Melorheostosis Studies at Oxford

Yun Zhang

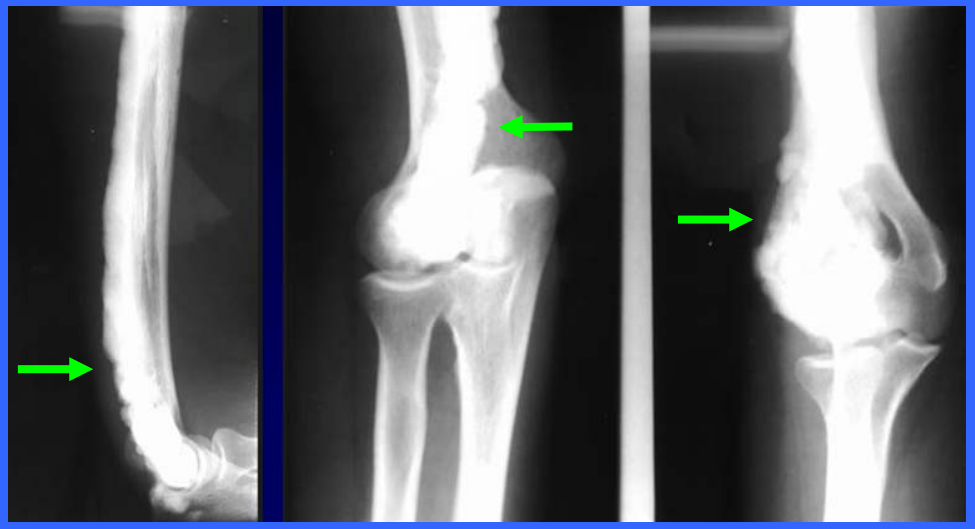
Senior Genetics Research Fellow

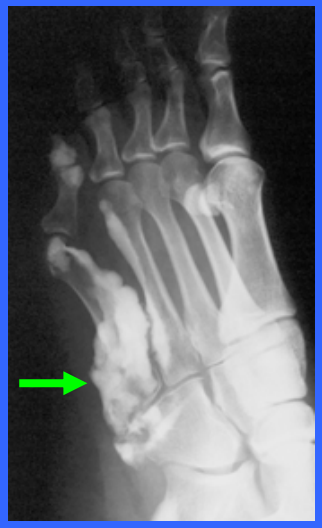
yun.zhang@ndos.ox.ac.uk

Melorheostosis (MEL)

- Rare disease (~1 in a million??)
- Involved sites: tubular bones, hands and feet
- Clinical problems
  - abnormal bone shape
  - limb deformity
  - soft tissue involvement causing contractures
  - chronic pain

MEL Irregular flowing hyperostosis “candle wax”





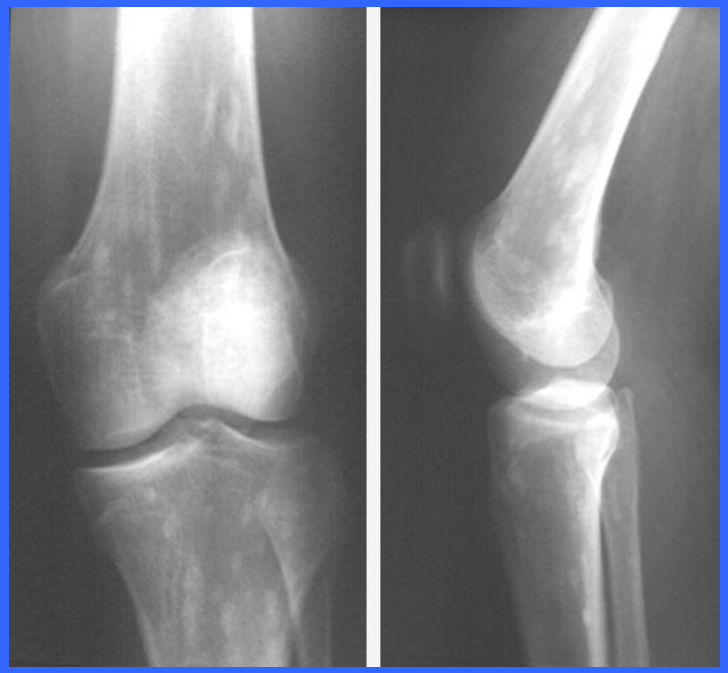
Osteopoikilosis (OPK)

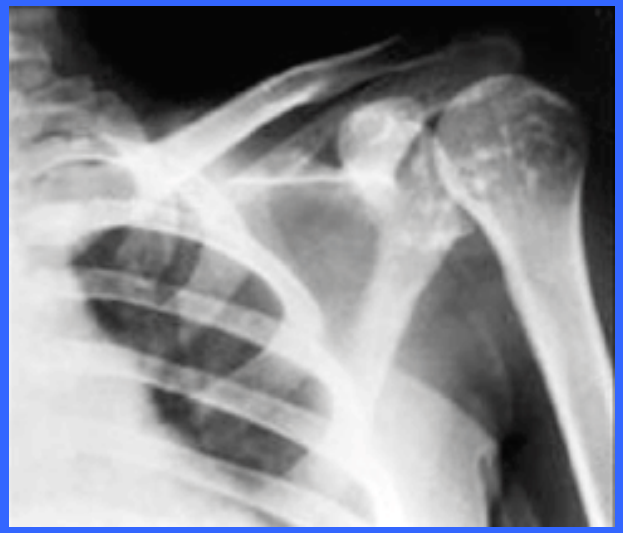
- Rare autosomal dominant
- Asymptomatic
- Symmetric unequal distribution of hyperostotic lesions
- Involved sites: long tubular bones, pelvis, scapulae
- Isolated/associated with bone/skin problems:

