Published in final edited form as:

J Pediatr Orthop. 2009 June ; 29(4): 385–392. doi:10.1097/BPO.0b013e3181a567e3.

Analysis of Radiographic Characteristics of Anterolateral Bowing of the Lower Leg Prior to Fracture in Neurofibromatosis Type 1

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Abstract

Background—Anterolateral lower leg bowing is associated with neurofibromatosis type 1 (NF1) frequently leading to fracture and non-union of the tibia. The objective of the study is to characterize the radiographic findings of tibial dysplasia in NF1.

Methods—Retrospective review of radiographs of tibial dysplasia from the Shriners Hospitals for Children, Salt Lake City over 52 years between 1950 and 2002, and peripheral quantitative computed tomography (pQCT) imaging of three individuals with anterolateral bowing of the leg without fracture compared to age- and gender-matched controls.

Results—NF1 individuals with bowing of the lower leg have the appearance of thicker cortices with medullary narrowing on plain film radiographs. The pQCT images of NF1 individuals with anterolateral bowing show an unusual configuration of the tibia.

Conclusions—Anterolateral bowing of the lower leg in NF1 is associated with the appearance of thicker cortices with medullary narrowing on plain film radiographs rather than “thinning of long bone cortex” as currently utilized as a qualifier in the 6th diagnostic criterion for the clinical diagnosis of NF1. Individuals with NF1 who have anterolateral bowing of the lower leg have differences in tibial geometry compared to age- and gender-matched controls.

Clinical Relevance—The characterization of the radiographic findings of long bone bowing in NF1 helps clarify the NF1 clinical diagnostic criteria.

Introduction

NF1 is a common autosomal dominant condition due to mutations in the *NF1* gene.¹ The diagnosis of NF1 is typically based clinically on fulfillment of 2 out of 7 diagnostic criteria,^{2,3} and one criteria focuses on the skeletal abnormalities associated with NF1 including long bone dysplasia. The clinical presentation of tibial dysplasia generally begins with anterolateral bowing of the lower leg. The bowed long bone typically progresses to fracture and non-union (pseudarthrosis).^{4,5} Anterolateral bowing of the lower leg with subsequent pseudarthrosis is quite specific for NF1 and in and of itself should alert the physician to the potential diagnosis of NF1.

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The NF1 diagnostic criterion for the skeletal abnormalities states: “A distinctive osseous lesion such as sphenoid dysplasia or thinning of long bone cortex, with or without pseudarthrosis.”^{2,3} Our anecdotal clinical experience is that cortical thinning was not a consistent component of tibial dysplasia in NF1.⁶ This prompted us to systematically investigate our clinical suspicions and better characterize the geometry of the tibia and fibula in individuals with NF1 with anterolateral bowing of the lower leg. In order to characterize the architecture of the lower leg in individuals with NF1, a retrospective review of radiographs of the lower leg of individuals with tibial dysplasia was performed. Additionally, a cross-sectional analysis of the lower leg of NF1 individuals with anterolateral bowing of the lower leg without fracture or surgery compared to healthy controls using peripheral quantitative computed tomography (pQCT), a modality that allows for the separation of the bone and muscle compartments with cross-sectional volumetric measurements, was performed.⁷

Materials and Methods

Archived Radiograph Review

Radiographs were obtained of the lower leg of patients with the following diagnostic codes: (pseudarthrosis of bone, pseudarthrosis of tibia, neurofibromatosis generalized, neurofibromatosis of the tibia, and non-union of fracture) at the Shriners Hospitals for Children, Salt Lake City over 52 years between 1950 and 2002. Radiographs with instrumentation or fracture of the tibia were excluded in attempt to more accurately assess the initial radiographic findings of tibial dysplasia. Radiographs in which the individual had a known genetic disorder or condition besides NF1 were excluded. All eligible radiographs were reviewed by one pediatric radiologist (KM).

Peripheral Quantitative Computed Tomography (pQCT)

Patients—Inclusion criteria for cases included: 1. clinical diagnosis of NF1 based on NIH diagnostic criteria;^{2,3} 2. anterolateral bowing of the lower leg without fracture or surgical intervention. Individuals <4 years of age were excluded due to patient cooperation and pQCT machine limits for the ability of positioning based on leg length. NF1 individuals were recruited from an NF1 clinic and NF1 Registry at the University of Utah. Medical histories were obtained and physical examinations performed on all cases, and information such as orthopedic management, medication use, handedness, and pubertal maturation (determined by self-reported questionnaire using Tanner stage criteria⁸) was obtained. Controls were selected from a reference group of 474 healthy children without NF1 collected by the Center for Pediatric Nutrition Research at the University of Utah enrolled over the years 2000-2007 from the same geographic area.

