# Melorheostosis

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# History

- 1922 – Léri and Joanny (define the disorder)
- “Léri’s disease”
- 5000 BC (Chilean burial site 2-year-old girl)
- 1500-year-old skeleton in Alaska

# Definitions

(Greek) melo="limb" rhein="to flow" osteon="bone"

- Melorheostosis means "limb and I(me)-Flow"
- Flowing Periosteal Hyperostosis
- Candle guttering (dripping wax) on x-ray in adults
- OMIM (Online Mendelian Inheritance of Man)
  % 155950

# DISORDERS THAT CAUSE OSTEOSCLEROSIS

## Dysplasias

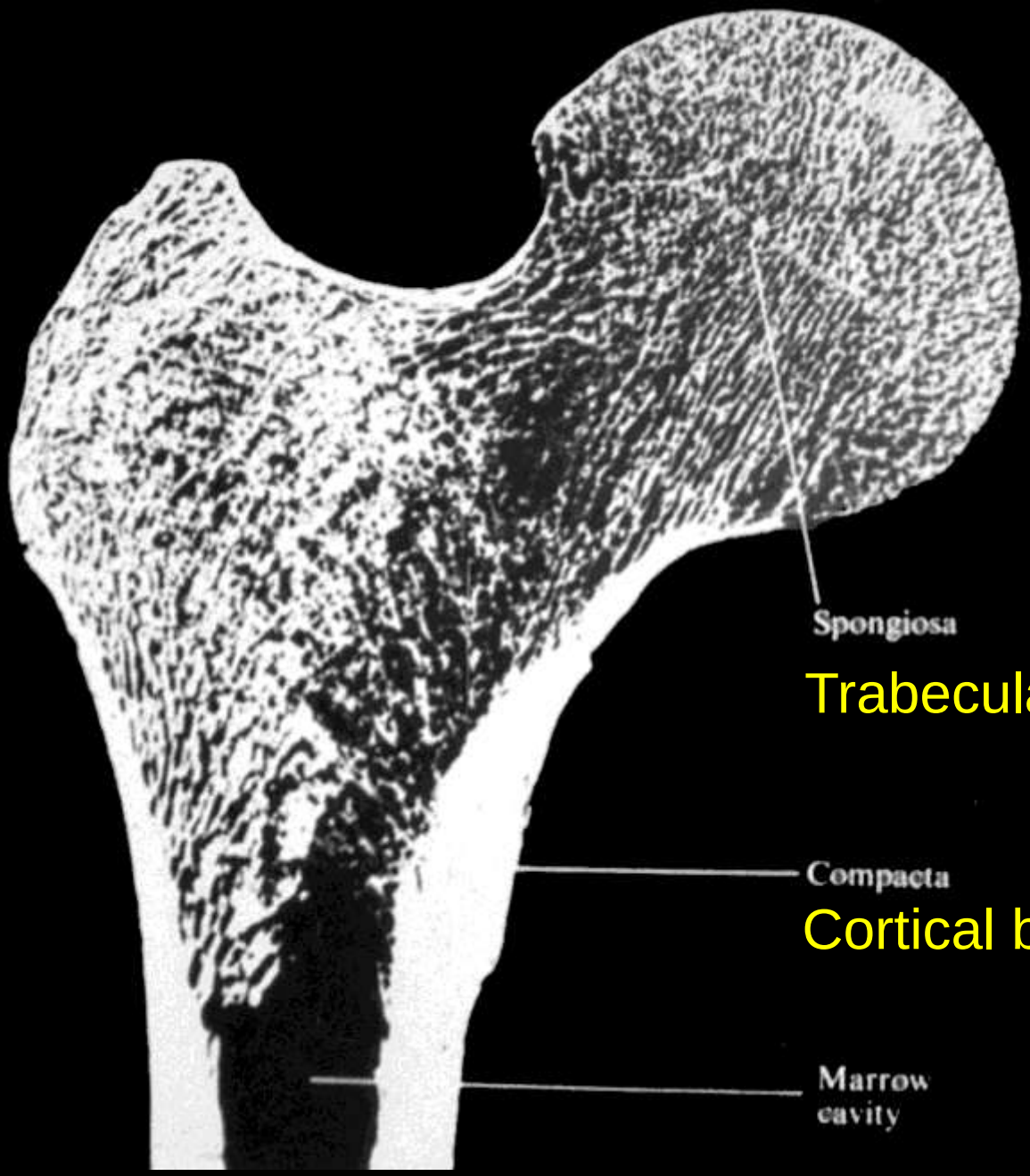
Craniodiaphyseal dysplasia
Craniometaphyseal dysplasia
Dysosteosclerosis
Endosteal hyperostosis
    Van Buchem Disease
    Sclerosteosis
Frontometaphyseal dysplasia
Infantile cortical hyperostosis
    (Caffey disease)
Melorheostosis
Metaphyseal dysplasia (Pyle disease)
Osteoectasia with hyperphosphatasia
Mixed sclerosing bone dystrophy
Oculodento-osseous dysplasia
Osteodysplasia of Melnick and Needles
Osteoectasia with hyperphosphatasia
    (hyperostosis corticalis)
Osteopathia striata
Osteopetrosis
Osteopoikilosis
Progressive diaphyseal dysplasia
    (Engelmann disease)
Pyknodysostosis

## Metabolic

Carbonic anhydrase II deficiency
Fluorosis
Heavy metal poisoning
Hypervitaminosis A,D
Hyper-, hypo- and pseudohypoparathyroidism
Hypophosphatemic osteomalacia
Milk-alkali syndrome
Renal osteodystrophy

## Other

Axial osteomalacia
Fibrogenesis imperfecta ossium
Ionizing radiation
Lymphoma
Mastocytosis
Multiple myeloma
Myelofibrosis
Osteomyelitis
Osteonecrosis
Paget's disease
Sarcoidosis
Skeletal metastases
Tuberous sclerosis


Spongiosa
Trabecular bone
Compacta
Cortical bone
Marrow cavity

# Definitions

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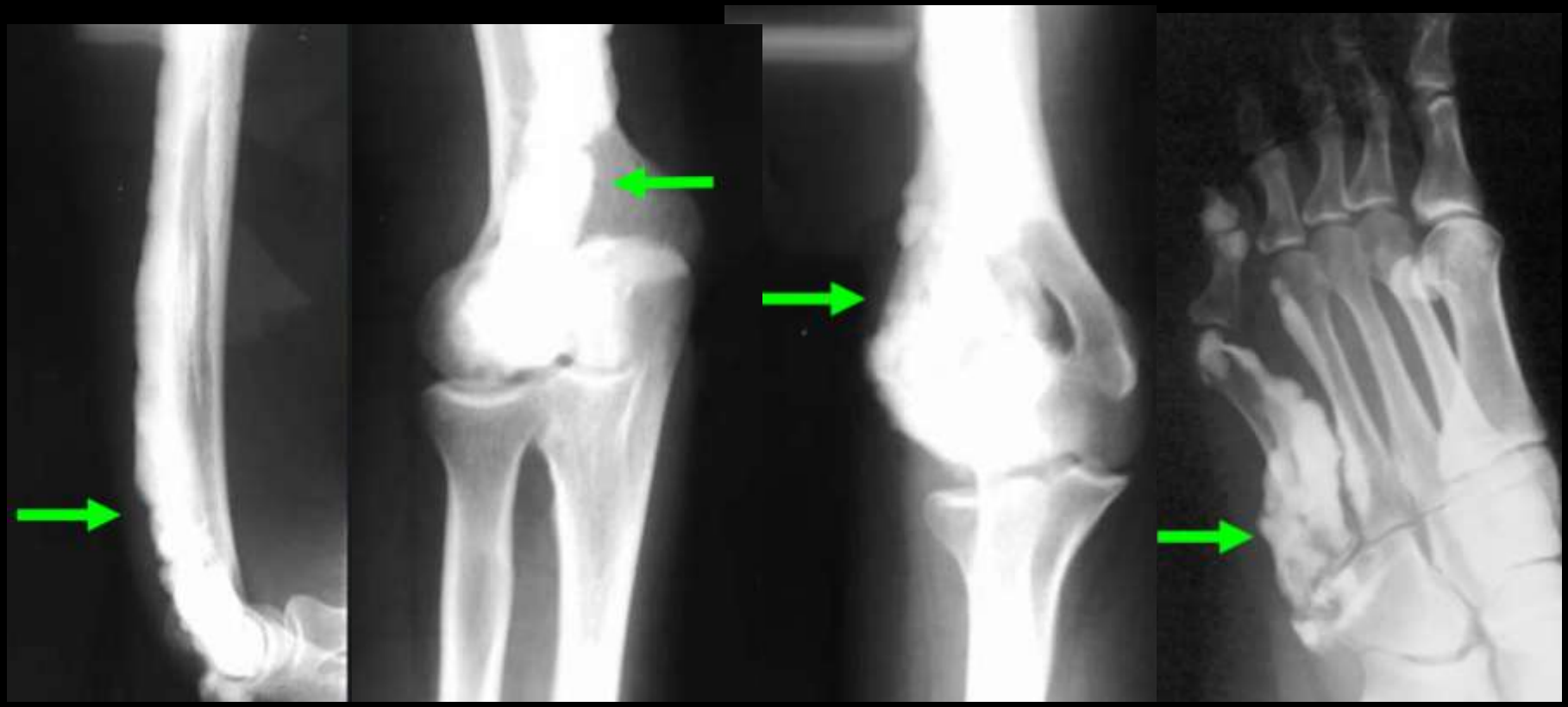
# *‘ flowing candle wax ’*



Source: Yun Zhang, “Melorheostosis Studies at Oxford” 2008 Melorheostosis Conference

# Dysostosis

Peculiar
formation of one or more
individual bones
(asymmetrical)

# Prevalence

- 1 – 1.5 million worldwide (1 per 6,000 people)

  ‘One-in-a-million’