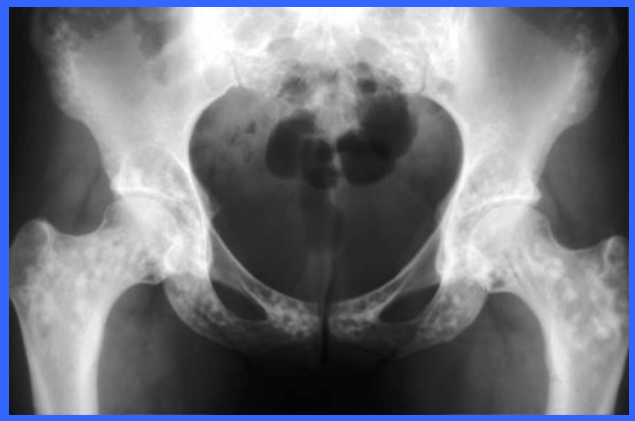
  - melorheostosis

  - Buschke-Ollendorff syndrome (BOS): autosomal dominant disorder with disseminated connective tissue nevi

OPK Spotty dense lesions





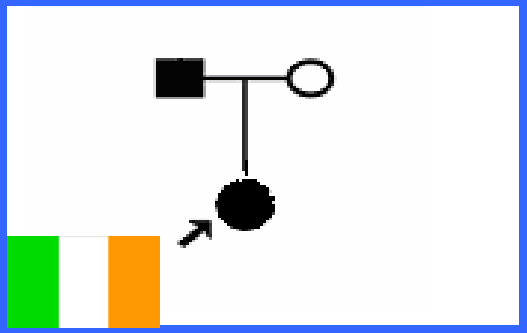


1. Diameter: 2 – 10 mm
2. No effect on the shape of the bone or soft tissue

Patients

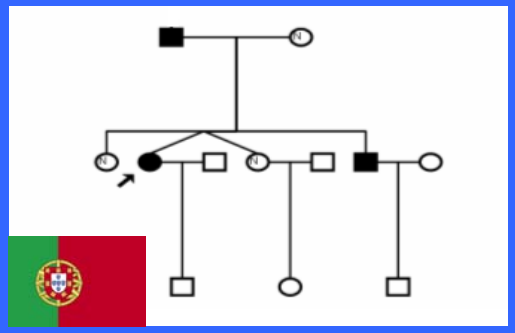
(1) Families

MEL, OPK



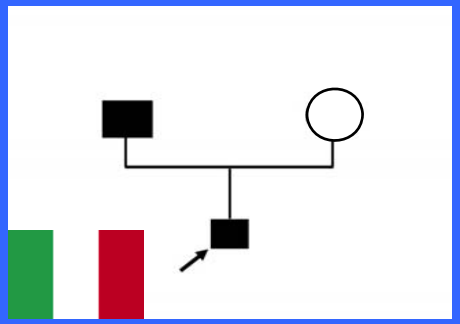
IR

OPK



AZ

BOS, OPK