Imaging Procedures (pQCT)—Cross-sectional slices of the affected leg(s) in individuals with NF1 and of the non-dominant leg in controls were measured by pQCT (XCT-2000; Stratec Medical Systems/Orthometrix, White Plains, NY) at relative distances of 4%, 38%, and 66% from the distal tibial growth plate to assess numerous bone variables including volumetric bone mineral density (vBMD), bone mineral content (BMC), and Strength Strain Index, which relates to the bending and torsional strength of tubular bone. Dominance of the leg was based on self-reported handedness. The distal end of the medial malleolus and the internal point of articulation at the knee were marked with an erasable pen. Distances between the two marks were measured in triplicate, and the two measurements within 2 mm of each other were averaged. The 4% distal tibial site was calculated by dividing 8 by the total length of the leg. Measurement of the 66% distal tibial site was obtained by calculating 66% of the average total length measurement of the leg and marked with erasable pen. Placing the non-dominant leg through the pQCT gantry, the pQCT laser was aligned with the distal reference mark (medial malleolus). A scout scan was performed to determine the position of the endplate and placement

of the reference line in the distal tibia. The reference line was placed at the most proximal line to the distal growth plate or at the endplate if the growth plate was fused. Once the reference line was defined, the scanner automatically measured the calculated 4% and 38% distal tibial sites. Then the leg was manually slid back to the marked 66% distal tibial site and scanned. The 4% distal cross-section was used to determine trabecular vBMD (mg/cm^3). The 38% and 66% distal cross-section was used to determine cortical vBMD and BMC as well as the bone geometric properties. Imaging was performed by a densitometry technologist certified by the International Society for Clinical Densitometry (HS).

Scans were analyzed utilizing XCT software. The 4% site analysis was based on 0.4 voxel size, with a threshold of 169 mg/cc , contour mode = 1, peel mode = 1, with the filter on. The 38% site analysis was based on 0.4 voxel size, with a cortical bone threshold of 711 mg/cc and cort mode = 1. The 66% site analysis was based on 0.8 voxel size, with a cortical threshold of 711 mg/cc and cort mode = 1.

Statistical Analyses

NF1 Individuals with Anterolateral Bowing of the Lower Leg—In order to avoid secondary changes due to surgical manipulation or trauma, individuals with previous fracture and/or pseudarthrosis of the tibia were excluded. NF1 individuals were individually compared to selected age- and gender-matched controls, and Z-scores were generated.

Results

Archived Radiograph Review

A total of 23 cases with anterolateral bowing of the tibia without fracture or instrumentation were identified from the archived radiographs available at the Shriners Hospitals for Children, Salt Lake City between 1950 and 2002. The cortex appeared thickened with medullary canal narrowing near the apex of the bowing in all 23 cases (see example in Fig. 1). The fibula was dysplastic in 19/23 cases. The apex of the anterolateral bowing was most consistently located near the junction of the middle and distal thirds of the tibia. Gender was listed in 20 cases and 80% were male and 20% were female. We were unable to confirm if all of these individuals had a diagnosis of NF1 based on this retrospective review, but 16/23 individuals had a diagnosis of NF1 documented [(gender: 11 male; 4 female; 1 unknown); (fibula dysplastic 13/16)]. Of the 7 individuals without a known diagnosis of NF1 could not be confirmed there were no obvious radiographic differences that could distinguish them from the individuals with a reported diagnosis of NF1.

