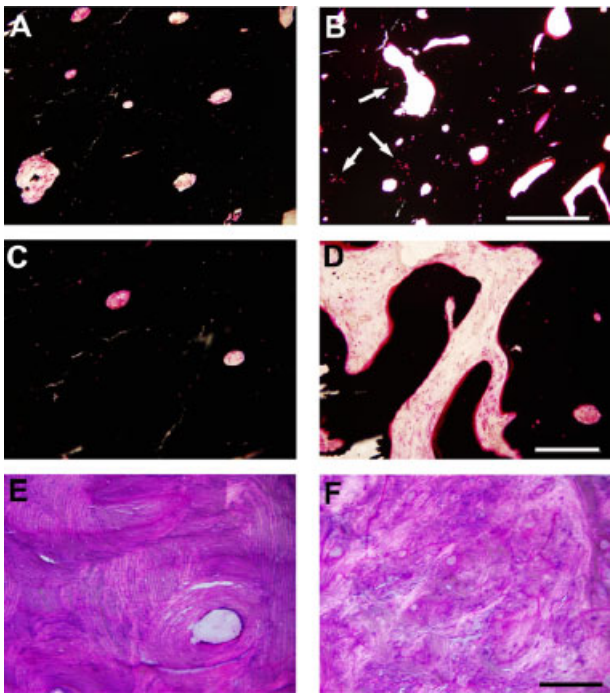

FIG. 2. Bone fragments taken from a fracture repair procedure were embedded in methymethacrylate, sectioned, and stained with VonKossa stain, which highlights calcified bone in black. The nuclear fast red counterstain demonstrates osteoid and cellular elements in red. Although one fragment showed cortical bone composed of unremarkable osteons (**A**, **C**), the second fragment (**B**, **D**) contained many irregularly shaped spaces, lined by abundant osteoid. Additionally, osteocytes, seen as small red spots (arrows), are irregularly clustered. In these areas, polarization of a decalcified section shows disorganized collagen fibers (**F**), in contrast to the lamellar bone found in the more normal area (**E**). Scale bar: A, B 500 μm. Scale bar: C–F 200 μm. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

examination revealed marked weakness of the legs and less markedly weak arms. Two muscle biopsies have not yielded a specific diagnosis. Results of EMG studies of the right deltoid and vastus lateralis were normal, although there was a tendency to early recruitment of small amplitude motor unit potentials; results of nerve conduction studies were normal. Right median, ulnar, and posterior tibial motor conduction studies showed normal latency, contour, and amplitude with normal sensory conduction velocities. Although she does not appear to have bone involvement, one of her sons,V-1, has had four fractures.

Individual V-1, the 21-year-old son of IV-1, has had four fractures since age 10 years, twice of his right tibia, and once of his left radius and right humerus. The fractured right distal humerus developed a bone infection at the site of its inserted plate requiring subsequent surgeries. This individual has not presented with any signs of myopathy.

Individual IV-5 is a 60-year-old woman diagnosed by her physicians as having "osteogenesis imperfecta" because of multiple fractures since age 24 years of her femora, and chronic "sterile osteomyelitis" of the left femur treated with intramedullary rodding. X-ray studies demonstrated patchy osteoporosis and sclerosis of the distal tibia and fibula considered suggestive of "Paget disease", and smooth sclerotic margins of the distal femoral shaft fracture suggestive of non-union. A 5×2 cm lucent area was present in the adjacent medullary cavity of the distal fragment suggestive of osteomyelitis. Mild generalized osteopenia of the long bones and spine was present. Muscular weakness began at the age of 40 years. She has evidence of diffuse myopathy with wasting of temporal, masseter, and neck muscles including sternocleidomastoid muscles. She now drops objects and has dysphagia. EMG showed small, slightly polyphasic motor unit potentials with rapid recruitment as non-specific myopathic findings. Other problems include early hair loss.

Individual V-7, the 39-year-old son of IV-5, sustained several fractures commencing at age 12 years including four femoral fractures. He has muscular weakness of arms and legs and had severe atrophy of the biceps by age 22 years. He has diffuse pain of his joints and lower back; additionally, he has had an inguinal hernia and has translucent sensitive teeth attributed to thin enamel. Roentgenograms show gracile femoral shafts and of the spine a spondylolisthesis with a 5-mm slip of L5 on S1.