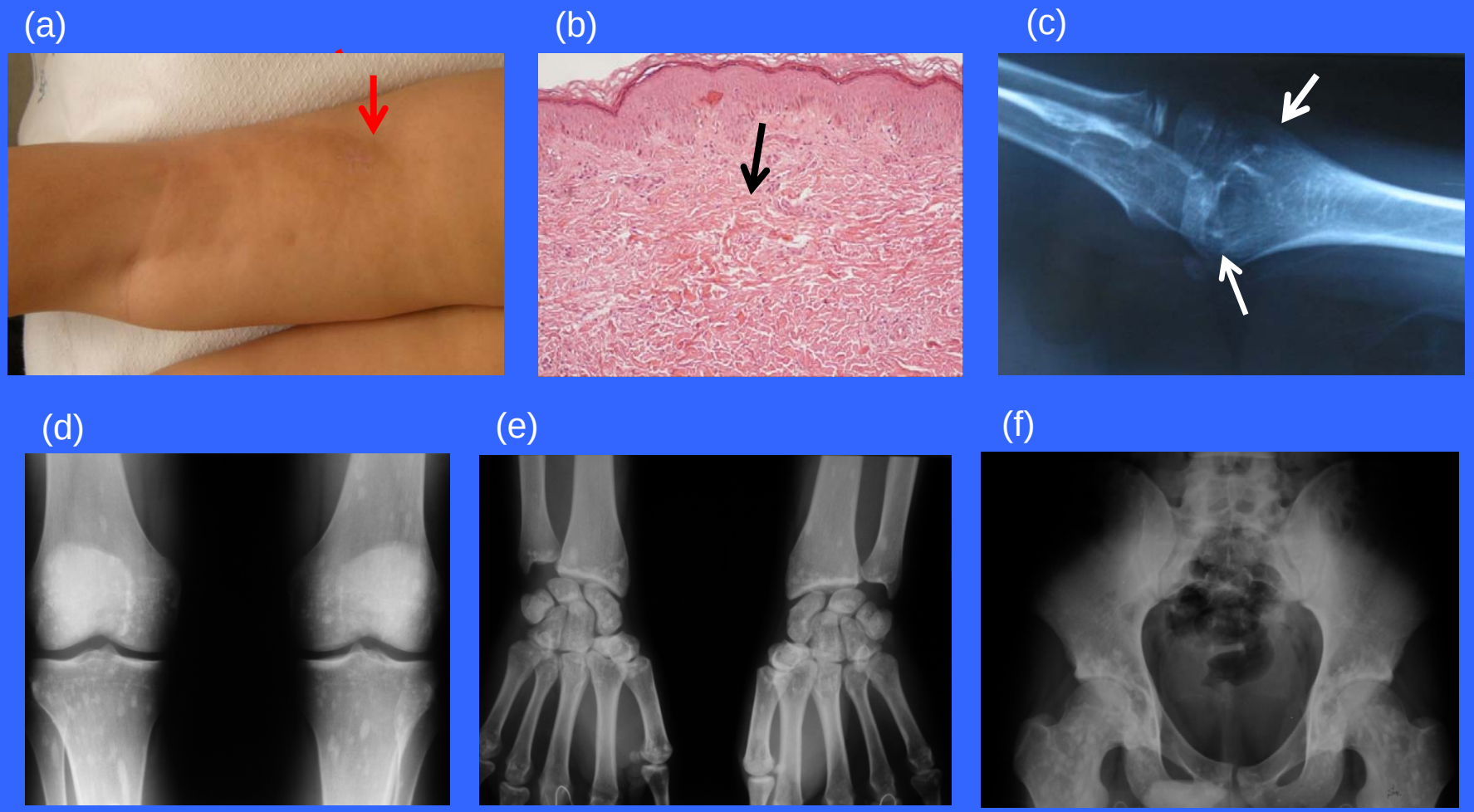


IT

(2) Sporadic cases

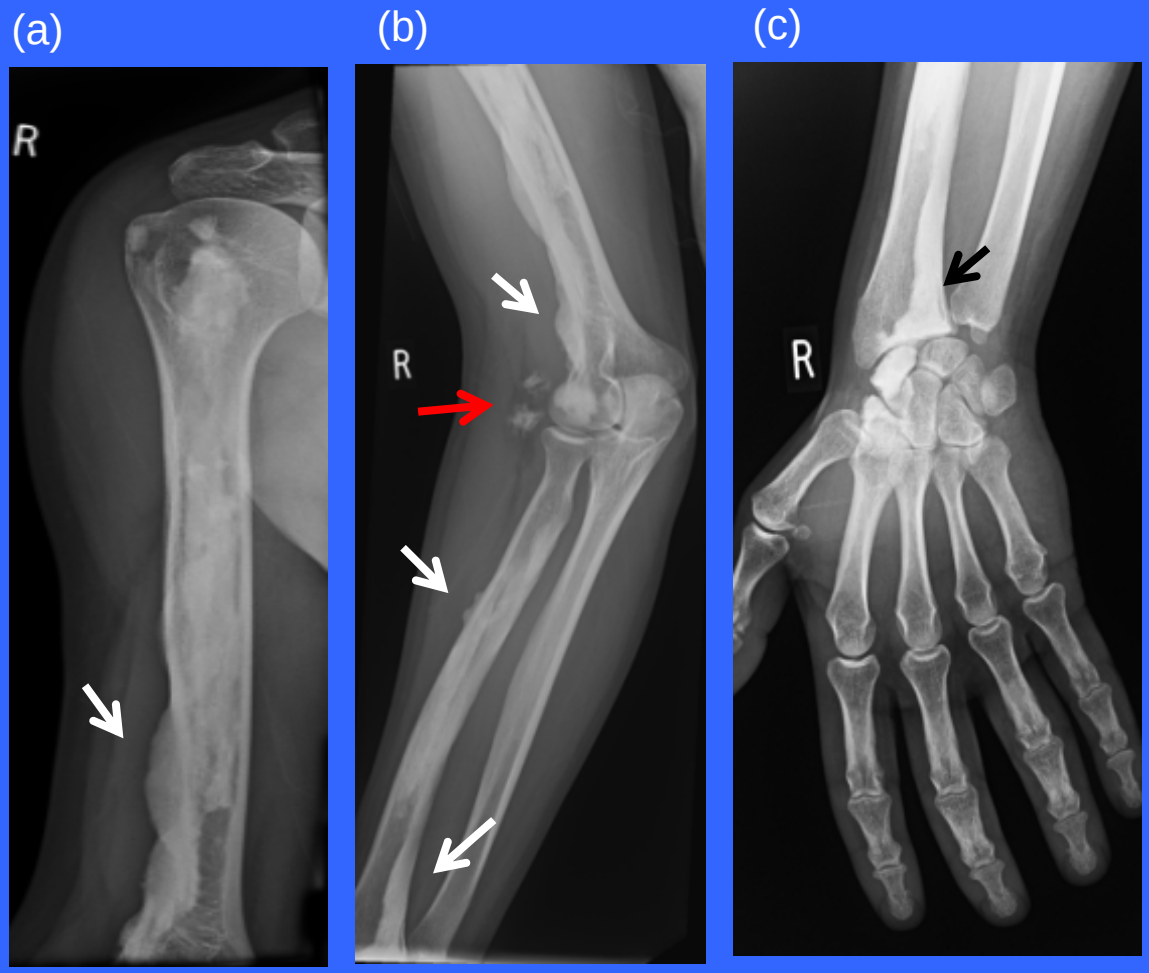
- 14 sporadic MEL patients
- 1 BOS patient

Italian BOS and OPK family



(a) Connective-tissue nevi (red arrow); (b) accumulation of densely packed collagen bundles in the dermis (black arrow; magnification x100). (c) small roundish, sclerotic lesion (white arrow) on his left elbow. The proband's father: spoty lesions all over his (d) knee, (e) hands and wrists, and (f) pelvis.