Peripheral Quantitative Computed Tomography (pQCT)

A total of 3 individuals with NF1 with anterolateral bowing of the lower leg without fracture or surgical intervention were identified and their clinical history, pQCT data, and analyses are reported individually:

Case #1: This 4-year-old boy has bilateral anterolateral bowing of the lower legs without fracture or surgical intervention. Bracing of both legs was started at approximately 10 months of age, which has continued since that time. Radiographs of the lower legs at 4 years of age show severe bilateral anterolateral bowing with cortical thickening with medullary canal narrowing at the apex of the bowing (Fig. 2A,B). The pQCT images confirm an unusual shape to the tibial cross-section with the appearance of a thickened cortex with medullary canal narrowing of both tibia when compared to an age- and gender-matched control (Fig. 2C,D,E). The Z-scores from pQCT values of each leg compared to the non-dominant leg of 7 healthy gender- and age-matched controls (age 3.5-4.5 years) are listed in Table I. When one compares the 38% distal tibial sites (Fig. 2C,D) to the

radiographs (Fig. 2A,B) one notes that this is the pQCT region closest to the apex of the bowing on both legs. The Z-scores were higher for cortical thickness with a Z-score of +2.6 for the left leg, and +2.1 for the right leg, while the endosteal circumferences were lower with a Z-score of -1.2 and -2.4 respectively. In addition, the Strength Strain Index was -1.3 for the left leg and -0.9 for the right leg.

Case #2: This 7-year-old boy has mild left anterolateral bowing of the lower leg. His clinical course has been relatively unremarkable without fracture. Bracing of the leg was intermittent with poor compliance from infancy to 5 years of age, and has since not worn the brace. Radiographs at 1 year of age show mild anterolateral bowing with subjective cortical thickening and medullary canal narrowing. Radiographs at 4 and 7 years of age show the appearance of improvement of the anterolateral bowing, cortical thickening, and medullary canal narrowing radiographically over time (Fig. 3A,B,C). Evaluation of the pQCT images performed at 6 years of age does not reveal a striking change in the shape of the tibia (Fig. 3D) compared to an age- and gender-matched control (Fig. 3E). Upon comparison of the latest plain film radiograph (Fig. 3C) one observes only minimal residual bowing. The Z-scores from pQCT values of the affected left leg compared to the non-dominant leg of 20 healthy gender- and age-matched controls (age 5.5-6.5 years) are listed in Table I. At the 38% site, which again roughly correlates with the maximum area of bowing on plain film radiographs, the Z-scores were negative for all values except the cortical thickness which had a positive Z-score (Table I), although not as dramatic as the Z-scores observed in Case #1.

Case #3: This 17-year-old girl has left anterolateral bowing of the lower leg without fracture or surgical intervention. Bracing of the affected leg was started at 6 months of age and was used intermittently until approximately 13 years of age when bracing was discontinued. Upon comparison of previous serial radiographs the tibial appearance changed over time (Fig. 4A-F). The pQCT images show a dramatically altered configuration of the tibia, with the appearance of a flattened and elongated tibia upon cross-section (Fig. 4G) when compared to an age- and gender-matched control (Fig. 4H). The fibula also appears dysplastic (Fig. 4G). The z-scores from pQCT values of the affected left leg compared to the non-dominant leg of 21 healthy gender- and age-matched controls (age 5.5-6.5 years) are listed in Table I. There were no positive Z-scores for any variable.

Discussion

Based on our previous clinical experience, NF1 individuals with anterolateral bowing of the lower leg prior to fracture have medullary canal narrowing with cortical thickening.⁶ Our retrospective radiographic review confirmed the appearance of cortical thickening with medullary canal narrowing near the apex of the bowing most consistently located near the junction of the middle and distal thirds of the tibia on plain films. This is in opposition to the example of “thinning of the cortex, with or without pseudarthrosis” currently used in the 6th diagnostic criterion originally established by a panel of experts at a National Institutes of Health Consensus Development Conference in 1987.^{2,3} The appearance of cortical thickening may be a response to the anterolateral bowing, as the cortex appears more thickened on the posterior concave aspect. Yet the bowing is typically present early in life before a significant amount of loading forces on the lower limb are placed, although one cannot discount prenatal forces and the strains from movement during infancy.

There may be a selection bias of radiographs selected, as we only included radiographs prior to fracture on our retrospective review, and it is likely that radiographic changes can develop after fracture and surgical manipulation. In addition, the radiographic findings may change with age as the bone remodels in response to mechanical strains and loading. Many individuals

with early or more severe presentations may have fractured prior to radiographic imaging. In addition, bone is a 3-dimensional structure and plain radiographs cannot fully assess the geometry of the tibia. Our opinion of cortical thickening and medullary canal narrowing on plain radiographs may be the result of rotational factors and cortical shadowing.