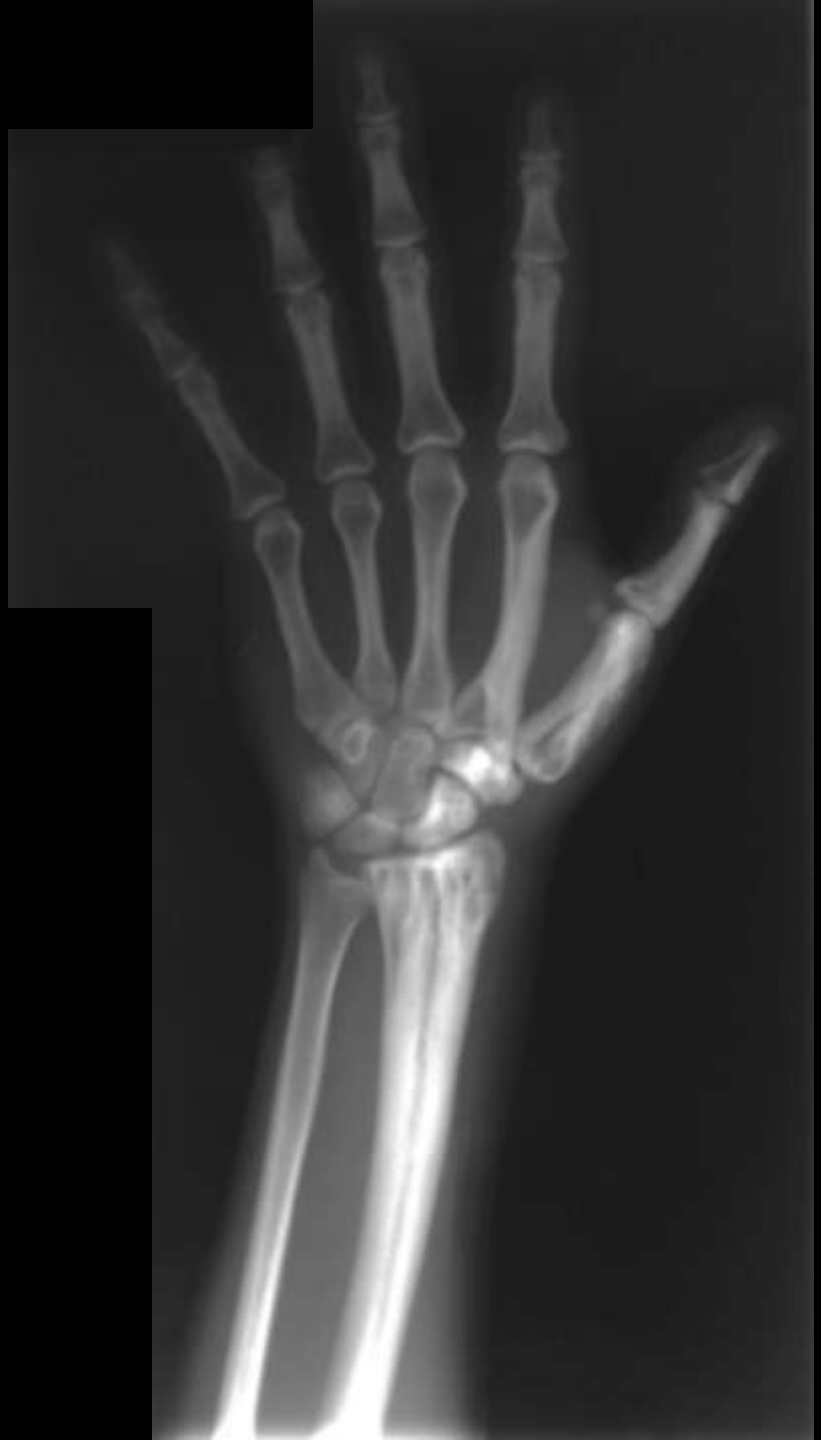
- Both genders
- 400 case reports
- 364 PubMed results

# Where in the Skeleton ?

- Focal Skeletal Disease
  (Appendicular > axial skeleton)
- Most Common: Arms, hands, legs, feet
  (Can be Unilateral / Bilateral)
- Less Common: Pelvis, hips, sternum, ribs
- Rare: Spine and skull

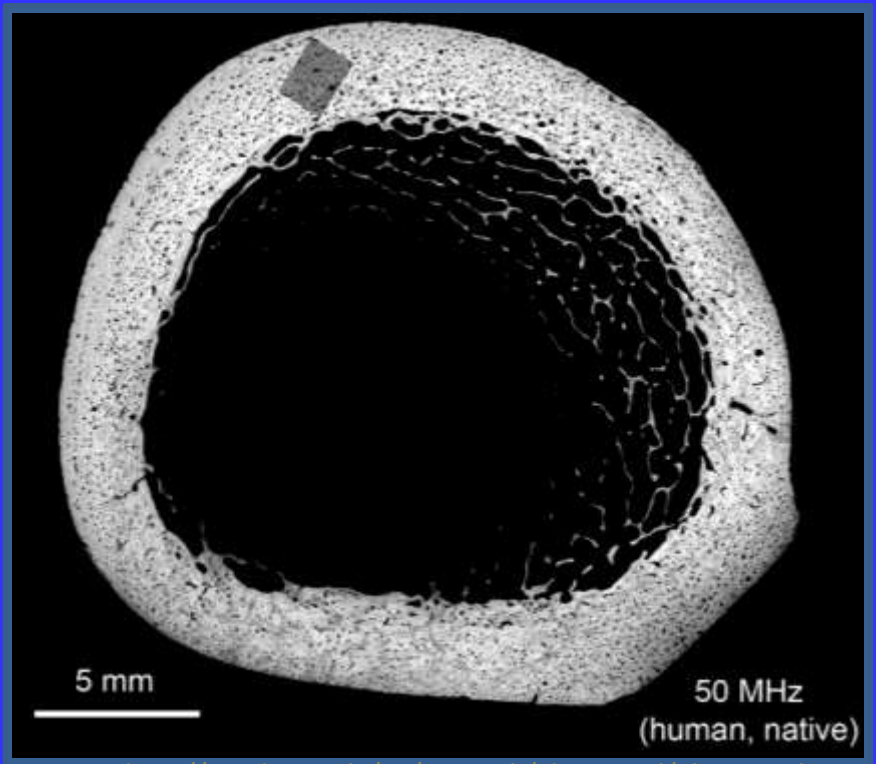
# Where ?

- Lower limbs more frequently than upper
- One bone (monostotic); several bones (polyostotic)
- One limb affected in several usually contiguous areas (monomelic)
- Lesions may affect only one side of a bone (same sclerotome or group of sclerotomes)



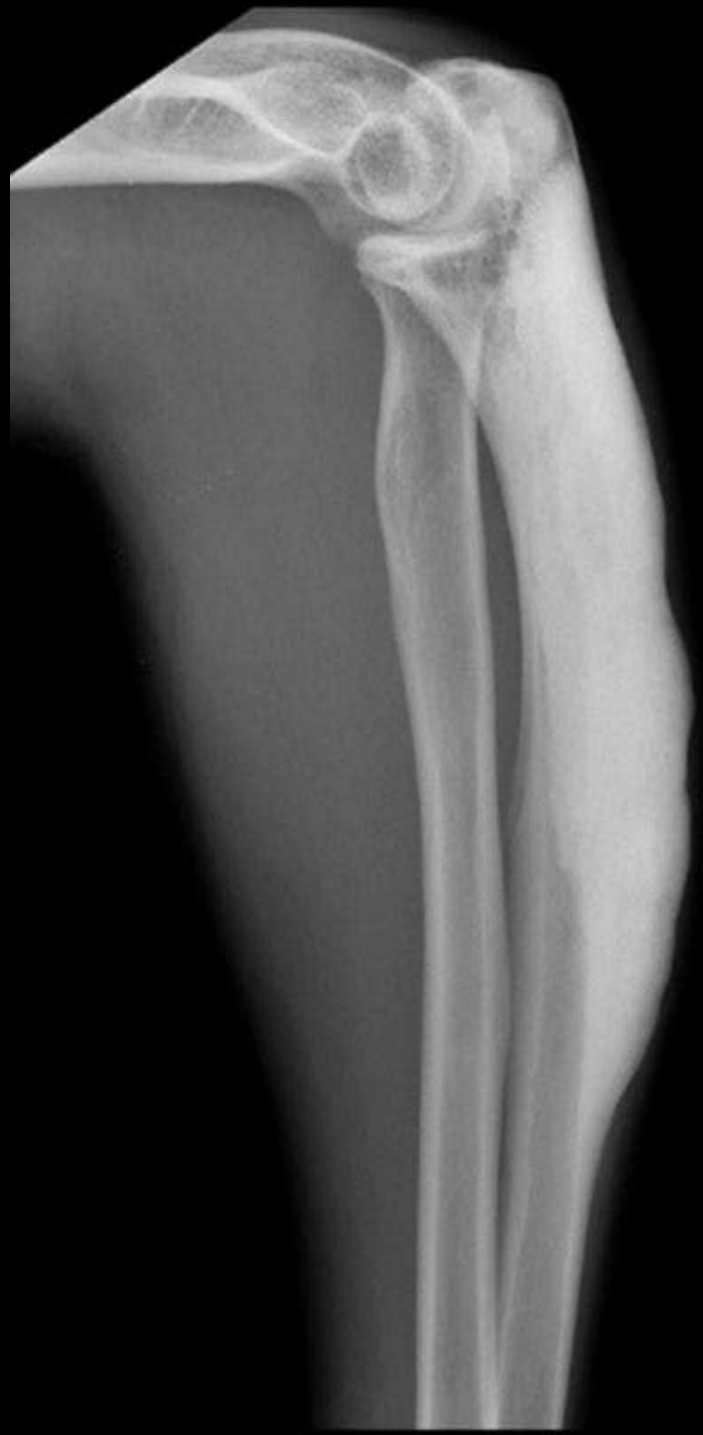
# Imaging Findings

- Cortical hyperostosis with an undulating appearance
- Hyperostosis (widened bones), including the endosteal (inner) surface
- Soft tissue lesions adjacent to involved bone that may calcify
- May grow to compress nerves
- Bone scan is markedly positive (different stages of activity)
- Usually low signal on MRI
- Enhance with Gadolinium




Source: http://jwi.charite.de/en/research/ultrasound/ultrasound_spectroscopy_acoustic_microscopy/microelastic_imaging_of_bone/

Source: DeGroot H., in http://www.learningradiology.com/archives2009/COW%20358-Melorheostosis/melorheocorrect.htm