UK sporadic MEL patient

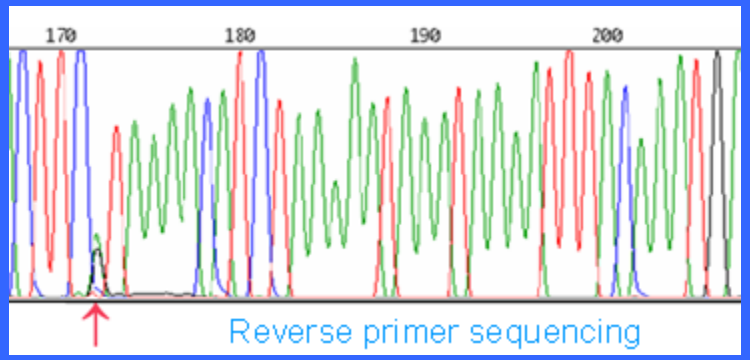


Photo, radiograph: candle wax appearance in his humeral, radial shaft and epiphysis in (a), (b) and (c). Ectopic calcification at ante-cubital fossa (b).

Result of Mutation Identification in *LEMD3*

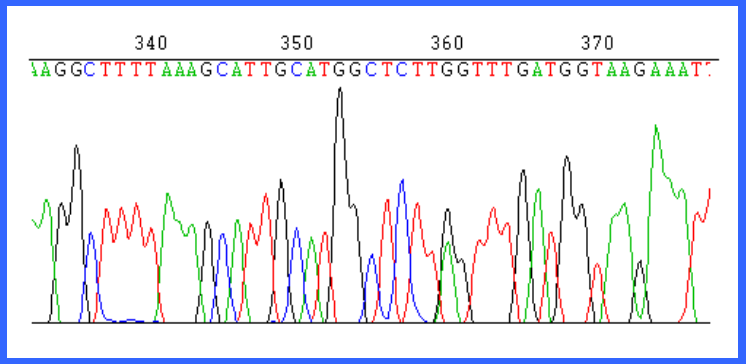
1. Families: two mutations segregate with osteopoikilosis

IR (OPK, MEL), AZ (OPK)



- Exon 8
- C 2032 T mutation
- Arg (678) to STOP codon

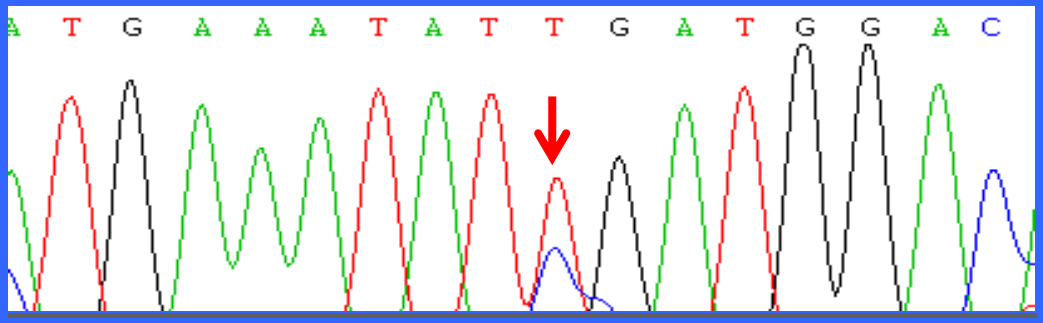
IT (BOS, OPK)



- Exon 12
- G 2564 A mutation
- Trp (855) to STOP codon

Result of Mutation Identification in *LEMD3*

2. The UK BOS individual



- C to T substitution at exon 7 cDNA1963 changing aa at position 655 from Arg to a stop codon.
- Has been previously identified in an American patient with OPK and MEL, her three siblings all have OPK.

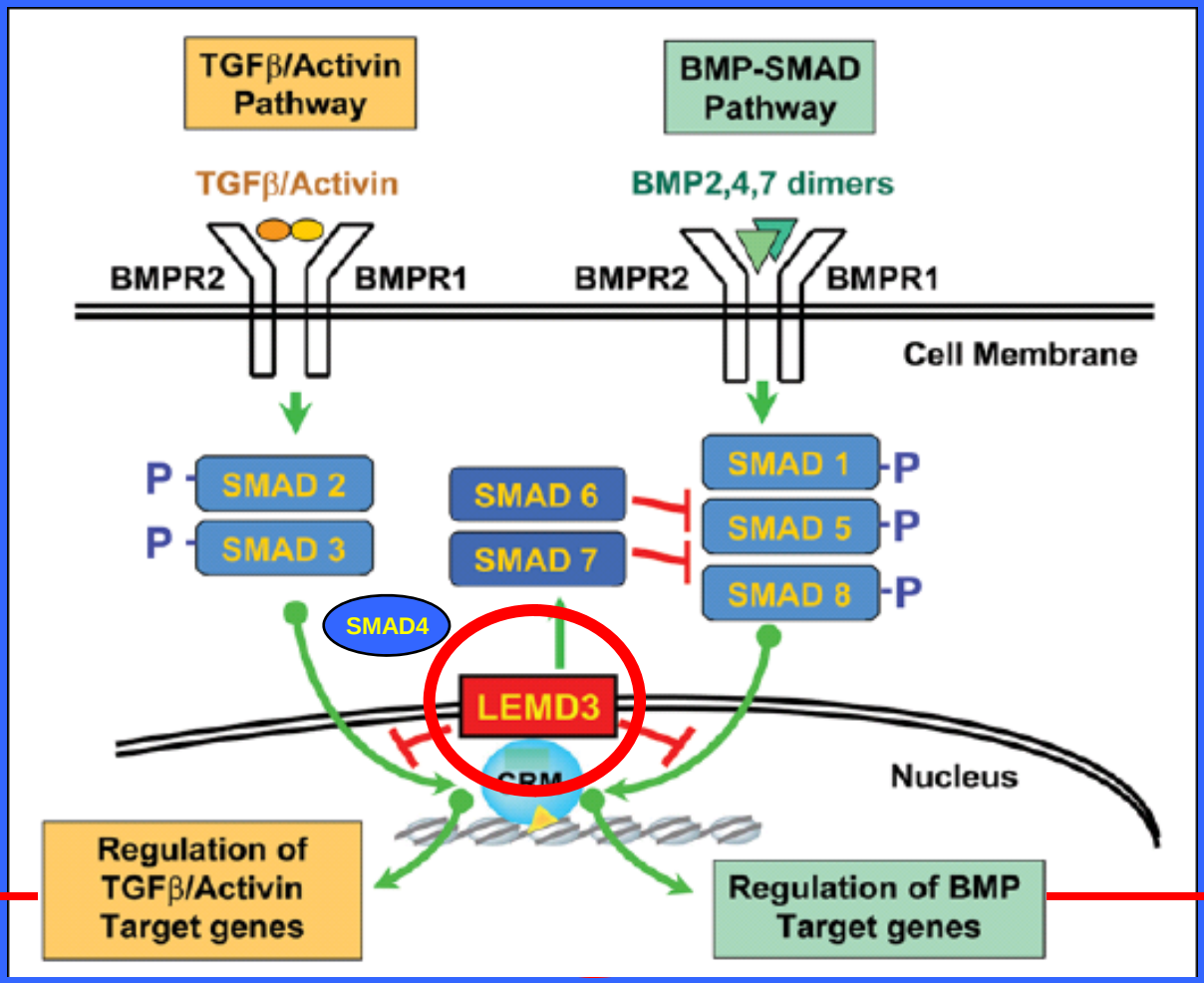
3. Sporadic melorheostosis: no mutations in *LEMD3*