Individual III-1, deceased, had lower limb fractures at 13 and 19 years of age in addition to patella fractures. Malunion of the bones led to multiple operations, including intramedullary rodding. He fractured into his late 40s/early 50s and then developed osteomyelitis. He died at approximately age 60 years of osteosarcoma of the left femur that metastasized to the lung. He was the only individual in this family with a known osteosarcoma.

Radiological Evaluation

Over the years, the skeletal findings have been considered as suggestive of polyostotic fibrous dysplasia, diaphyseal dysplasia, metaphyseal dysplasia of the Engelmann type, and osteopathic striata. The common findings are coarse sclerotic trabeculation with increased cortical thickening of the long bones and narrow medullary cavity (Fig. 3A). Many individuals have patchy sclerosis, and the bones have been described as radiolucent and osteopenic or osteoporotic (Fig. 3B). The main involvement has been in the long bones but one individual also had radiolucency of ribs, clavicles, scapulae, spine, and pelvis. The findings that have been described are atypical for PDB. The fractures are slow to heal. Many individuals have also had osteomyelitis, which has been difficult to treat, leading to amputations in some cases. The findings that have been described are atypical for PDB.

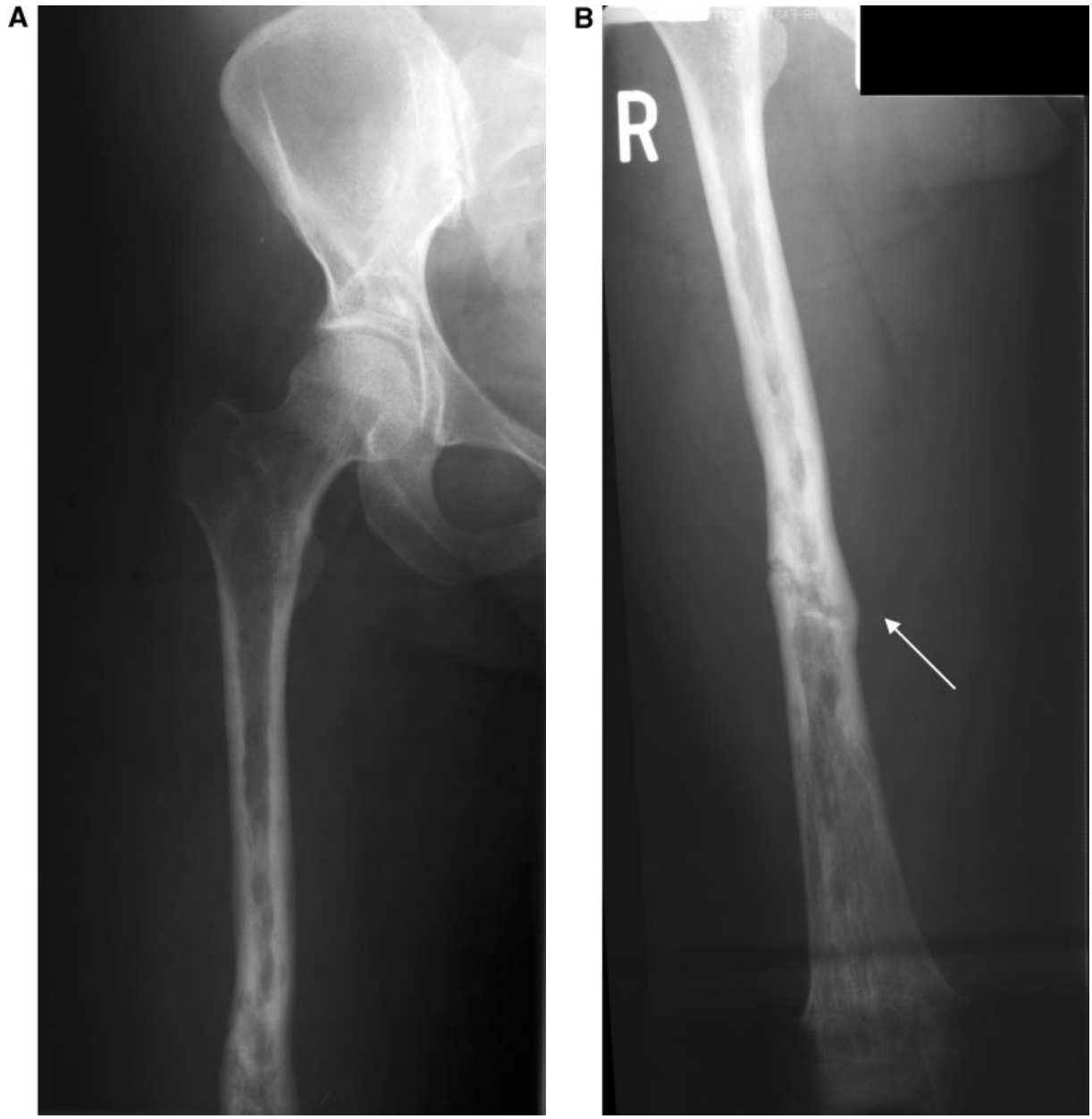

FIG. 3. **A**: Radiograph of the right hemipelvis and femur of individual V-4 at age 36 y. shows coarse sclerotic trabeculation with increased cortical thickening of the femur. The medullary cavity is narrowed. **B**: Roentgenogram of the right femur in individual V-4 shows patchy sclerosis and radiolucent and osteopenic bones. The arrow indicates an old fracture that has not completely healed with only some normal callus formation.

RESULTS

Molecular Studies

Genotype analysis. Linkage analysis concerning members of the family excluded all known loci for PDB, SPMD (scapuloperoneal myopathy), LGMD (limb-girdle muscular dystrophy), and ALS (amyotropic lateral sclerosis) (Table II). In particular, we excluded the IBMPFD critical region on chromosome 9p [Kovach et al., 2001]; individual IV-1 and her son who both have the familial disorder did not share a common haplotype for the critical region. Knockout *ZMPSTE 24* deficient mice have spontaneous bone fractures with muscle weakness and a prelamin A processing defect [Bergo et al., 2002]. Zinc metallopeptidase (STE 24 homolog,yeast) is an integral membrane metalloproteinase of the endoplasmic reticulum. We excluded this potential candidate gene by performing linkage to markers spanning the region of interest.