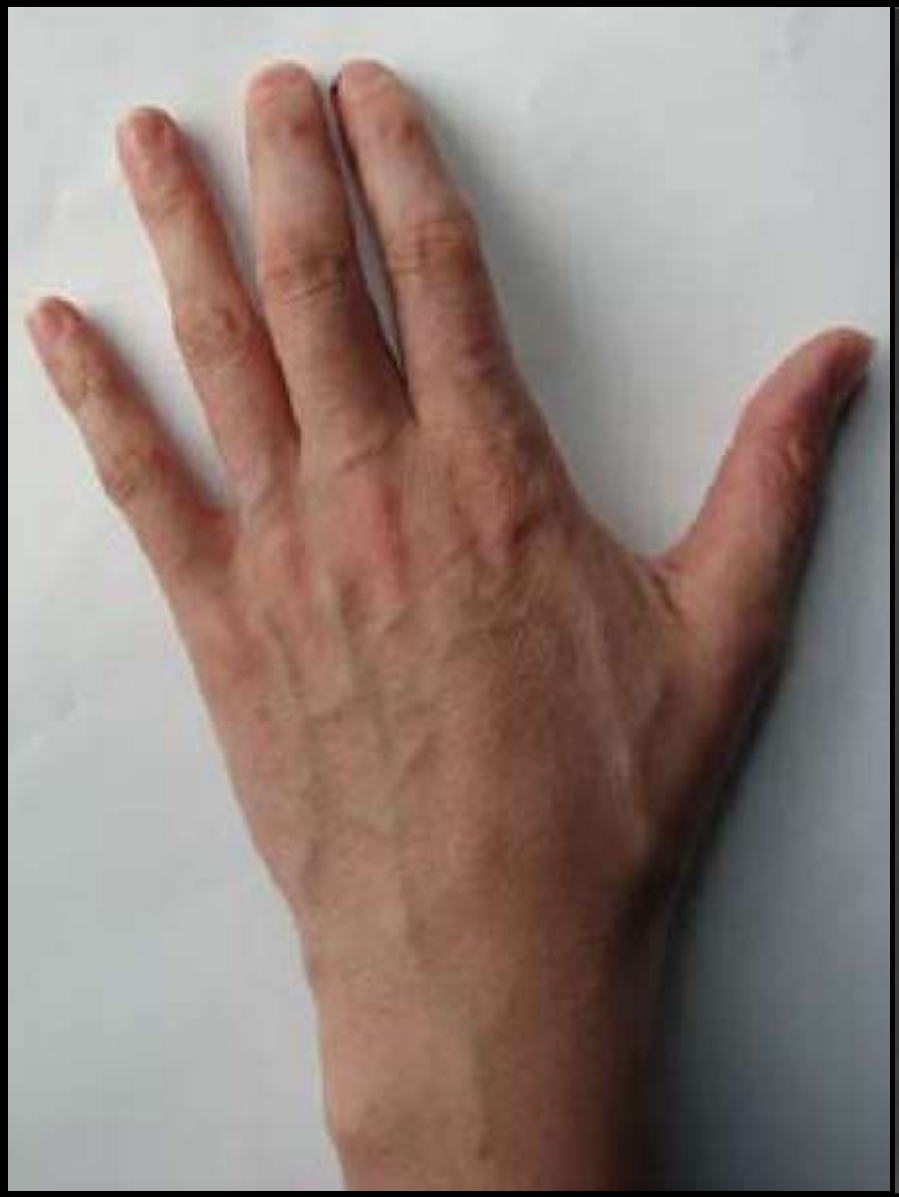


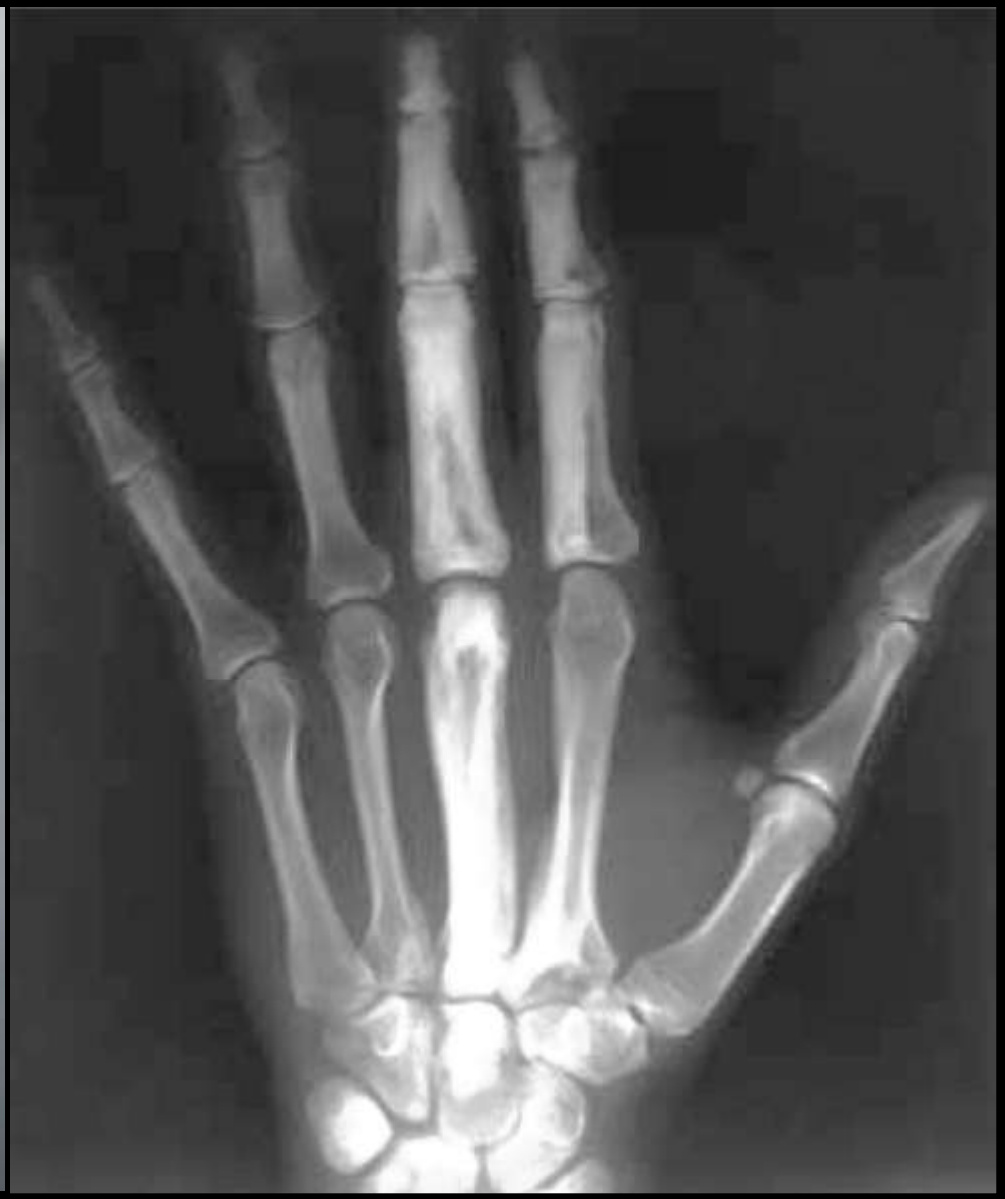
# Radiographic Findings

- Excrescences (outgrowths from the surface)
- Affect tubular bones as “bands” or “spots”
- Epiphyseal spotting (that is not osteopoikilosis)
- Specific patterns of involvement

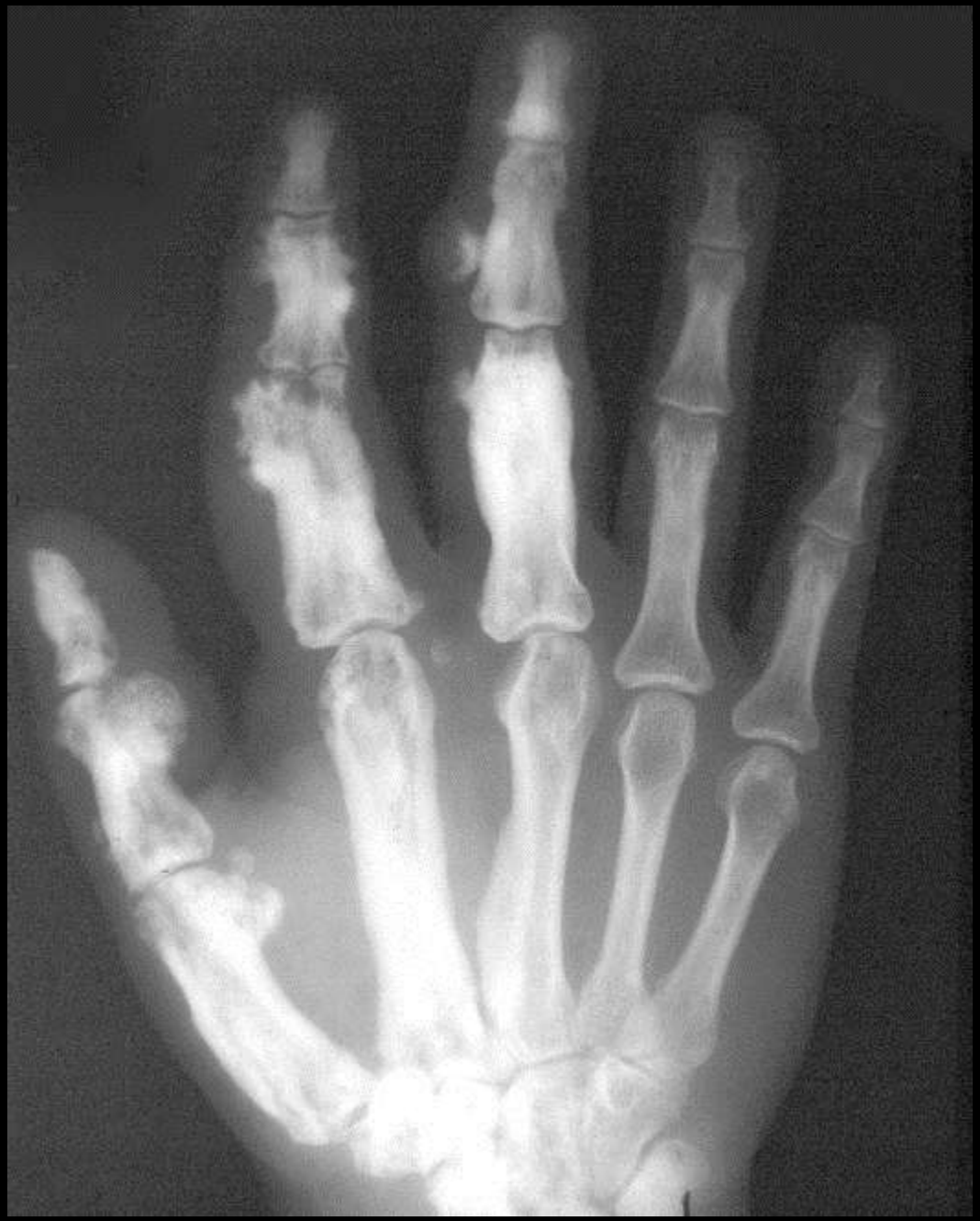
# Radiographic Findings

- In childhood, streaking of inside of long bones
- Adults have classic bony changes
- Soft tissue lesions can be mistaken for cancers
- Cortical lesions are progressive
- Spinal cord impingement
- Motor or sensory nerves may be compressed
- Cortical hyperostosis may expand into nearby joints