no evidence of somatic mosaicism from the biopsies

LEMD3 Mutations

18 mutations have been identified in *LEMD3*

1. Isolated OPK
2. familial OPK, or with MEL, or BOS
3. BOS
4. Familial cutaneous collagenomas with BOS
5. Familial MEL with OPK



Ben-Asher, et al 2005

Proliferation
Differentiation
Migration
Immune responses

Limb development
Ossification
Patterning
Repair

Mechanisms of MEL

MEL co-occurs with OPK:

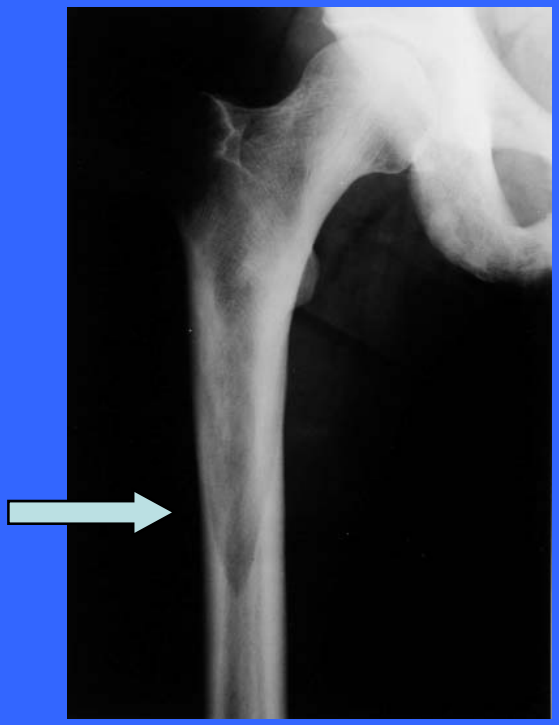
- 2 nd hit in *LEMD3*?
- 2 nd hit in another gene?
- Methylation issue in addition to *LEMD3* mutation?

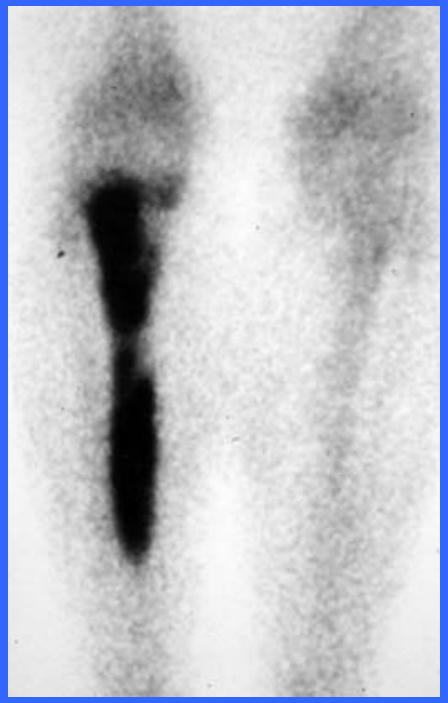
Mechanisms of MEL

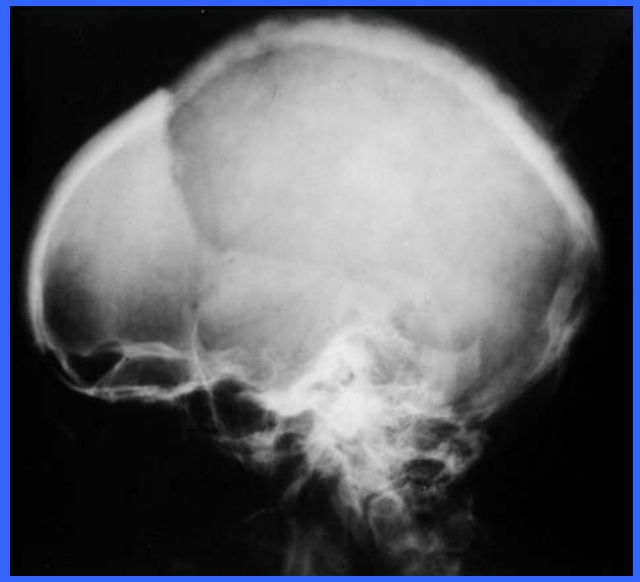
Isolated MEL:

- *LEMD3* somatic mutation?
- Epigenetic?
- Another gene – somatic mutation?
- Another gene – germline mutation?