Given that the analysis of the plain radiographs was a retrospective review, we cannot determine if all of the individuals had NF1. We were able to conclude that at least 70% (16/23) of the radiographic cases had a diagnosis of NF1 recorded, but it is likely that the majority of the remaining individuals also had NF1. The rationale for this assumption is based on a prospective Shriner Hospital cohort, in which 91% of individuals with tibial dysplasia had NF1 (unpublished data).

Of the 23 cases in which radiographs were retrospectively reviewed, there was an excess of males (80%) with tibial bowing. A previous study reported increased male gender with more surgeries and an earlier age of fracture in an international cohort of NF1 individuals with long bone dysplasia.⁴ The increase in male gender reported by Stevenson et al.⁴ was primarily due to the group of individuals with complications of fracture, pseudarthrosis, surgery, and/or amputation, and colleagues have postulated that the excess number of males was due to increased activity leading to the subsequent complications. However, in this report, the retrospective review of radiographs excluded those individuals with tibial fracture, pseudarthrosis, or surgical manipulation. Therefore, it appears that male gender may be a risk factor for anterolateral bowing of the tibia. Perhaps hormonal influences could contribute to the development of tibial bowing.

Several radiographic classification systems have been proposed for tibial pseudarthrosis.⁹⁻¹⁶ The Crawford classification system¹²⁻¹⁴ is the most recent system proposed and has been utilized in research protocols. However, none of these classification systems are in wide clinical use, and some do not separate out individuals with and without NF1 nor separate out radiographs with anterolateral bowing without previous fracture or pseudarthrosis. Moreover, these radiographic classification systems have not been systematically studied for reliability or validity. Other authors have correctly noted that the radiographic appearances often change during growth and in response to surgical interventions limiting the value of a radiographic classification system.^{16,17} Still, these classifications have been used in clinical studies and certain classification types have been suggested to predict eventual outcome.¹⁷⁻²² Therefore, description of radiographic findings prior to fracture or surgical intervention may be important in anticipatory guidance in individuals presenting with anterolateral bowing prior to fracture. Future studies should evaluate the reliability and validity of the various radiographic classification systems for utilization in clinical studies and translation to clinical practice.

Upon analysis of the pQCT data on the small number of individuals with anterolateral bowing without fracture or surgical intervention, the cortical thickness was increased at the 38% distal tibial site with a decrease in the endosteal circumference in Case #1 and #2 compared to controls. The 38% distal tibial site is the pQCT measurement most likely nearest to the apex of the bowing of the sites measured. These findings are in concert with those observed on the retrospective review of plain radiographs with cortical thickening at the apex of the bowing, and support our recommendation to revise the example of long bone thinning in the NF1 diagnostic criterion.⁶ However, the Z-scores for cortical thickness and endosteal circumference were decreased in Case #3 compared to controls. Even though there is an increase in the cortical thickness, the BMC, vBMD, and the Strength Strain Index were decreased in these individuals with tibial and/or fibular dysplasia compared to controls suggesting a potential risk of fracture with specific mechanical forces. The number of cases and controls are small and other confounders such as height, pubertal development, activity level, diet, etc. may contribute to the measurable differences.

The appearance of the tibia from the pQCT images at the 38% distal tibial site of the three individuals with anterolateral bowing was abnormal with an unusual configuration. We question whether or not accurate numeric values using pQCT can be obtained when measurements used to calculate the values are based on a circle with equivalent bone area (“ring model”) if the tibia is abnormally shaped. It is also interesting that although the pQCT images appeared abnormal, each of the three cases had variable geometric findings.