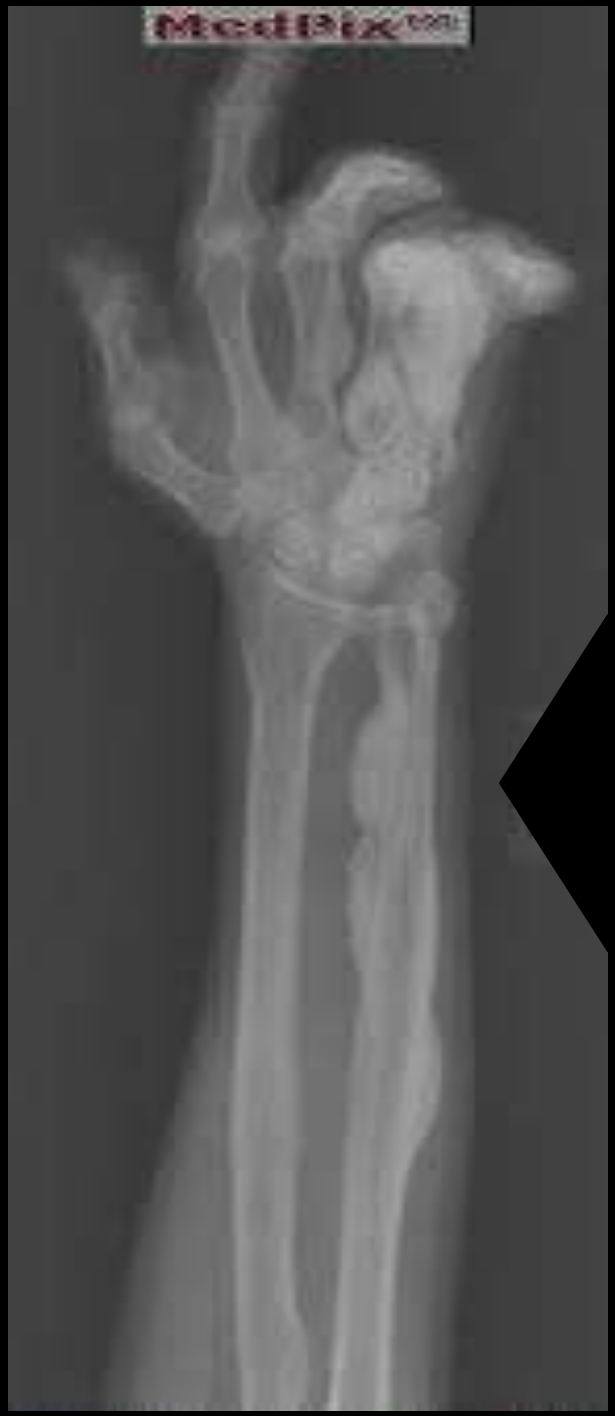


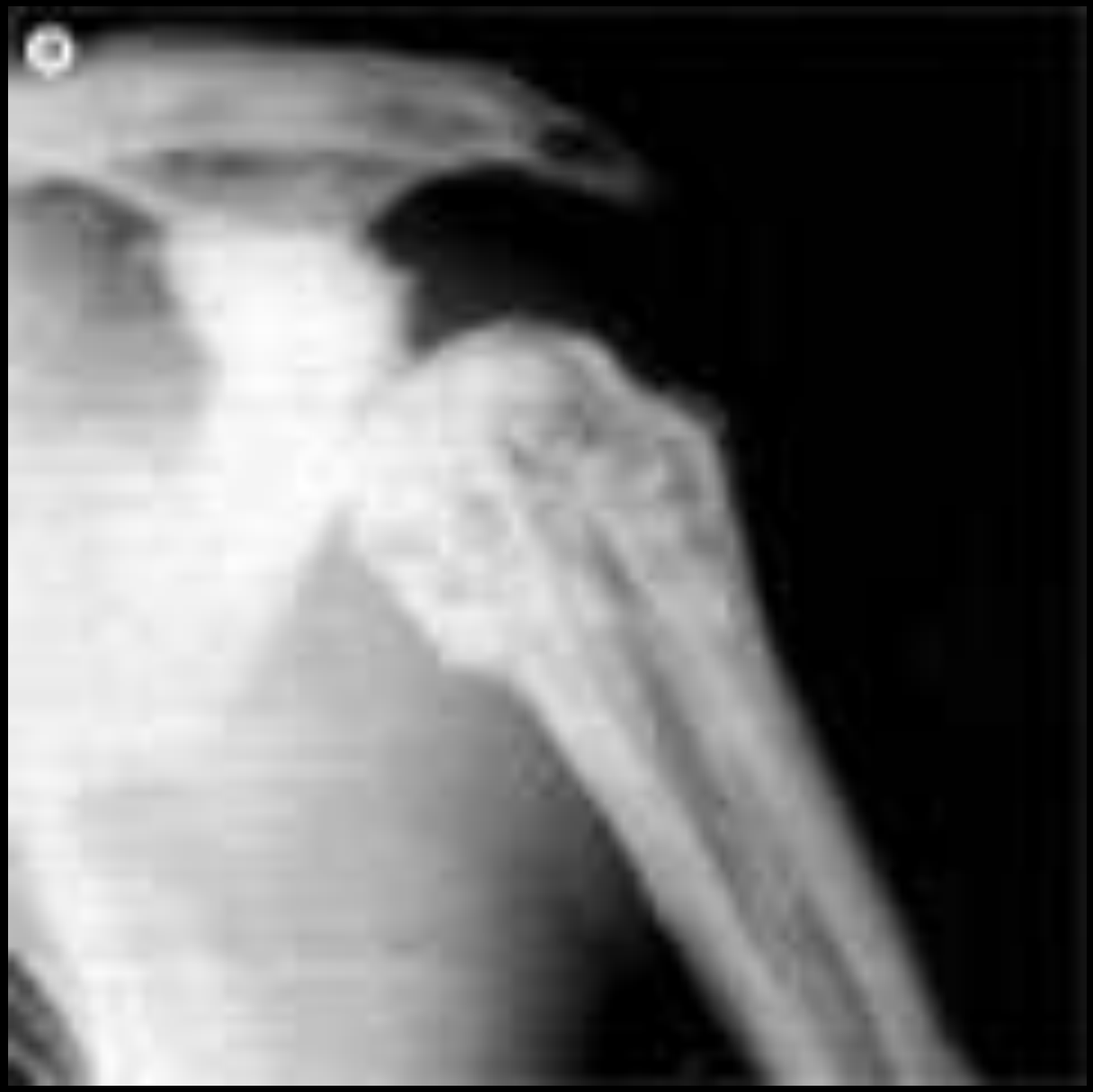
Source: Yun Zhang, “Melorheostosis Studies at Oxford” 2008 Melorheostosis Conference



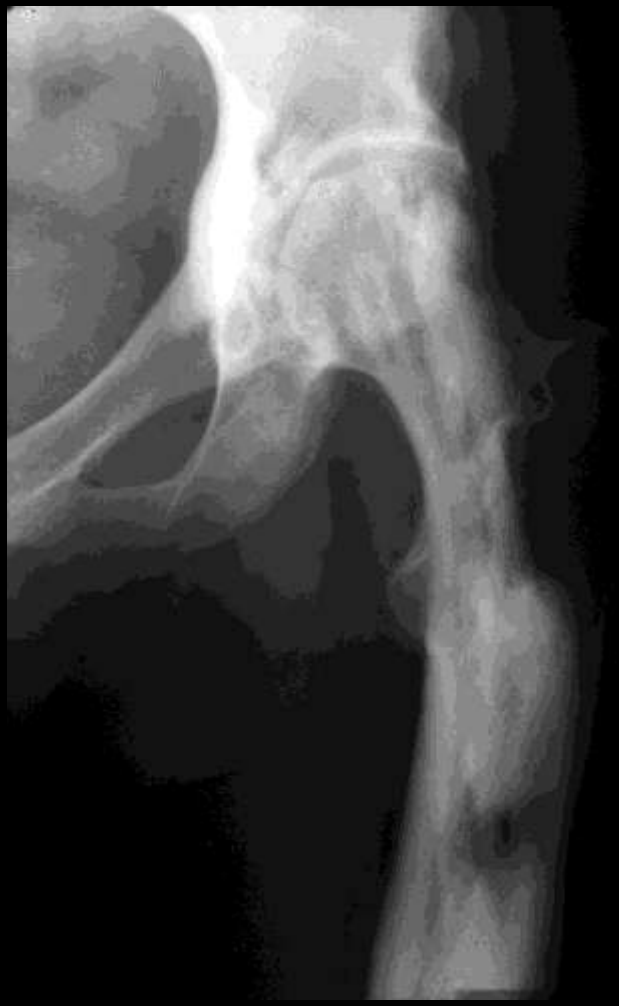
Macrodactyly of the first through third rays.

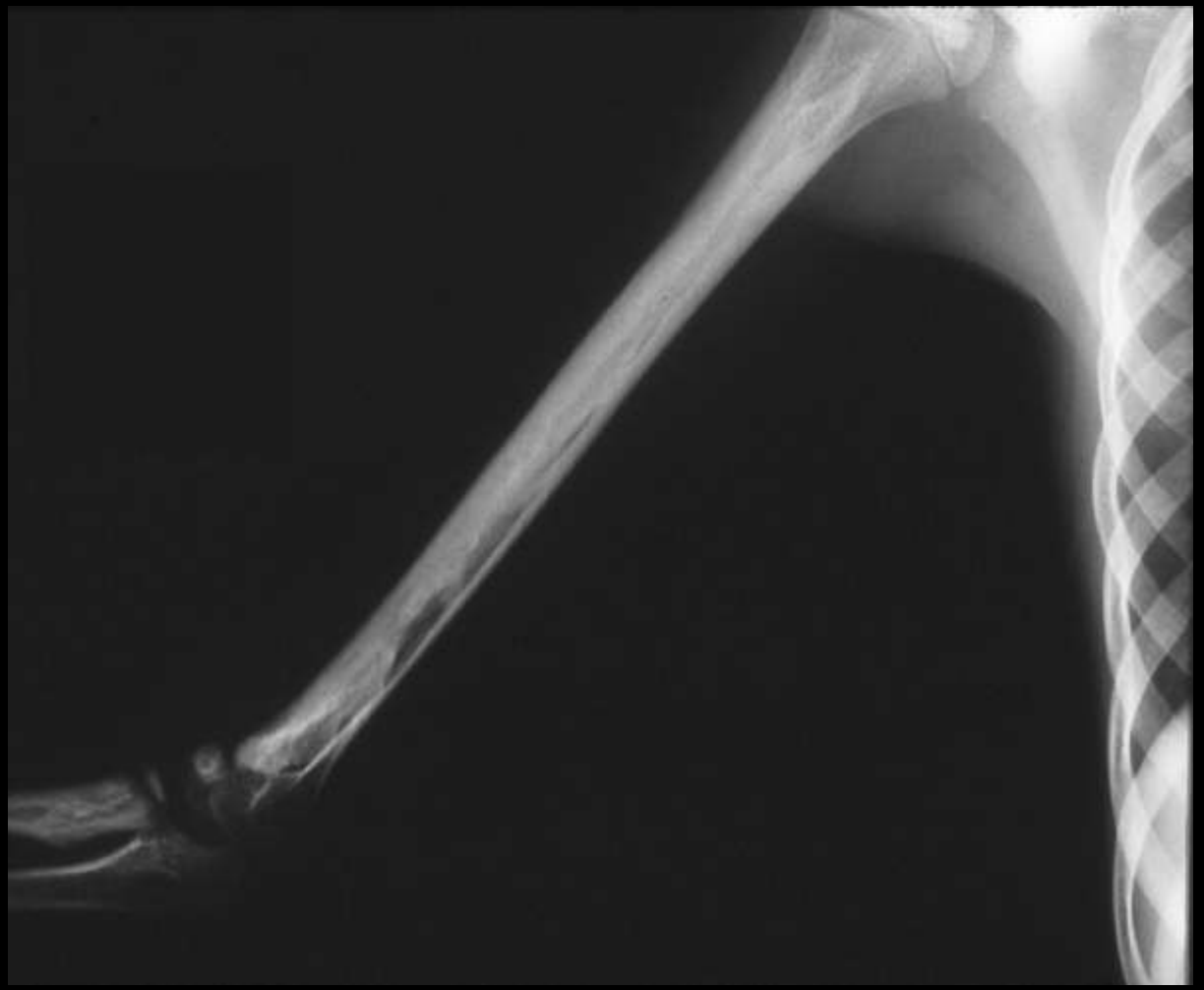
Reader and Felsons
*Gamuts in Radiology*


MedRix



SOURCE: Anna Kutkowska-Kazmierczak, Ewa Obersztyn, Kazimierz Kozlowski
Melorheostosis - Ritka megjelenési forma. Magyar Radiológia - 2004;78(6





# Pathology

- Very dense bone
- Irregularly arranged haversian systems with dense, thick trabeculae
- Markedly irregular bone with mixed lamellar woven bone
- Increased angiogenesis
- Mixture of osteocartilagenous, fibrovascular, and adipose tissue
- Fibrocartilage in  joint spaces

# Onset & Progression

- Usually apparent in early childhood (even first days of life)
- Infant through old age
- 50% will have symptoms by age 20 years
- Can be: incidental finding.
  with deformity or contracture.
  with pain or other neurologic symptoms.
- Adults: pain and joint stiffness
- Skin and soft tissue abnormalities (can precede bony changes)

# Symptoms and Presentation

In children, the condition affects mainly the bones of the extremities and pelvis, and may result in limb length inequality, deformity, or joint contractures.