* Paget disease: a monostotic or spatially limited manifestation is caused by inherited germline mutation in SQST1

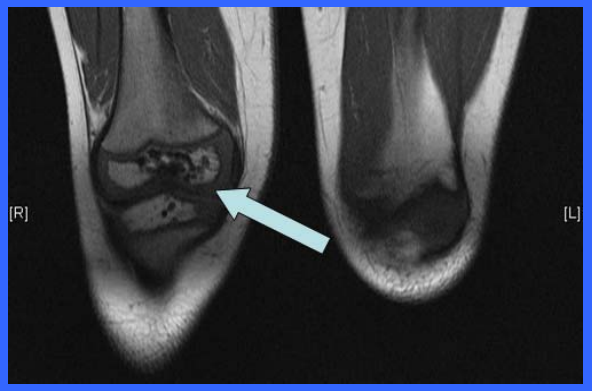




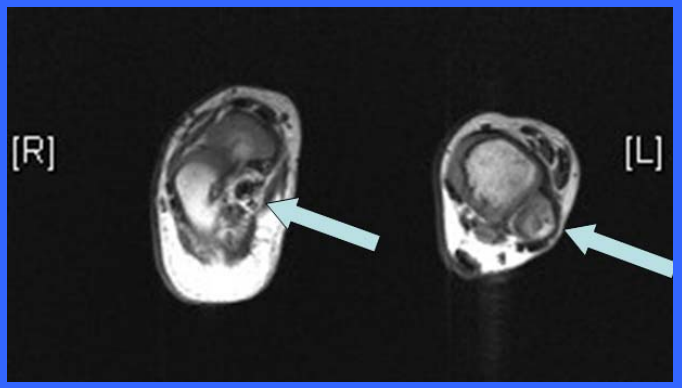


Flame-shaped resorption front

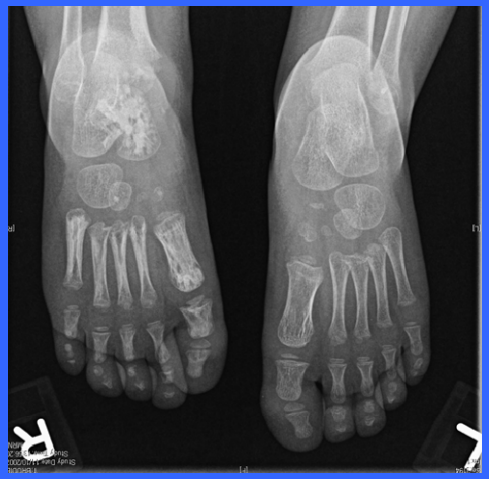
* MEL can be more extensive than the clinical features might suggest



