Melorheostosis

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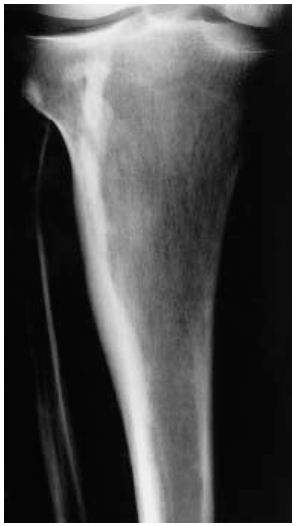
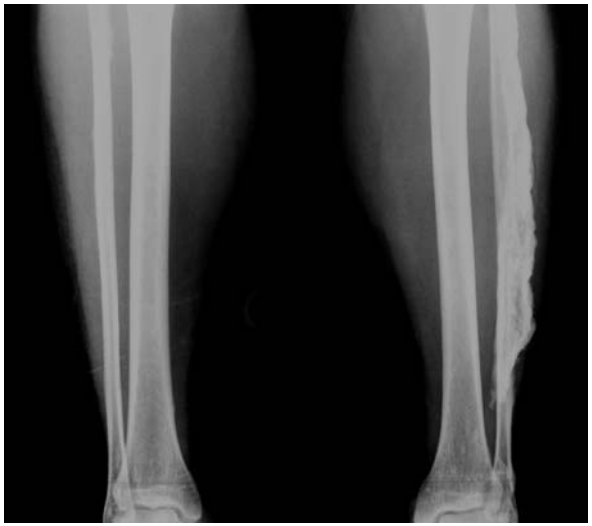
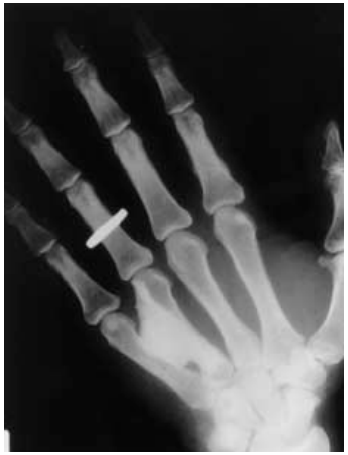
Melorheostosis

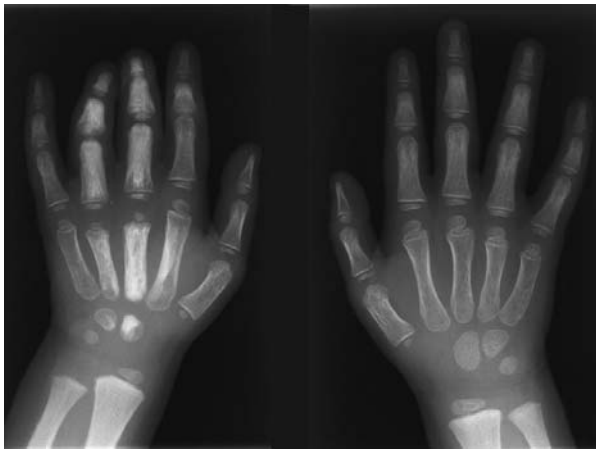
- skeletal dysplasia with increased bone density
- prevalence: 1/1.000.000
- Léri A, Joanny J (1922):
  Hyperostose “en coulée” ou mélorhéostose
- usually sporadic occurrence
- affecting bone and surrounding connective tissues
- asymmetric (sclerotome) distribution
- characteristic radiographic lesions