Adults generally complain of pain, joint stiffness, and progressive deformity.

Joint contractures may be accompanied by extraosseous bone formation.

http://www.bonetumor.org/tumors-foot-and-ankle/melorheostosis

# Physical Examination

- Band type, scleroderma circumscripta
- Anomalous pigmentation
- Vascular changes (hemangiomas and nevi)
- Nevoid telangiectasia, anterioraneous aneurysm
- Edema (lymphedema)
- Contractures
- Fibrosis of muscle and tendons

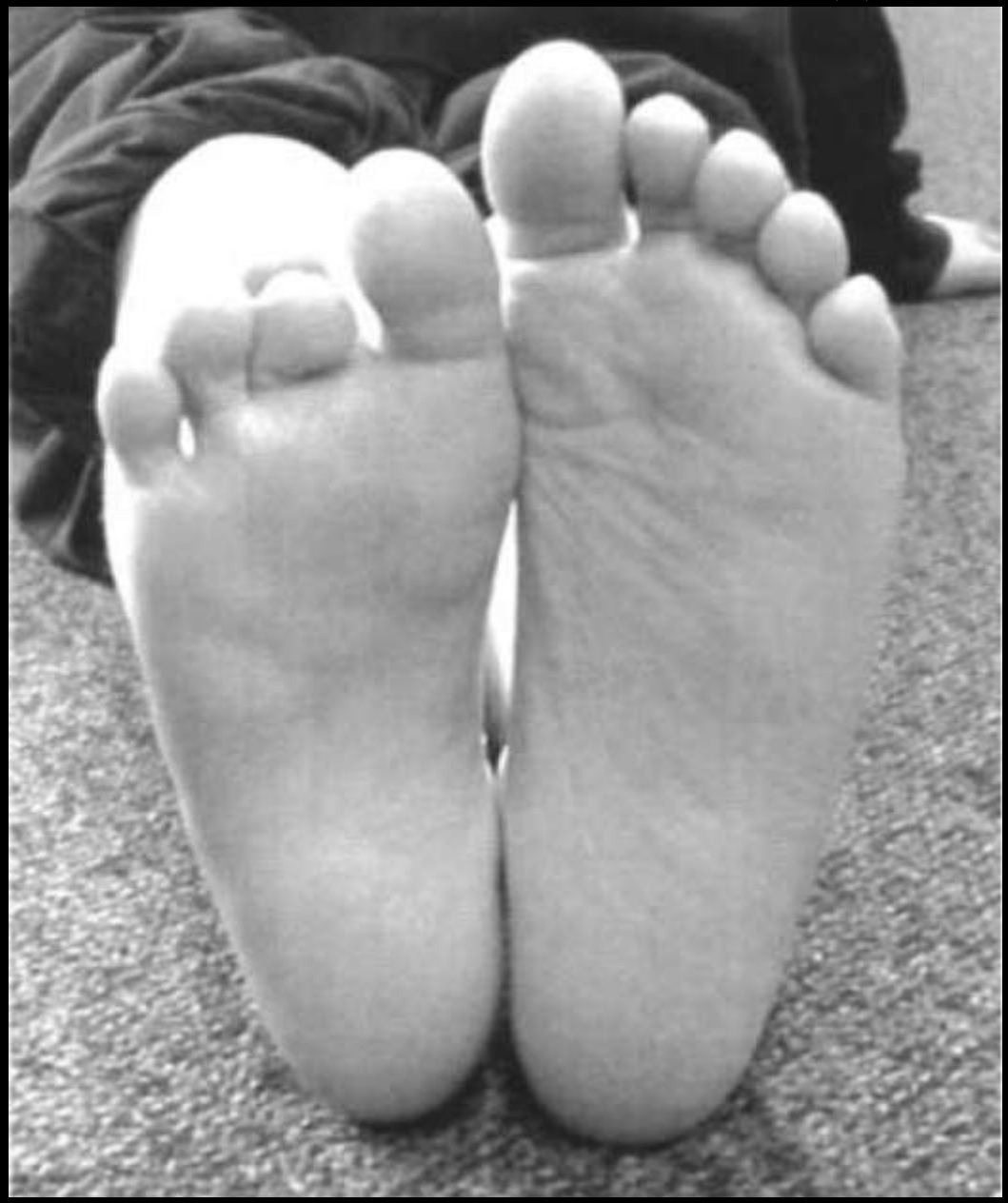
# Physical Examination

- Muscle wasting
- Excrescences (outgrowths on the surface) along longitudinal bone axis
- Glomus tumors
- Desmoid tumors

# Complications

- Progressive Deformity
- Limb/Hand/Foot Deformity
- Bone pain
- Joint stiffness
- Nerve compression (adults only, and rare)
- Increased finger size
- Scoliosis
- Shortening of affected bones (also lengthening)

Schreck M. Am Podiatr Med Assoc 2005;95(2): 167–70.



http://www.japmaonline.org/content/95/2/167.abstract

# Complications

- Soft tissue contractures of joints
- Palmar/plantar fasciitis
- Intermittent swelling of affected joints
- Juxta-articular masses
- Intermittent, painful swelling of affected joints

# Clinical Complications

- Malignant bone tumors (osteosarcoma & malignant fibrohistiocytoma)
- Nephrotic syndrome
- Mesenteric fibromatosis
- Lipoma of spinal cord
- Fibrolipomatosis lesion
- Oncogenic rickets
- Carpal-tunnel syndrome

# Clinical Complications

- Renovascular hypertension
- Glomus tumors
- Sebaceous nevus
- Desmoid tumors (soft tissue tumor of limbs)
- Vascular compromise
- Raynaud's phenomenon

# Other Associations

- Osteopoikilosis
- Osteopathia Striata
- Neurofibromatosis Type 1
- Tuberous Sclerosis
- Infantile Cortical Hyperostosis

  (Juvenile Paget Disease)
- Gardner Syndrome

# Symptoms

- Bone pain
- Joint stiffness
- Muscle wasting
- Segmental or total asymmetry of limbs
- Skin and soft tissue abnormalities

# Symptoms

May be progressive.

Initially pains and swelling in joints, and problems in movement.

When severe -- muscle contractures, tendon and ligament shortening, and other soft tissue problems.

Also, anxiety, depression, obsession, severe low back pain

# Outcomes

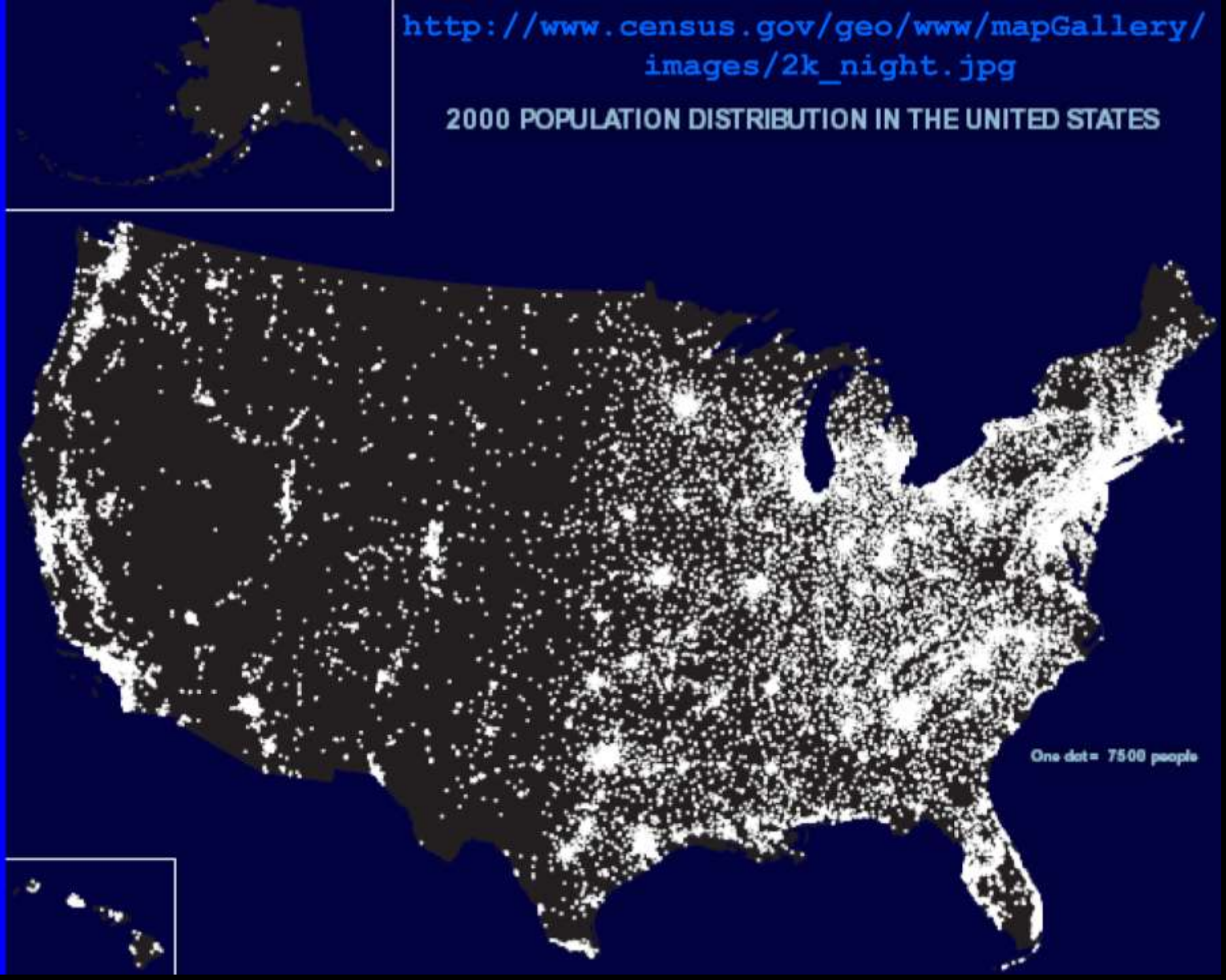
- Non-lethal bone disease – one patient died from pleural effusions due to vascular malformations
- Progressive disorder
- Earlier presentation and multiple limb involvement may predict a poorer prognosis