Mutation analysis. Five genes that code for major proteins involved in bone remodeling, and in which mutations cause sclerosing bone diseases,

TABLE II. Loci Excluded by Linkage Analysis

Marker	MIM number	Locus	Chromosome
D1S498, D1S484	159001	LGMD1B	1q21.2
D2S338, D2S125	120250	Bethlem/COL6A3	2q37
D2S368, D2S286	603689	Edstrom's myopathy	2q24-q31
D3S1263, D3S1304	607801	LGMD1C	3p25
D4S405, D4S1592	604286	LGMD2E	4q12
D5S2115, D5S436	159000	LGMD1A	5q31
D5S470	601287	LGMD2F	5q33
D6S276, D6S1610	167250	PDB1	6p21.2
D7S2465, D7S798	603511	LGMD1D	7q
D9S1776, D9S1682	254110	LGMD2H	9q31-q34.1
D12S351, D12S346	181430	SPMD	12q13.3-q15
D13S175, D13S217	253700	LGMD2C	13q12
D15S994, D15S978	253600	LGMD2A	15q15.1-q21.1
D17S1868, D17S787	608099	LGMD2D	17q12-q21.33
D17S798, D17S250	601954	LGMD2G	17q12
D18S64, D18S68	602080	PDB2	18q21-q22
D21S263, D21S1252	105400	ALS1	21q22.1
D21S266	120220	Bethlem/COL6A1	21q22.3

LGMD, limb girdle muscular dystrophy; SPMD, scapuloperoneal myopathy; ALS, amyotropic lateral sclerosis.

were screened for defects in two affected individuals from this family. These genes include: (1) *VCP* in which mutations cause IBMPFD, (2) Sequestosome 1 (*SQSTM1*) where mutations cause familial Paget disease, (3) Transforming growth factor beta 1 (*TGFβ1*) where mutations cause Camurati-Engelmann disease, (4) Tumor necrosis factor receptor super family, member 11A (*TNFRSF11A*) which encodes receptor activator of nuclear factor kappa-B (RANK) in which activating mutations cause familial expansile osteolysis (FEO) and the related disorder expansile skeletal hyperphosphatasia (ESH), and (5) *TNFRSF11B* encoding osteoprotegerin (OPG) where deactivating mutations cause juvenile Paget disease (JPD, also called idiopathic hyperphosphatasia) [Hughes et al., 2000; Janssens et al., 2000; Kinoshita et al., 2000; Laurin et al., 2002; Whyte and Hughes, 2002; Whyte et al., 2002b; Whyte and Mumm, 2004]. For the *VCP*, *TGFβ1*, and *TNFRSF11B* genes, all the coding exons and adjacent splice sites were amplified by PCR and sequenced in both directions. For *SQSTM1*, only exon 8 (where all mutations have been found) was sequenced. For *TNFRSF11A*, only exon 1 (encoding the signal peptide), where mutations causing FEO and ESH are localized, was amplified and sequenced. No mutations were found in any of these genes that would explain this family's bone disease.