The three NF1 individuals with anterolateral bowing of the lower leg in which pQCT images were performed had not, as of yet, sustained a fracture. The average age of fracture of NF1 individuals with anterolateral bowing of the lower leg is approximately 5 years of age.⁴ Given the limitations of obtaining pQCT imaging in children <4 years of age due to machine limits based on leg length, there may be some bias in this cohort of NF1 individuals with tibial bowing as they had not yet sustained a fracture. Potentially, individuals who sustained a fracture and progressed to pseudarthrosis, who were younger, could have different pQCT values. In addition, we do not know if the herein reported individuals with anterolateral bowing of the lower leg will progress to fracture and non-union. Given that Case #1 is only 4-years-of-age he may be more likely to sustain a fracture and non-union compared to Case #2 and Case #3. Case #2 only had mild anterolateral bowing which seemed to improve over time and likely lies along the milder end of the phenotypic spectrum of tibial dysplasia. Case #3 is 17-years-of-age without a fracture and it is difficult to determine why she did not sustain a fracture previously. The bone modeling and remodeling based on intrinsic genetic factors and extrinsic forces on an anterolaterally bowed leg during her period of growth may have altered the tibial geometry from its original shape as it adapted over time. It is also possible that the geometric properties of the tibia in these three individuals have protective effects against fracture compared to other NF1 individuals with anterolateral bowing who progress to fracture. It is also likely that other genetic modifiers, in the context of a heterozygous *NF1* background, can affect long bone geometry differently. Prospective information will be useful to determine if any of the pQCT variables are prognostic indicators of fracture and pseudarthrosis.

Since bone is a dynamic organ that is constantly changing due to bone formation and resorption, it is reasonable to assume that therapeutic strategies could be directed to bone structure in individuals with NF1. The utilization of pQCT imaging may serve as an appropriate surrogate marker to assess the effects of bracing techniques, physical activity regimens, and pharmacologic targets in clinical trials for NF1 individuals with anterolateral bowing of the lower leg. Future longitudinal studies to assess if pQCT imaging is a valid and reliable tool in the context of NF1 will be needed.

Acknowledgments

We thank Jeanne Siebert, Susan Geyer, Janice Davis, Meredith Winn, and the radiology staff from the Shriners Hospitals for Children, Salt Lake City for coordination and collection of radiographs. We would like to acknowledge investigators and staff at the University of Utah (Dr. James Roach, Heather Hanson, Stacy Maxwell, Diane Hartford, Amy Watkins, Bronte Clifford, and Ann Rutherford), the University of Manchester (Judith Eelloo, Dr. Judith Adams, Dr. Gareth Evans, Dr. Susan Huson, Dr. Zulf Mughal), Cincinnati Children’s Hospital Medical Center (Dr. Elizabeth Schorry, Dr. Alvin Crawford, Dr. Heidi Kalkwarf, Martha Walker, Donna Buckley), the University of British Columbia (Dr. Linlea Armstrong, Dr. J. Friedman, Patricia Birch, Deetria Egeli, Dr. Heather McKay, Melanie Burrows), and Dr. Heather Macdonald (University of Calgary), for their help, discussion, and insight. We would also like to acknowledge the Centre for Hip Health and Musculoskeletal Diseases at Vancouver Coastal Health Research Institute, University of British Columbia, and the Center for Pediatric Nutrition Research at the University of Utah for their expertise. We thank the participants and their families. This research was carried out with support from a Public Health Services research grant #M01-RR00064 from the National Center for Research Resources, research grant #1 K23 NS052500 from the National Institute of Neurological Disorders and Stroke, Shriners Hospitals for Children, the Children’s Health Research Center at the University of Utah, the Clinical Genetics Research Program at the University of Utah, and the Primary Children’s Research Foundation.

Funding Sources: A Public Health Services research grant #M01-RR00064 from the National Center for Research Resources, research grants #1 K23 NS052500 and #R01 NS050509 from the National Institute of Neurological

Disorders and Stroke, Shriners Hospitals for Children, the Primary Children's Medical Center Research Foundation, and the Children's Health Research Center, Center for Pediatric Nutrition Research, and Clinical Genetics Research Program at the University of Utah.

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Fig. 1. Example of anterior-posterior (AP) and lateral radiographs of the lower leg of an individual with anterolateral bowing of the lower leg prior to fracture. Radiographs show the appearance of cortical thickening with medullary canal narrowing with apex of the anterolateral bowing located near the junction of the middle and distal thirds of the tibia

Fig. 2.

Radiographs (AP and lateral views) of the right (A) and left (B) leg of Case #1 with bilateral anterolateral bowing at 4-years-of-age. The cortex appears thickened with medullary canal narrowing at the apex of the bowing bilaterally. (C,D) The pQCT images obtained at the 4%, 38% and 66% distal tibial site of the (C) left and (D) right leg at 4-years-of-age. The fibula also appears dysplastic. (E) PQCT images obtained at the 4%, 38% and 66% distal tibial site of the non-dominant leg of a healthy age- and gender-matched control.