# Etiology

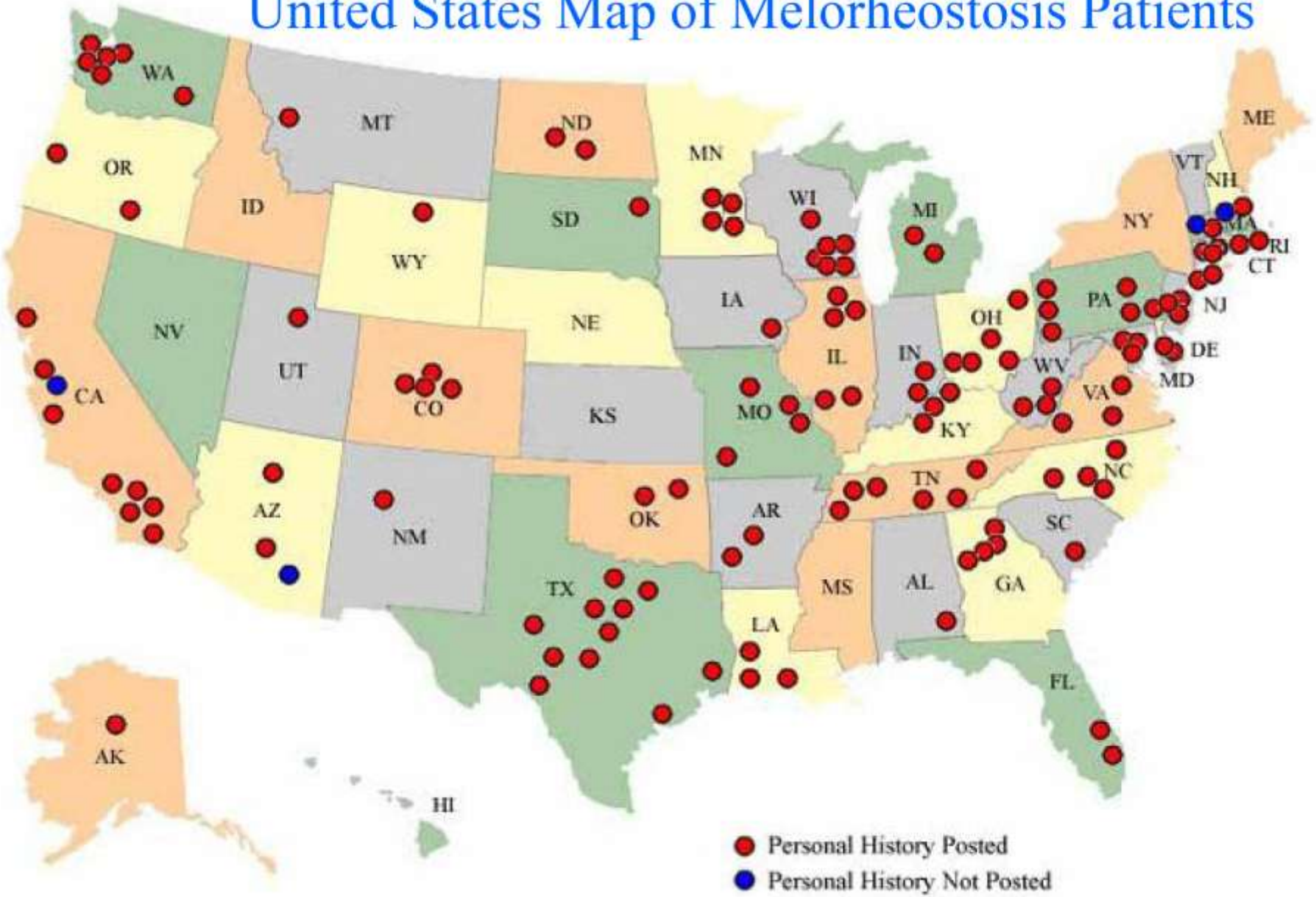
Hypotheses have included:

- Reaction to infection
- Reaction to trauma
- Autoimmune diseases
- Sensory neuropathy
- Vascular abnormality
- Post-zygotic mutation
- Mesenchymal cell differentiation problem (“mesenchyme madness”)
- Excessive estrogen or $E_2$ receptors

http://www.census.gov/geo/www/mapGallery/images/2k_night.jpg



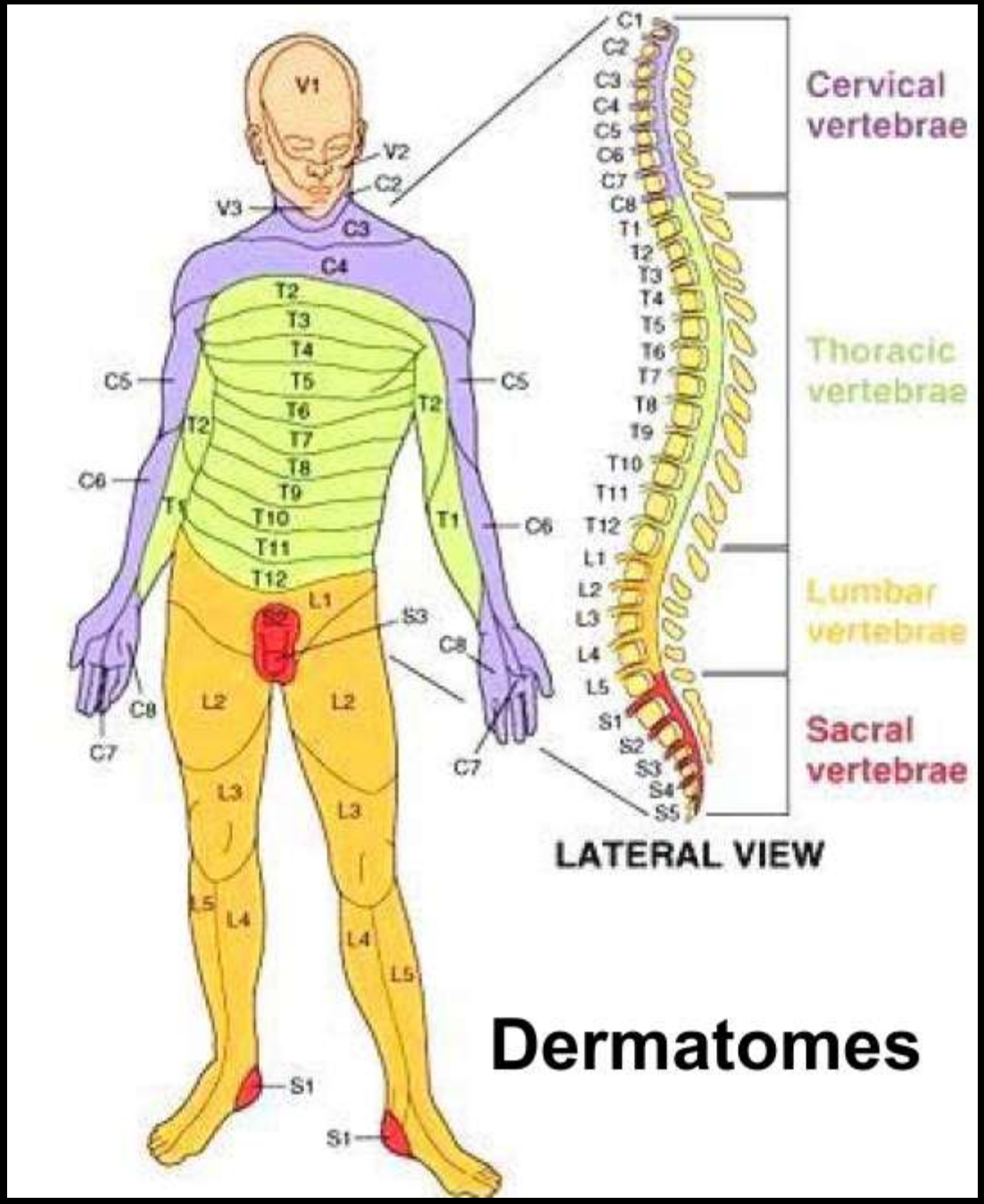
# United States Map of Melorheostosis Patients




http://www.melorheostosis.com/default_files/Page1000.htm

# Etiology

- Postnatal
- Sporadic (usually)
- All tissues of mesenchyme can be deranged (skin, fascia, muscle, tendons, and ligaments)
- No hereditary basis, or sometimes autosomal dominant
- Somatic mutation ? (Segmental, Type 2)
  - Sclerotomes reflect the segmental pattern of early development
  - Melorheostosis lesions may correspond to a ‘sclerotome’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L4
L5
S1
S2
S3
S4
S5
Cervical vertebrae
Thoracic vertebrae
Lumbar vertebrae
Sacral vertebrae
LATERAL VIEW
Dermatomes

# Etiology

*A sclerotome is a zone of the skeletal supplied by an individual spinal sensory nerve, and represents a basic unit of vertebral embryonic development*

- ? Areas of the embryonic skeleton supplied by individual spinal sensory nerves
- ? Sensory sclerotomes perhaps with defects in the sensory nerve supply to the area of melorheostosis
- ? Acquired, postnatal neuropathy of sensory nerves

- ? Vascular pathogenesis (inflammation followed by obliteration)

American Journal of Medical Genetics 125A:221–223 (2004)

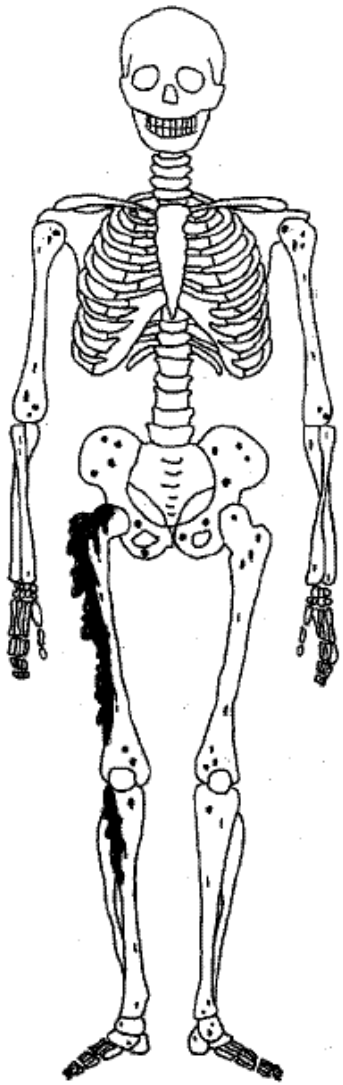
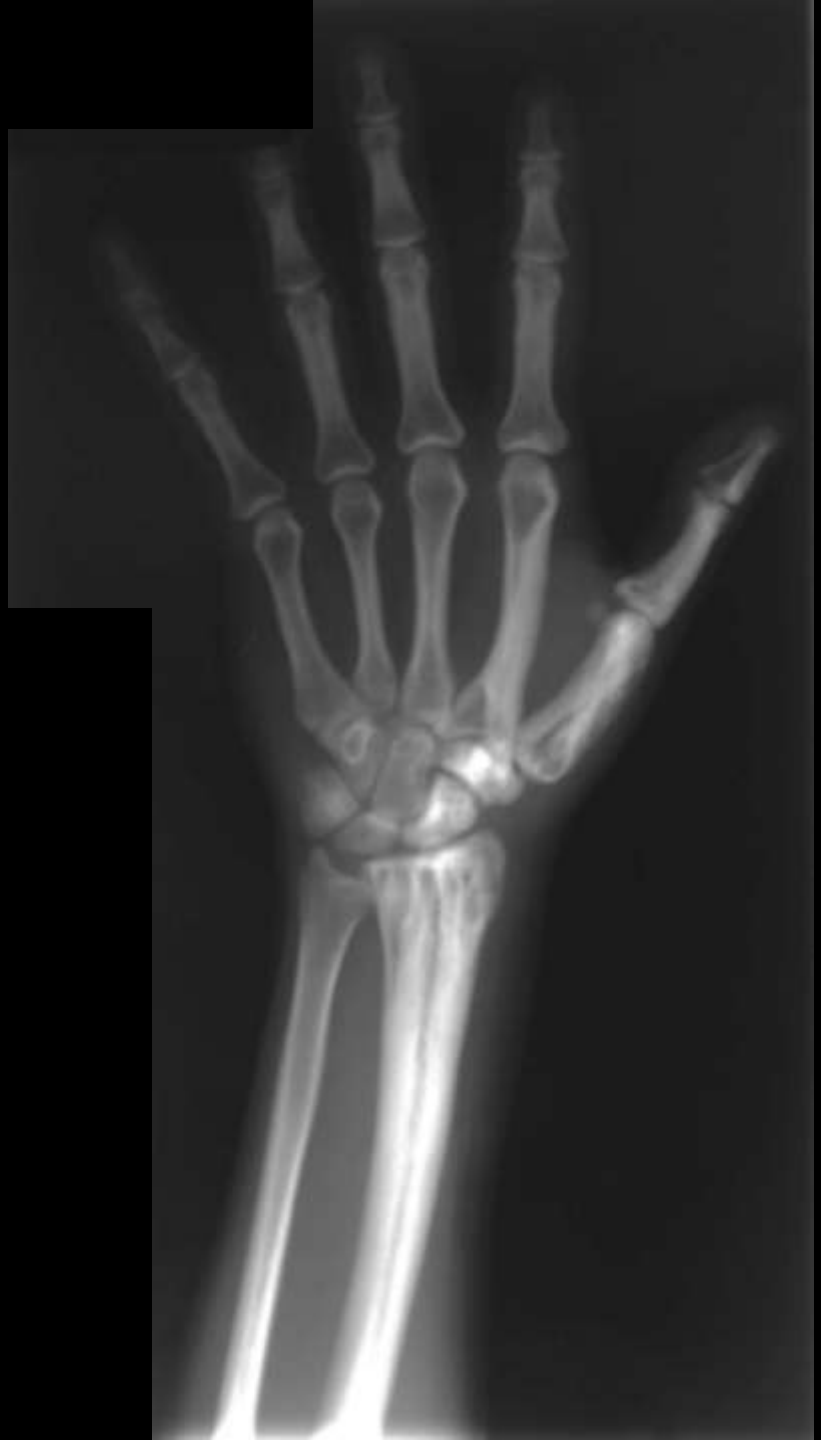