DISCUSSION

Henry et al. [1958] described the condition in this family as dominant and possibly sex-limited because the original pedigree included seven affected males. However, with further generations being studied, with both males and females affected, and male-to-male transmission noted, it could be considered an autosomal dominant trait. The average age-of-onset of fractures in the present family is 24 years, some occurring spontaneously, suggestive of pathological bone fragility. The serum ALP levels were markedly lower (often despite fractures) in this family (64 U/L, normal 30–130) than in the families described by Kovach et al. [2001], in whom the average value was 389 U/L. Most members of the family have had several operations for debridement, bone grafting, and rodding for defective wound healing and osteomyelitis. Bisphosphonates, which have proven to be efficacious in fracture prevention in osteoporosis, PDB, and osteogenesis imperfecta [Reid, 2003], have benefited some individuals with this unique disorder. Osteosarcoma, a rare complication of PDB [Nellissery et al., 1998] and fibrous dysplasia [Yabut et al., 1988], was noted in one individual in this family; however, this could have been related to a prolonged history of chronic osteomyelitis. Many individuals appear to also have manifestations of a connective tissue disorder with premature graying, thin fragile skin, and inguinal hernia. Some individuals have also complained of sensitive teeth. Results of biochemical studies of collagen on a skin biopsy from the propositus were normal.

Proximal myopathy was present in 87% of individuals at an average age of onset of 31 years; therefore one individual is still at risk of developing the myopathy. The family's proximal-to-distal limb girdle weakness is progressive with many individuals becoming wheelchair-bound and unable to carry out normal activities of daily living. There are also symptoms of bulbar dysfunction in several individuals causing difficulty swallowing. Findings on muscle biopsy obtained in several individuals were non-specific, and the average creatine kinase (CK) was borderline high at a mean value of 213 U/L (normal range 20–220).

The association of familial PDB and neuromuscular disorders has been reported previously in unrelated families with distinct phenotypes [Caughey et al., 1957; McBride, 1966; Waggoner et al., 2002; Watts et al., 2004]. However, there is no dementia in this family, in contrast to a 31% dementia rate in affected IBMPFD individuals in 13 families, and we have excluded mutations of the *VCP* gene [Watts et al., 2004].

Although the radiographs have sometimes been described as resembling polyostotic fibrous dysplasia or McCune–Albright syndrome [OMIM 174800], clinical findings were not suggestive of the latter disorder that is associated with patchy cutaneous pigmentation, endocrine hyperfunction, and post-zygotic missense mutations of the alpha subunit of the G_s protein (*GNAS1* gene) in somatic cells [Shenker et al., 1993]. The disorder in our family bears resemblance to Camurati–Engelmann disease [CED, OMIM 131300], an autosomal dominant progressive diaphyseal dysplasia characterized by leg pain, progressive expansion, and sclerosis especially of the diaphyses of the long bones associated with cranial sclerosis, in addition to muscle weakness, facial nerve paralysis, hearing difficulties, exophthalmos, and loss of vision [Vanhoenacker et al., 2003]. It is caused by mutations in the transforming growth factor-beta-1 gene *TGFB1*, located at 19q13.1. *TGFB1* influences osteoblast and osteoclast function and acts as a coupling factor between bone deposition and resorption [Janssens et al., 2000]. PDB is a common disorder affecting up to 3% of Americans. Siris [1998] and Morales-Piga et al. [1995] respectively reported a 12–40% incidence of PDB among first-degree relatives of affected propositi. Cody et al. [1997] demonstrated that PDB could be linked to genetic markers in the same region of chromosome 18q as that for familial expansile osteolysis (FEO); mutations in the *TNFRSF11A* gene were shown to segregate with PDB in several families [Hughes et al., 2000]. Mutations in the *SQSTM1* gene were found to cause Paget disease in families with linkage to 5q35 [Laurin et al., 2002]. Lack of mutations in these genes excluded these disorders in this family.

ELECTRONIC DATABASE INFORMATION

Online Mendelian Inheritance in Man [OMIM]: http://www.ncbi.nlm.nih.gov/omim/

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