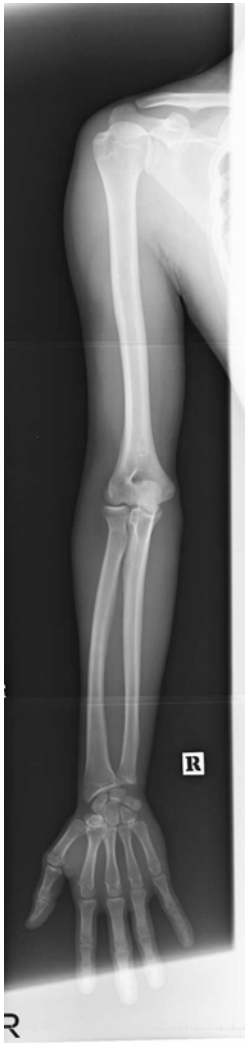
Melorheostosis – radiographic features

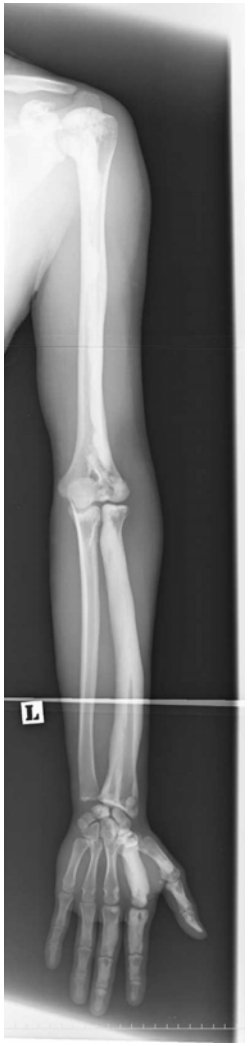












Melorheostosis – clinical features

- usually symptomatic with chronic pain
- scleroderma-like skin lesions
- joint contractures, stiffness
- shortening and deformation of affected bones
- vascular anomalies

Melorheostosis in association with osteopoikilosis

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

Clinical Report

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

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[2]*Department of Orthopedics, University Hospital Pellenberg, Weligerveld, Pellenberg, Belgium*

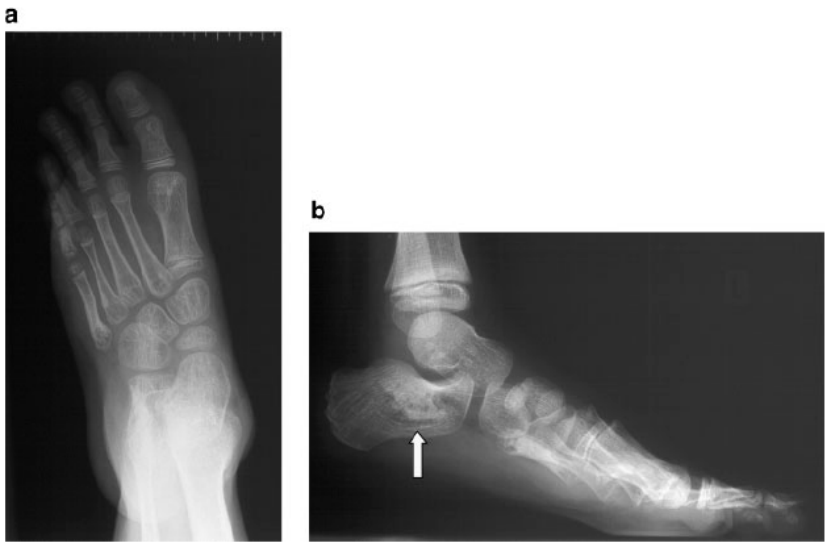
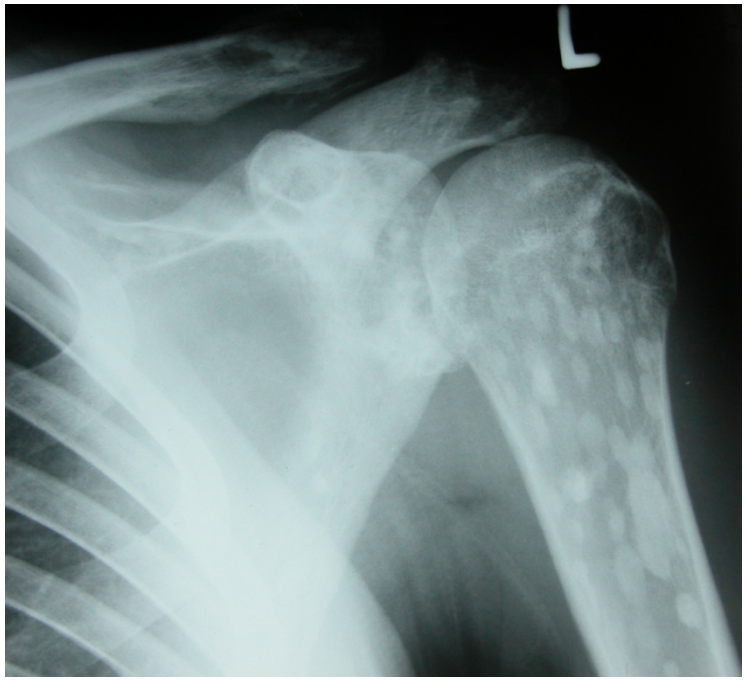
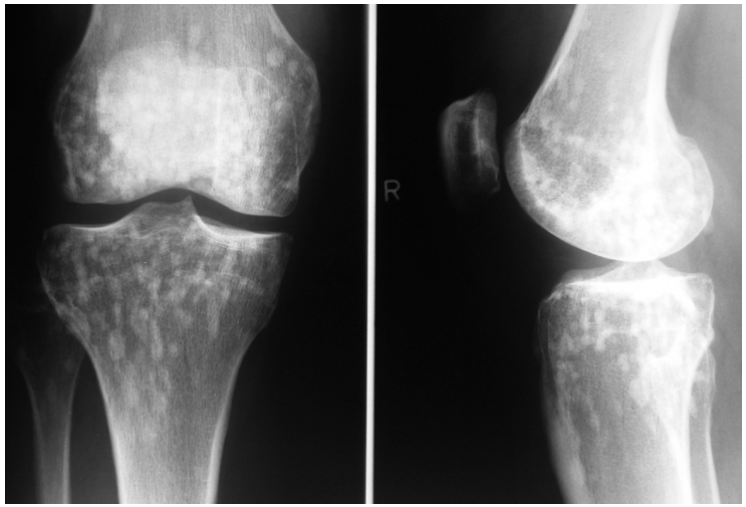