Fig. 1. Schematic drawing showing melorheostosis superimposed on mild disseminated bone lesions, suggesting a type 2 segmental manifestation of autosomal dominant osteopoikilosis.



American Journal of Medical Genetics 125A:221–223 (2004)

# Melorheostosis May Originate as a Type 2 Segmental Manifestation of Osteopoikilosis

**Rudolf Happle***

*Department of Dermatology, Philipp University of Marburg, Marburg, Germany*

**Melorheostosis is a non-hereditary disorder involving the bones in a segmental pattern, whereas osteopoikilosis is a rather mild disseminated bone disorder inherited as an autosomal dominant trait. Interestingly, melorheostosis and osteopoikilosis may sometimes occur together. In analogy to various autosomal dominant skin disorders for which a type 2 segmental manifestation has been postulated, melorheostosis may be best explained in such cases as a type 2 segmental osteopoikilosis, resulting from early loss of the corresponding wild type allele at the gene locus of this autosomal dominant bone disorder.** 

trically involving the bones, and represents an autosomal dominant trait [Chigira et al., 1991]. The two disorders may coexist in the same individual [Walker, 1964; Ostrowski and Gilula, 1992], and such sporadic co-occurrence may be found in a family with osteopoikilosis [Butkus et al., 1997; Nevin et al., 1999].

## MELORHEOSTOSIS MAY REFLECT MOSAICISM

Because melorheostosis is a non-hereditary trait and always shows a segmental arrangement, Fryns [1995] argued that it might result from a postzygotic mutation occurring during embryogenesis. Freyschmidt [2001] proposed the concept of a lethal mutation that can only

- Osteopoikilosis (OPK) =

  "Spotted bones"

- Buschke-Ollendorff Syndrome (BOS) =

  OPK + Connective Tissue Nevi

  (dermatofibrosis lenticularis disseminata & juvenile elastomas)

American Journal of Medical Genetics 82:409–414 (1999)

# Melorheostosis in a Family With Autosomal Dominant Osteopoikilosis

Norman C. Nevin,[1,2*] Paul S. Thomas,[3] Richard I. Davis,[4] and G. Harry Cowie[5]

[1]*Regional Genetics Centre, Belfast City Hospital, Belfast, Northern Ireland, United Kingdom*
[2]*Department of Medical Genetics, The Queen's University of Belfast, Belfast, Northern Ireland, United Kingdom*
[3]*Department of Paediatric Radiology, Royal Belfast Hospital for Sick Children, Belfast, Northern Ireland, United Kingdom*
[4]*Department of Pathology, Belfast City Hospital, Belfast, Northern Ireland, United Kingdom*
[5]*Regional Orthopaedic Service, Musgrave Park Hospital, Belfast, Northern Ireland, United Kingdom*

**We describe a 19-year-old woman with melorheostosis and osteopoikilosis (mixed sclerosis) of the lower limb. The radiological findings are irregular asymmetrical bands of sclerosis in an irregular linear**

# Patient # 2

American Journal of Medical Genetics 72:43–46 (1997)

# Melorheostosis in a Patient With Familial Osteopoikilosis

Christine E. Butkus,[1] Virginia V. Michels,[2*] Noralane M. Lindor,[2] and William P. Cooney III[3]

[1]*Department of Internal Medicine, University of Rochester, Rochester, New York*
[2]*Department of Medical Genetics, Mayo Clinic/Foundation, Rochester, Minnesota*
[3]*Department of Orthopedic Surgery, Mayo Clinic/Foundation, Rochester, Minnesota*

**We report on a 40-year-old woman with melorheostosis who also had radiographic findings of generalized osteopoikilosis. Three of her sibs have osteopoikilosis, but none of them have melorheostosis. Several cases of**

sulting from indurated soft-tissue contractures may be the first sign of the disease [Beauvais et al., 1977; Green et al., 1962; Thompson et al., 1951]. The severity is variable, and some cases may be discovered as an incidental radiologic finding [Campbell et al., 1968]. It

American Journal of Medical Genetics 119A:188–193 (2003)

*Clinical Report*

# Melorheostosis in a Family With Autosomal Dominant Osteopoikilosis: Report of a Third Family

**Philippe Debeer,[1,2]* E. Pykels,[1] J. Lammens,[2] K. Devriendt,[1] and J.-P. Fryns[1]**

[1]*Centre for Human Genetics, University Hospital Leuven, Herestraat, Leuven, Belgium*
[2]*Department of Orthopedics, University Hospital Pellenberg, Weligerveld, Pellenberg, Belgium*

**We describe a three-generation family with clinical and radiological findings of osteopoikilosis in five and melorheostosis in one individual. The co-occurrence of both rare**

mid and lower dermis, associated with clumping of hypertrophic elastic fibers (juvenile elastoma). Berlin et al. [1967] demonstrated that skin or bony lesions can be absent in some family members while other family

nature genetics

Nature Genetics Volume 36 Number 11 November 2004

# Loss-of-function mutations in *LEMD3* result in osteopoikilosis, Buschke-Ollendorff syndrome and melorheostosis

Jan Hellemans[1], Olena Preobrazhenska[2], Andy Willaert[1], Philippe Debeer[3], Peter C M Verdonk[4], Teresa Costa[5], Katrien Janssens[6], Bjorn Menten[1], Nadine Van Roy[1], Stefan J T Vermeulen[1], Ravi Savarirayan[7], Wim Van Hul[6], Filip Vanhoenacker[8], Danny Huylebroeck[2], Anne De Paepe[1], Jean-Marie Naeyaert[9], Jo Vandesompele[1], Frank Speleman[1], Kristin Verschueren[2], Paul J Coucke[1] & Geert R Mortier[1]



**Osteopoikilosis, Buschke-Ollendorff syndrome (BOS) and melorheostosis are disorders characterized by increased bone density[1]. The occurrence of one or more of these phenotypes in the same individual or family suggests that these entities might be allelic[2–4]. We collected data from three families in which affected individuals had osteopoikilosis with or without manifestations of BOS or melorheostosis. A genome-wide linkage analysis in these families, followed by the identification of a microdeletion in an unrelated individual with these diseases, allowed us to map the gene that is mutated in**

an autosomal dominant disorder, refers to the association of osteopoikilosis with disseminated connective-tissue nevi. Both elastic-type nevi (juvenile elastoma) and collagen-type nevi (dermatofibrosis lenticularis disseminata) have been described in BOS[8]. Skin or bony lesions can be absent in some family members, whereas other relatives may have both[9]. The co-occurrence of osteopoikilosis and melorheostosis in the same family has been reported in a few instances[2–4]. Melorheostosis (OMIM 155950) is characterized by a 'flowing' (rheos) hyperostosis of the cortex of tubular bones. These lesions are usually asymmetric: they may involve only one limb or correspond to a

# S. Mumm, et. al (2007) *J Bone Miner Res* 22:243-250

JOURNAL OF BONE AND MINERAL RESEARCH
Volume 22, Number 2, 2007
Published online on November 6, 2006; doi: 10.1359/JBMR.061102


## Deactivating Germline Mutations in *LEMD3* Cause Osteopoikilosis and Buschke-Ollendorff Syndrome, but Not Sporadic Melorheostosis*

Steven Mumm,[1,2] Deborah Wenkert,[2] Xiafang Zhang,[1] William H McAlister,[3] Richard J Mier,[4] and Michael P Whyte[1,2]

**ABSTRACT:** Autosomal dominant OPK and BOS feature widespread foci of osteosclerotic trabeculae without or with skin lesions, respectively. Occasionally, a larger area of dense bone in OPK or BOS resembles MEL, a sporadic sclerosing disorder primarily involving cortical bone. Others, finding deactivating germline *LEMD3* mutations in OPK or BOS, concluded such defects explain all three conditions. We found germline *LEMD3* mutations in OPK and BOS but not in sporadic MEL.

- *LEMD3* mutation found in:
  - 1 OPK family
  - 2 BOS families
  - 1 individual with MEL-like changes in familial OPK
- No *LEMD3* defect in 4 patients with sporadic MEL

# Conclusions

- "Melorheostosis - like" (? "melorheostosis #2") changes may occur in OP/BOS families with germline *LEMD3* mutations

  Precise cause of this type of melorheostosis is not known (study lesional tissue)
- Cause of sporadic (classic) melorheostosis remains unknown.

# Treatments

- Highly individualized

- Non-surgical
  - Deformity/stiffness
  - Pain relief

Source: *Overview of the Orthopedic Aspects of Melorheostosis: An Analysis of the Melorheostosis Association database* by Daniel Lewis, MD & Jeffrey C. King, MD at the Melorheostosis Conference, 2005

# Treatments

Surgical

- Deformity/stiffness
- Length inequality
- Pain relief
- Neurologic symptoms
- High recurrence rates
- De-bulking and decompression

Source: *Overview of the Orthopedic Aspects of Melorheostosis: An Analysis of the Melorheostosis Association database* by Daniel Lewis, MD & Jeffrey C. King, MD at the Melorheostosis Conference, 2005

# Treatments

- Analgesia
  - wrist
- Nerve blocks
- Surgery for relieving contractures
- Management directed at orthopedic complications ("occasional orthopedic measures“)
- Leg-lengthening
- Bone fusion
- Sympathectomy (nerve cutting)
- Amputation
- Bisphosphonates (e.g. pamidronate)

* See *Surgical Management of Melorheostosis: General Information and Considerations* by Jeffrey C. King, MD, and James Dobyns, MD.