Fig. 3.

Case #2: (A) Radiographs (AP and lateral views) of the left leg at 1-year-of-age. The cortex appears thickened with medullary canal narrowing at the apex of the bowing. (B) Repeat radiographs (AP and lateral views) of the left leg at 4-years-of-age. (C) Repeat radiographs (AP views) of the left leg at 7-years-of-age showing decreased lateral bowing with resolving cortical thickening and medullary canal narrowing. (D) The pQCT images obtained at the 4%, 38% and 66% distal tibial site of the left leg of Case #2 with left anterolateral bowing of the lower leg at 6-years-of-age. At the 38% distal tibial site, the cortex appears only mildly increased. (E) As a comparison, pQCT images obtained at the 4%, 38% and 66% distal tibial site of the non-dominant leg of a healthy age- and gender-matched control are provided.

Fig. 4.

Radiographs (AP and lateral views) of the left leg in Case #3 with left anterolateral bowing at 7-months-of-age (A), 3-years-of-age (B), and 7-years-of-age. The cortex appears thickened with medullary canal narrowing at the apex of the bowing. Repeat radiograph (AP view) of the left leg at 13-years-of-age (D) shows straightening of the lateral bowing, but anterolateral bowing persists as shown by lateral radiographs at 15- and 16-years-of-age (E, F). (G) The pQCT images obtained at the 4%, 38% and 66% distal tibial site of Case #3 at 17-years-of-age. The fibula also appears dysplastic. (H) As a comparison, pQCT images obtained at the 4%, 38% and 66% distal tibial site of the non-dominant leg of a healthy age- and gender-matched control are provided.

Table I
pQCT (NF1 with anterolateral bowing versus Controls)

Variable	<u>Z-scores</u> *		
	Case #1 (Left/Right)	Case #2 (Left)	Case #3 (Left)
4% Distal Tibial Site			
Total Area (mm ²)	(-0.4) / (-1)	-1	-0.8
Total vBMD (mg/cm ³)	(-2) / (-2.2)	-1.5	-4
Total BMC (mg/mm)	(-1.2) / (-1.7)	-1.5	-2.6
Trabecular Area (mm ²)	(-0.5) / (-1)	+1.1	-0.9
Trabecular vBMD (mg/cm ³)	(-1.5) / (-2.1)	-1.4	-3.3
Trabecular BMC (mg/mm)	(-1) / (-1.5)	-2	-2.2
38% Distal Tibial Site			
Total Tibial Area (mm ²)	(-0.7) / (-0.1)	-0.8	-1.3
Cortical Thickness (mm)	(+2.6) / (+2.1)	+0.1	-4.5
Periosteal circumference (mm)	(-0.6) / (0)	-0.8	-1.3
Endosteal circumference (mm)	(-1.2) / (-2.4)	-0.8	0
Cortical Area (mm ²)	(-0.1) / (+1.2)	-0.2	-2.6
Cortical vBMD (mg/cm ³)	(-1.6) / (-1.3)	-0.7	-1.3
Cortical BMC (mg/mm)	(-0.4) / (+0.8)	-0.3	-4.1
Strength Strain Index	(-1.3) / (-0.9)	-0.3	-2
66% Distal Tibial Site			
Total Tibial Area (mm ²)	(-0.6) / (-1.6)	-0.9	-2.1
Cortical Thickness (mm)	(-2.1) / (-1)	-0.9	-0.4
Periosteal circumference (mm)	(-0.6) / (-1.7)	-0.9	-1.5
Endosteal circumference (mm)	(+0.6) / (-0.8)	-0.3	-1.6
Cortical Area (mm ²)	(-2.3) / (-1.5)	-1.1	-1.5
Cortical vBMD (mg/cm ³)	(-2.6) / (-1.2)	-0.9	-3
Cortical BMC (mg/mm)	(-2.3) / (-1.5)	-1.2	-1.9
Strength Strain Index	(-3.4) / (-2.1)	-1	-1.8

* Comparison of the bone variables from pQCT imaging of the affected lower leg(s) of three NF1 individuals with anterolateral bowing of the lower leg compared to the non-dominant lower leg of age- and gender-matched controls without NF1 (number of controls for case #1 = 7; controls for case #2 = 20; controls for case #3 = 21).