Fig. 3. Radiological appearance of the left foot of the proband at the age of 5 years. **a**: Typical sclerotic areas can be seen in the first metatarsal head, the proximal phalanx of the hallux, the fifth metatarsal, the phalanges of the fifth toe, and the basis of the fourth metatarsal. There is shortening of the fifth ray. **b**: In the os calcaneum, there is also a dense sclerotic lesion (arrow).

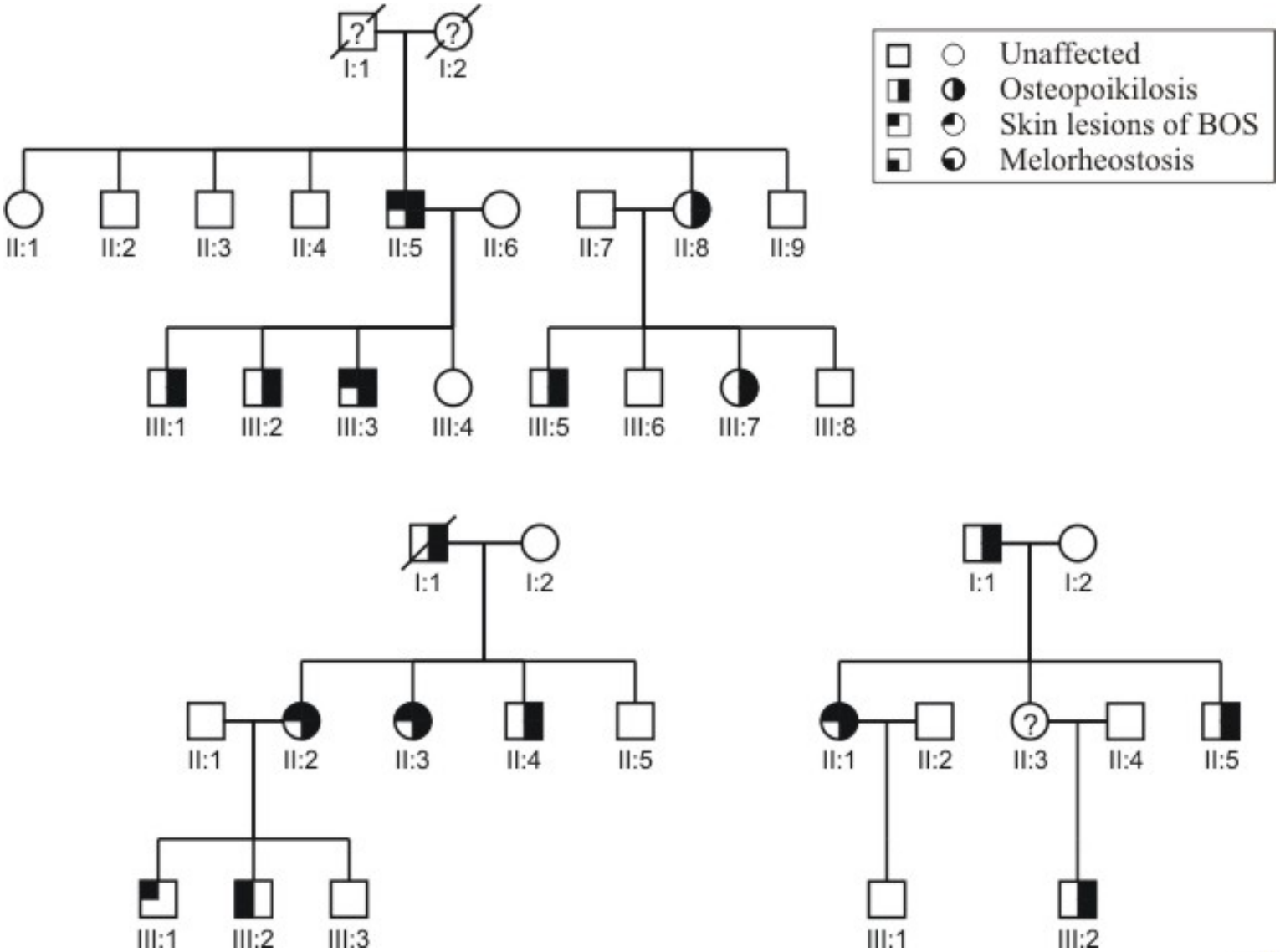
Osteopoikilosis



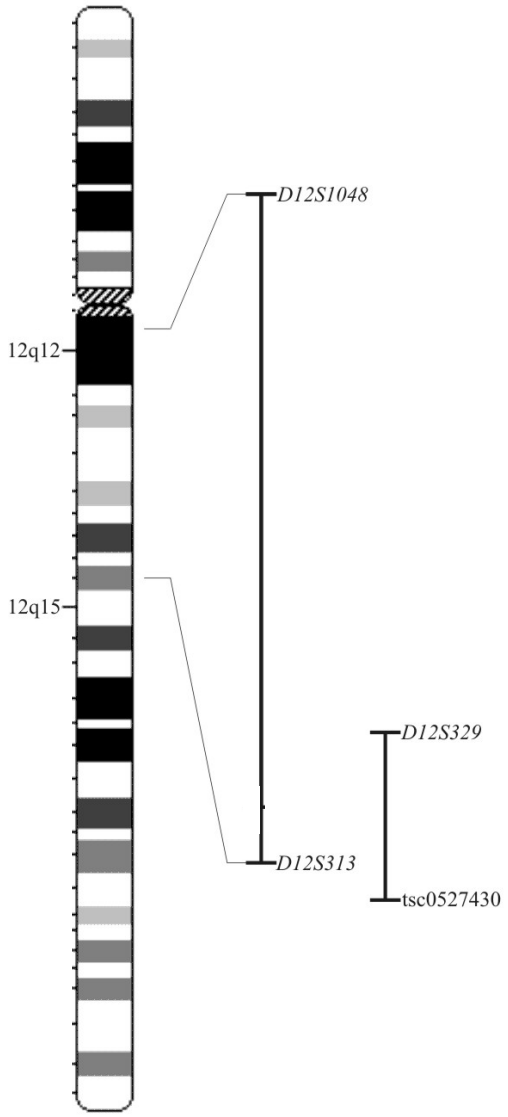


- benign condition
- autosomal dominant
- hyperostotic spots
- isolated or in association with other skin/bone lesions (Buschke-Ollendorff syndrome)

Genome search in three families with osteopoikilosis



Gene mapping



- Genome wide linkage analysis
- Linkage for two markers on 12q
- Region: D12S1048 – D12S1663
- Combined maximum two-point LOD score of 6.691
- Identification of microdeletion between D12S329 and tsc0527430
- Region of interest:
  - 3.07Mb
  - 23 genes
- Two candidate genes:
  - *WIF1*
  - *LEMD3*