*BMJ Case Reports* 2010; doi:10.1136/bcr.04.2009.1757

**Rare disease**

# Melorheostosis and its treatment with intravenous zoledronic acid

**Rosemary Jane Hollick**[1], **Alison Black**[1], **David Reid**[2]

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Rosemary Jane Hollick, rhollick@nhs.net

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## Summary

We report a case of melorheostosis, a rare bone disorder characterised by mesodermal dysplasia, and its successful and prolonged treatment with the intravenous bisphosphonate zoledronic acid. The middle-aged man presented with pain and swelling of his tibia, which was diagnosed by imaging and bone biopsy as being due to melorheostosis. There was early symptom control after a single infusion of intravenous zoledronic acid. Prolonged symptom relief was accompanied by long-term suppression of the bone resorption marker β cross-laps. We suggest that melorheostosis can be treated with intravenous zoledronic acid and that treatment can be monitored by the use of a specific bone resorption marker.

# Non-Surgical Treatments

Childhood deformity

- Splinting, bracing and serial casting are reported, but typically ineffective at preventing progression of deformity.

- Physical therapy is generally recommended to attempt to maintain joint mobility, but may fail as well.

Source: *Overview of the Orthopedic Aspects of Melorheostosis: An Analysis of the Melorheostosis Association database* by Daniel Lewis, MD & Jeffrey C. King, MD at the Melorheostosis Conference, 2005

# Non-Surgical Treatments

Pain management

- NSAIDS
- Nifedipine
- Nerve blocks/ sympathetic blocks

Symptomatic relief with vasodilator therapy

Physical & Occupational Therapy

Source: *Overview of the Orthopedic Aspects of Melorheostosis: An Analysis of the Melorheostosis Association database* by Daniel Lewis, MD & Jeffrey C. King, MD at the Melorheostosis Conference, 2005

"Every melorheostosis patient is unique"

"As soft tissue causes of deformity increase, the need for osseous, soft tissue, and skin correction increases"

"Surgery to alleviate mechanical effects from melorheostosis in adults seems to be fairly effective"

- Jeffrey C. King, MD, and James Dobyns, MD -

"Surgery for the sole purpose of relieving pain (non-mechanical) is rarely effective, unless that pain is a direct result of nerve pressure or irritation"

"Healing of osteotomies in melorheostotic bone is unpredictable and can be problematic"

"Contracture releases are more effective in adults than in children"

- Jeffrey C. King, MD, and James Dobyns, MD -

"If this information does not seem particularly encouraging, that is because the available information leads us to believe that surgical management for the orthopedic manifestations is unpredictable and fraught with complications."

- Jeffrey C. King, MD, and James Dobyns, MD -

"This does not mean that surgery should never be undertaken, rather that the surgeon and the family must have a clear understanding of the risks and benefits involved and clear and realistic expectations about the proposed procedures."

- Jeffrey C. King, MD, and James Dobyns, MD -


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# *Thank You*


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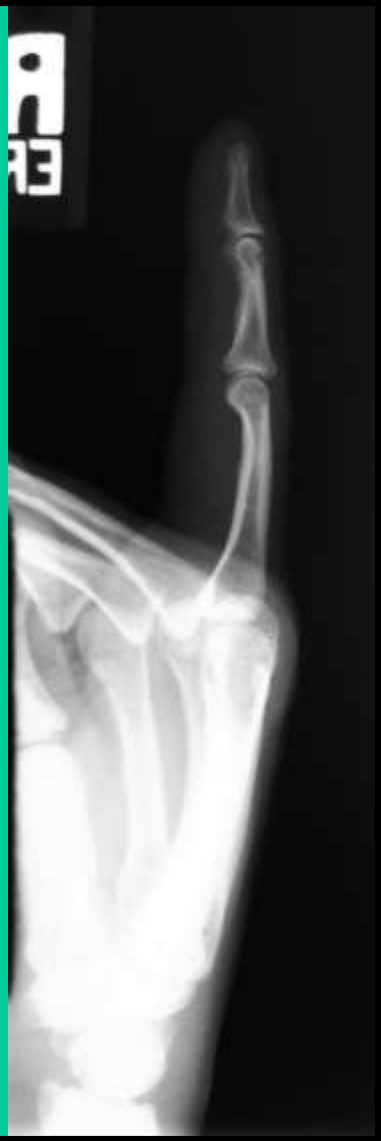

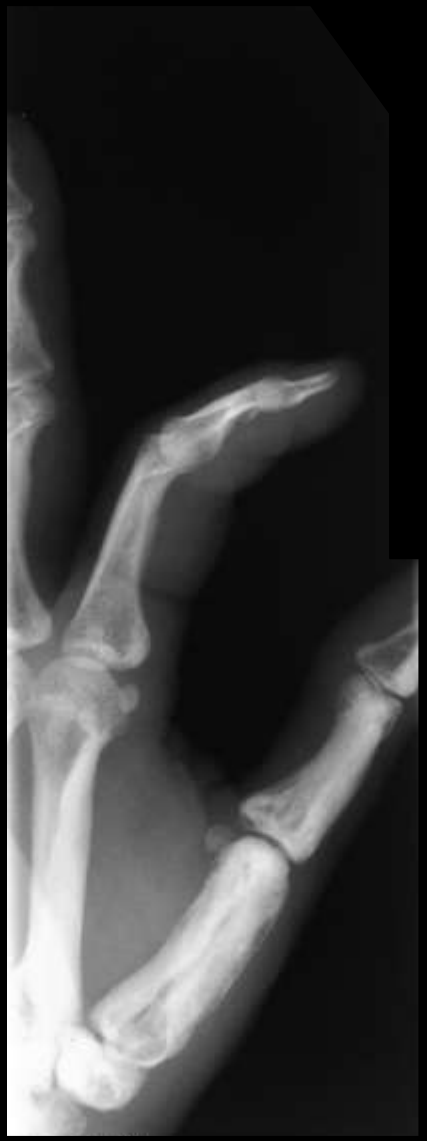

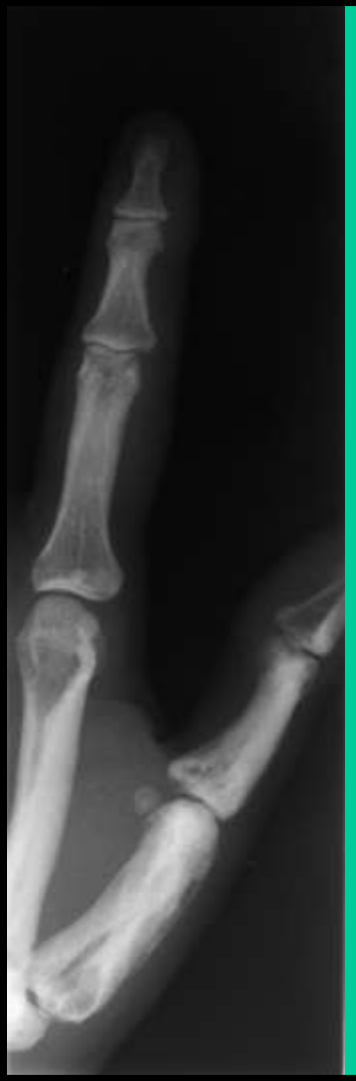

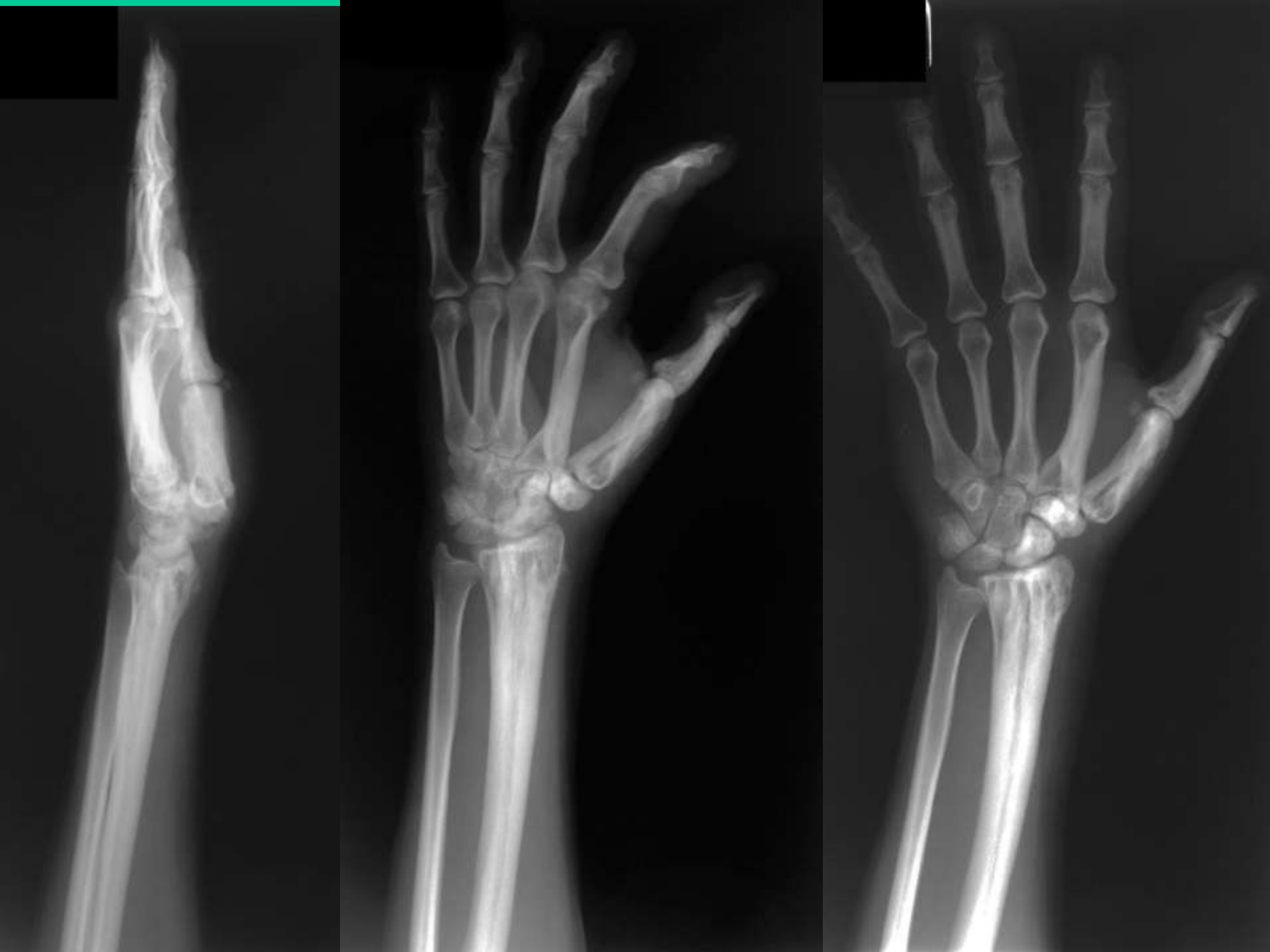

I think this is a beautiful case of melorheostosis. There is cortical and medullary hyperostosis of the radius, scaphoid, trapezium, trapezoid, first and second metacarpals, and proximal and distal phalanges of the thumb. Interesting that it is all on the radial side of the arm, wrist and hand—melorheostosis often follows a sclerotomal distribution which seems to be the case here. Upper extremity is more rare than lower—not sure if the patient has any lower extremity x-rays that show the same thing?

I've never seen a confirmed case where the patient has associated skin findings (there are reports of vascular skin and soft tissue lesions occurring in the same distribution as the bone findings)—if the patient does, please take some photographs as it would be a nice complement to the case!

Thanks for sending,
Jen (Demertzis)