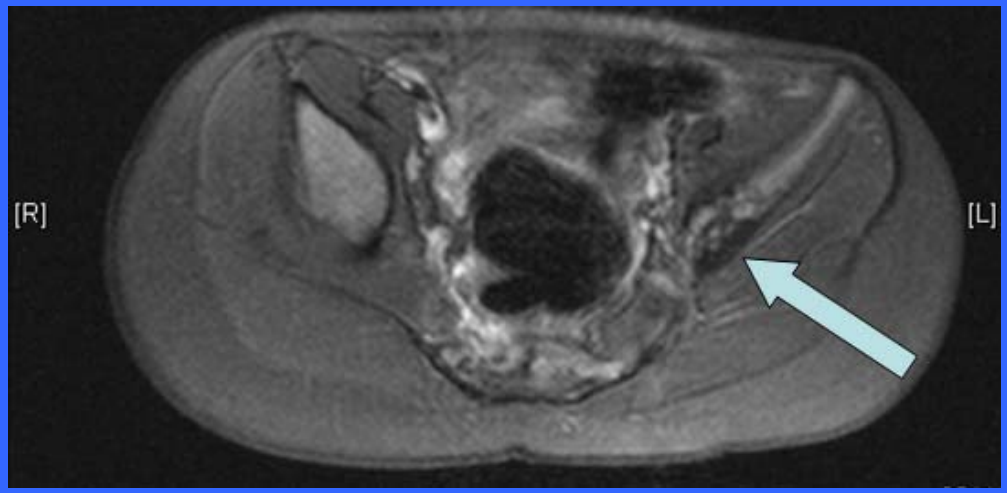
R knee



R tubua, L fibula



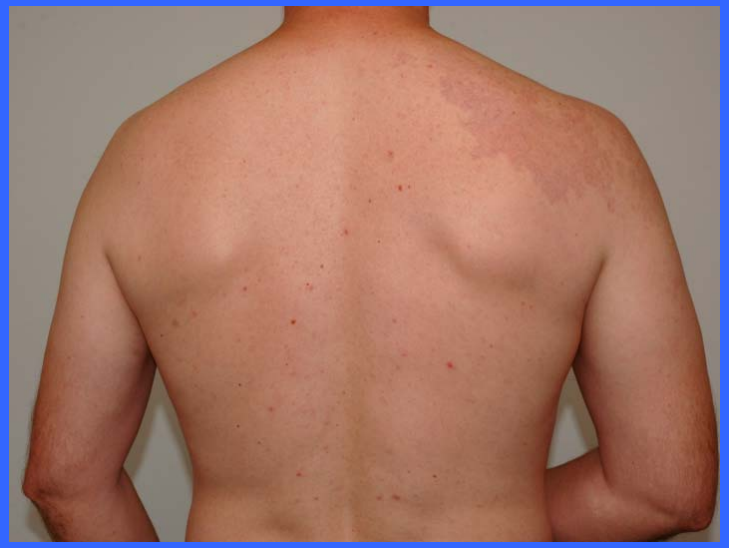
R foot

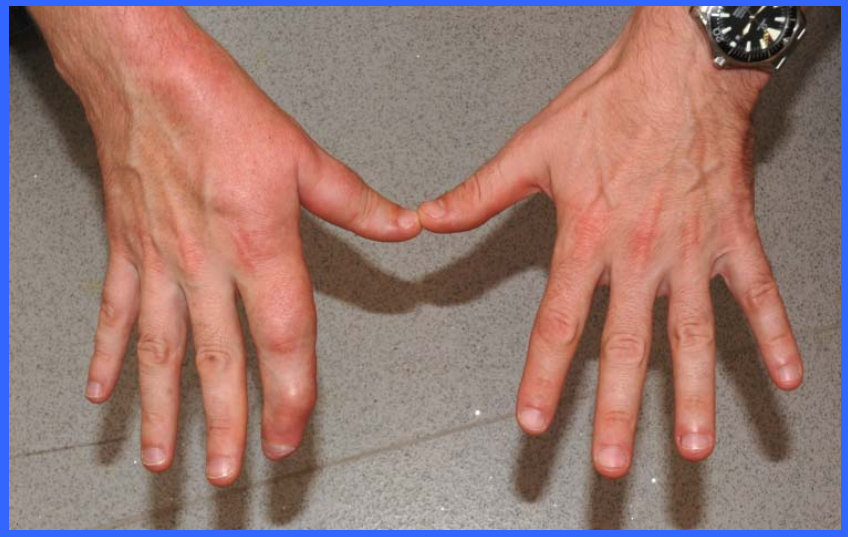


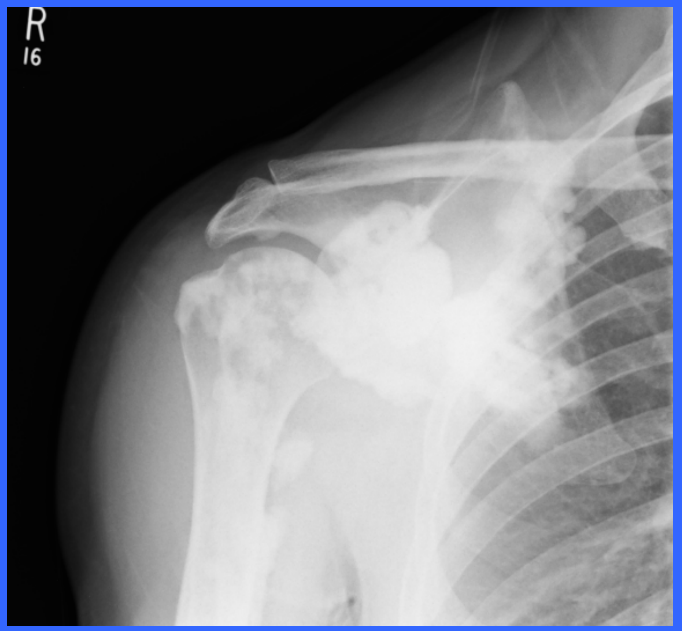
L pelvis

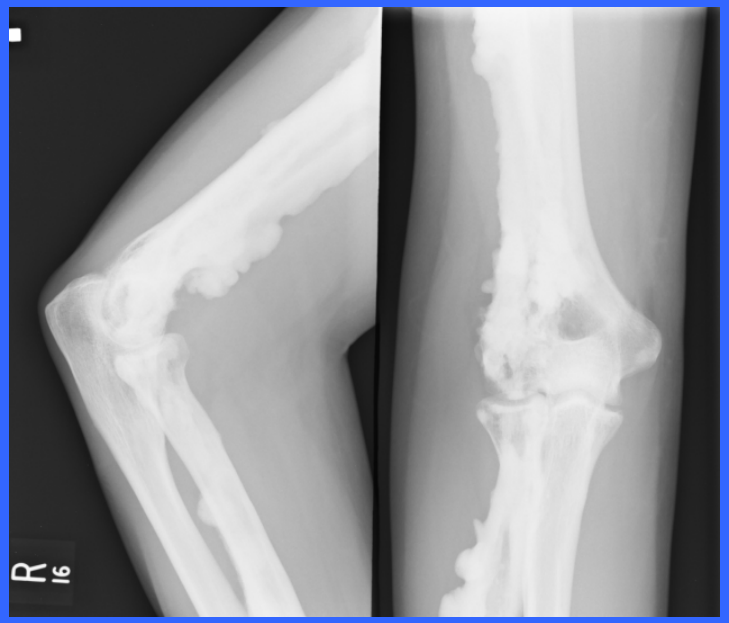
Current Research and Beyond

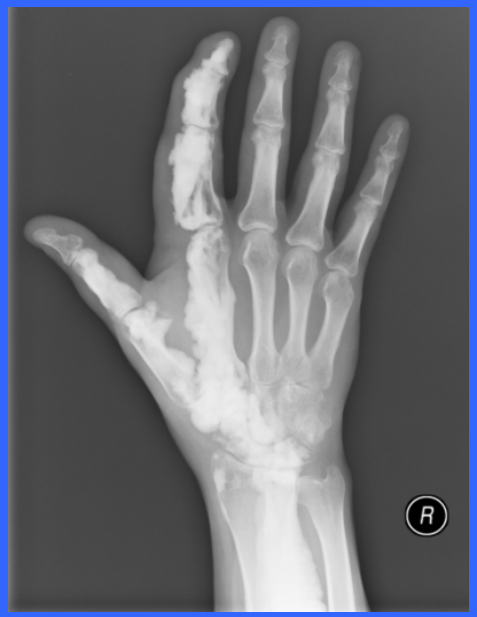
- Melorheostosis clinic day on 16th October 08: 13 patients (4 new) and relatives attended
- Total sporadic MEL to 18 patients