Hellemans J et al. Nat Genet 2004;36:1213

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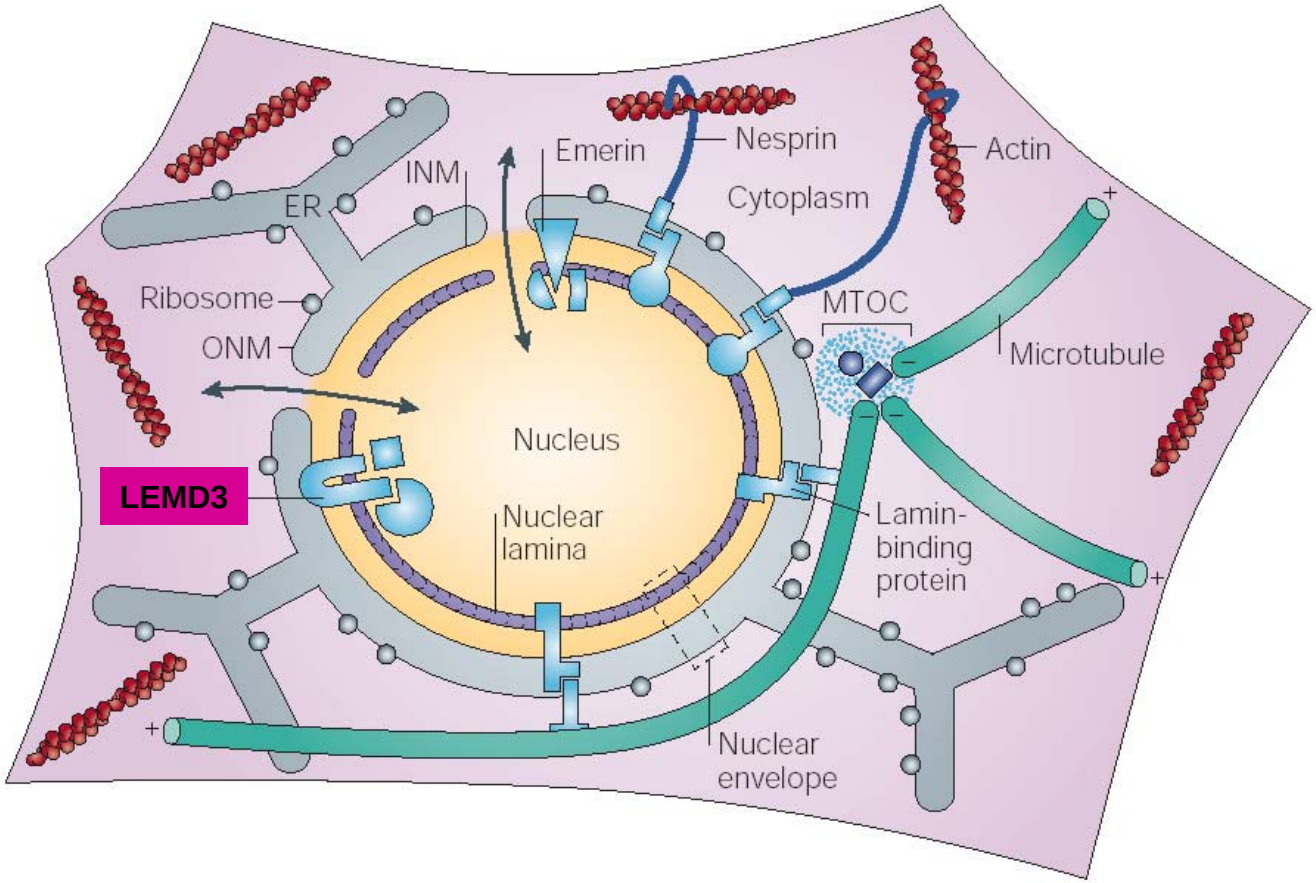
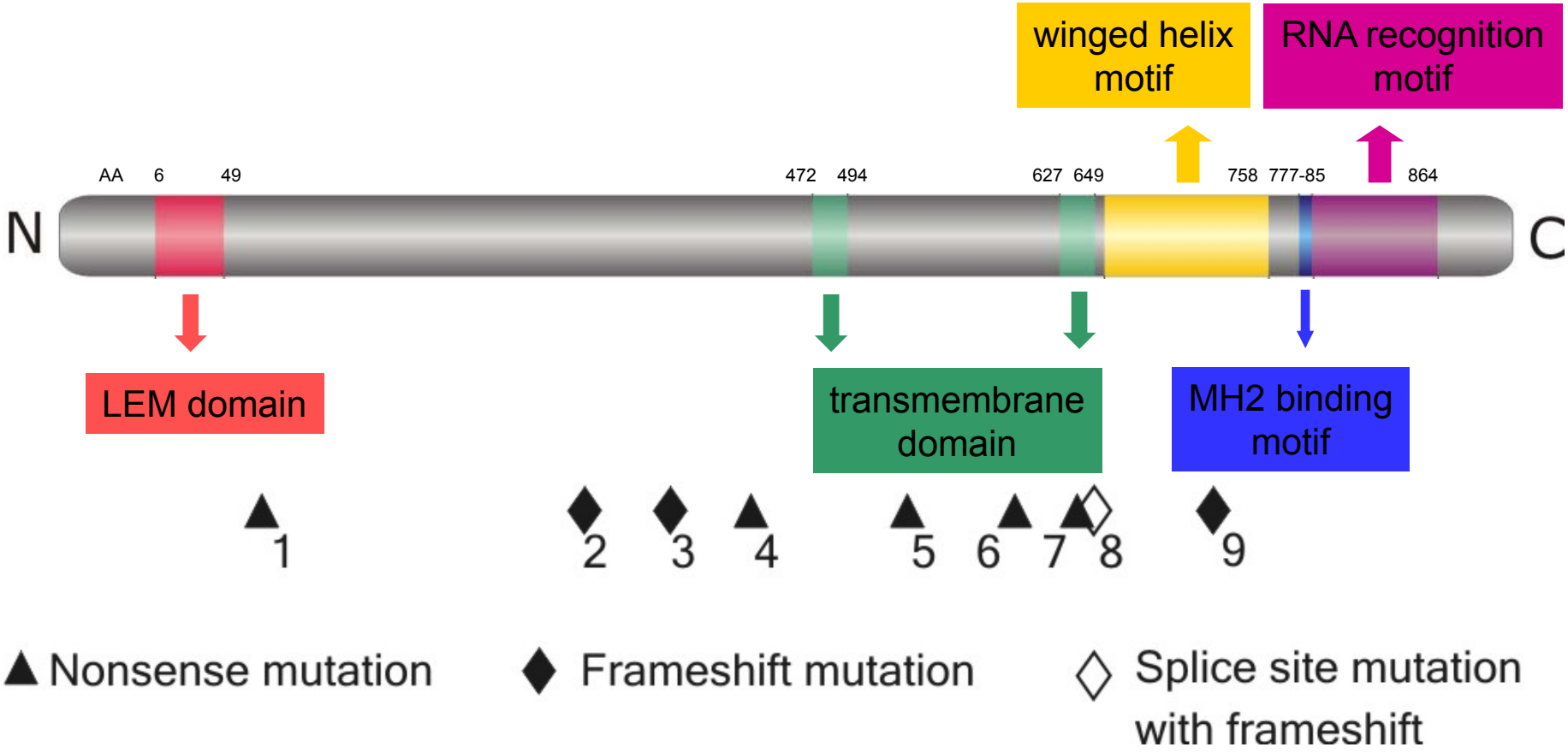
LEMD3: integral protein of the inner nuclear membrane