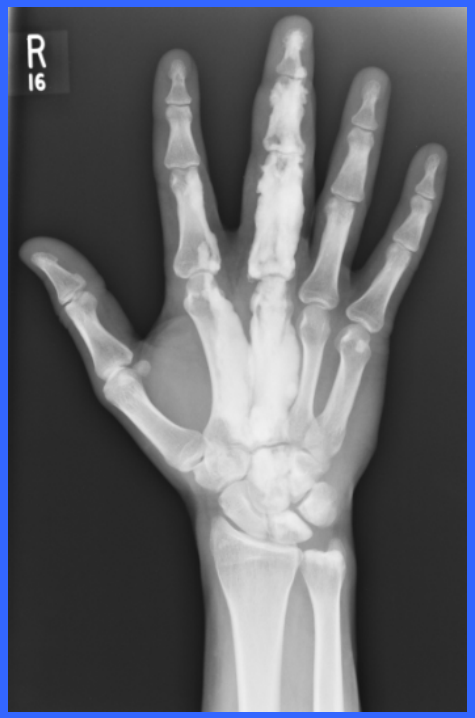


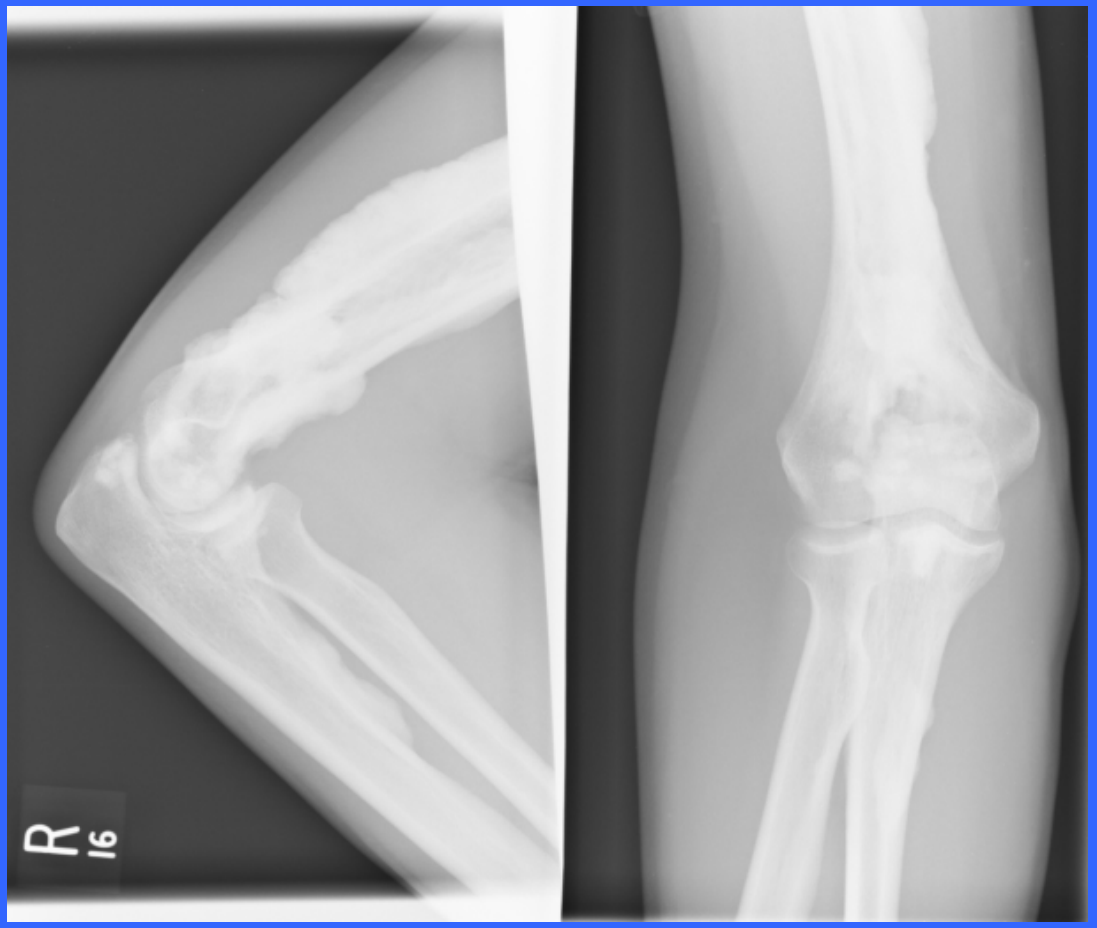



R
16


R
16


R


R
16


R
16

Current Research and Beyond

- Clinical Fellow appointed to identify and characterise patients in UK
- Sequence genes involved in bone morphogenesis (germline and from affected tissue)
- Definition of the osteopoikilosis/melorheostosis phenotypic spectrum
- Define benefits and hazards of treatment

Acknowledgements

Oxford
Paul Wordsworth
Roger Smith
Graham Russell

Brisbane
Matt Brown

Azores
Ana Rita Couto
Jácome Bruges Armas

Italy
Marco Castori

Oxfordshire Health Services Research Fund