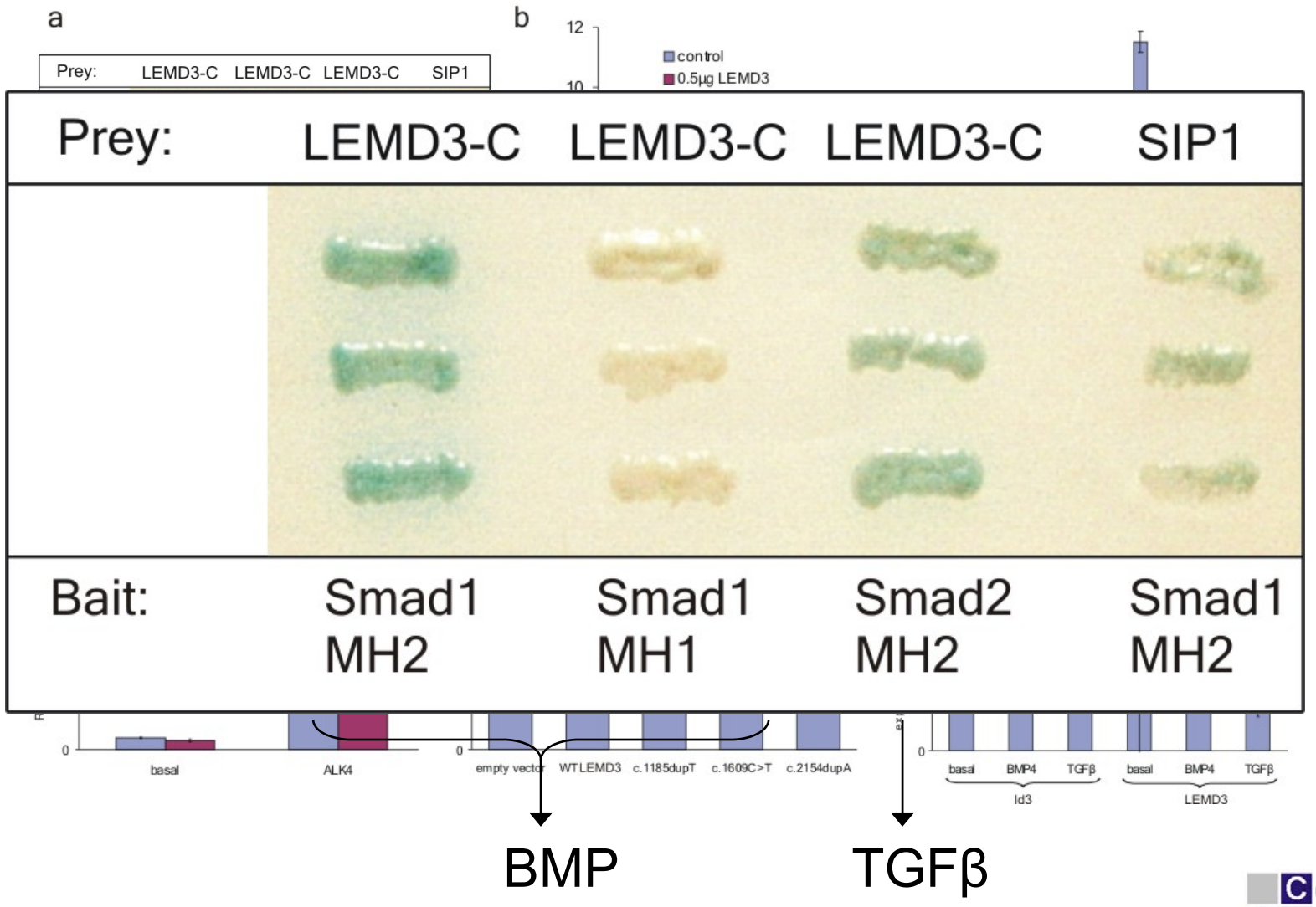
Adapted from Gruenbaum Y et al. Nature Rev Mol Cell Biol 6,21,2005

LEMD3 structure and mutations



Hellemans J et al. Nat Genet 2004;36:1213

LEMD3 in BMP/TGFβ signaling



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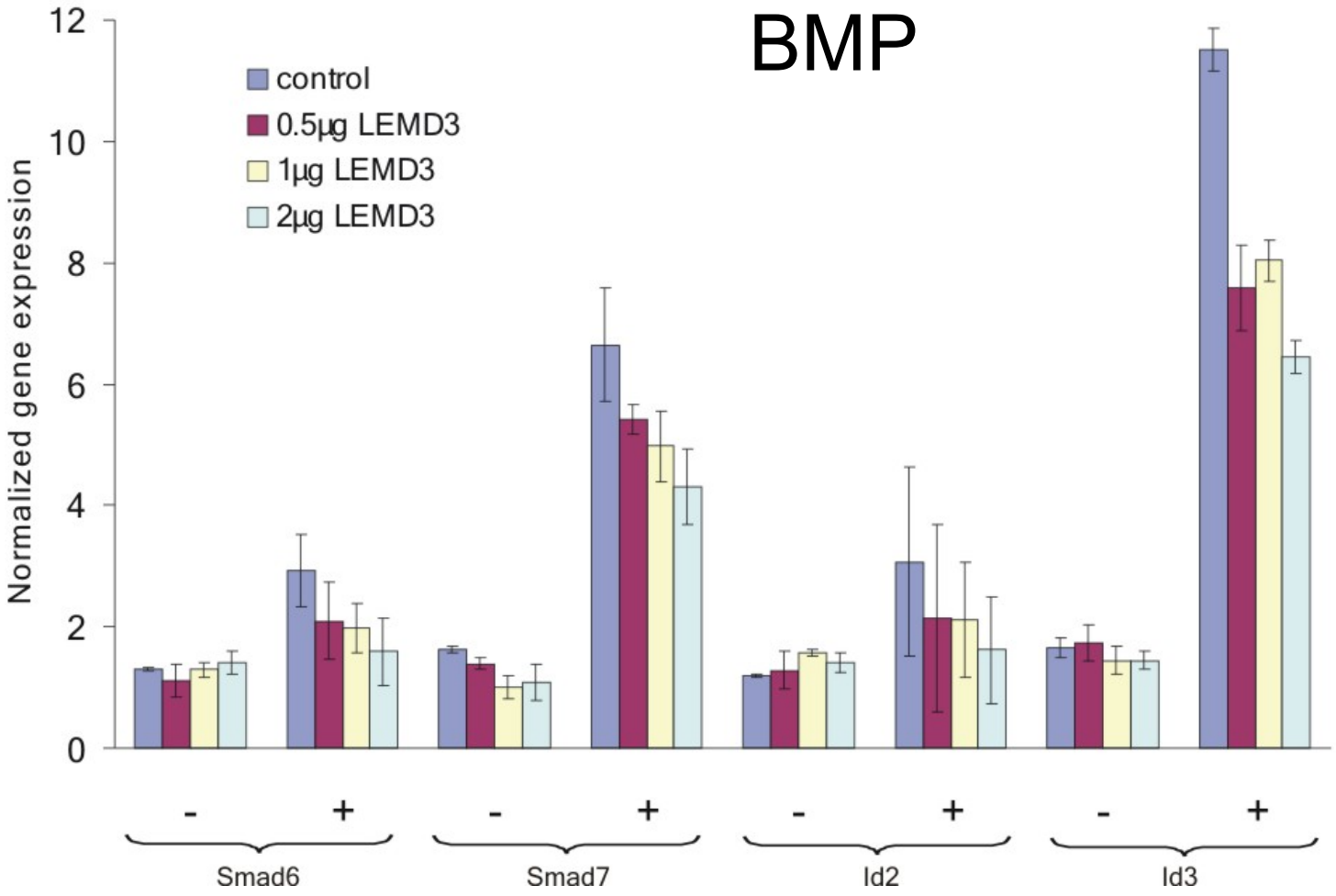

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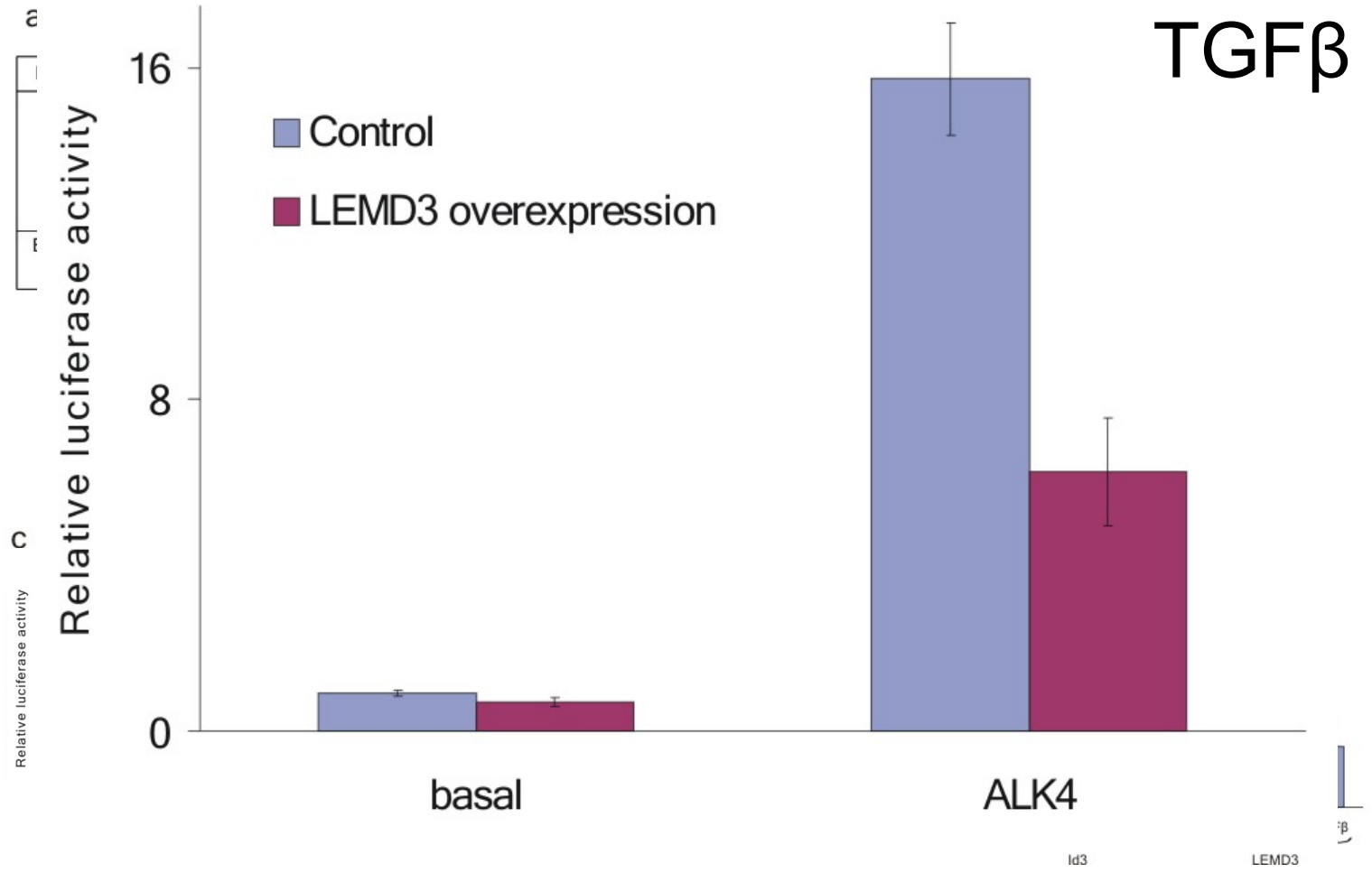
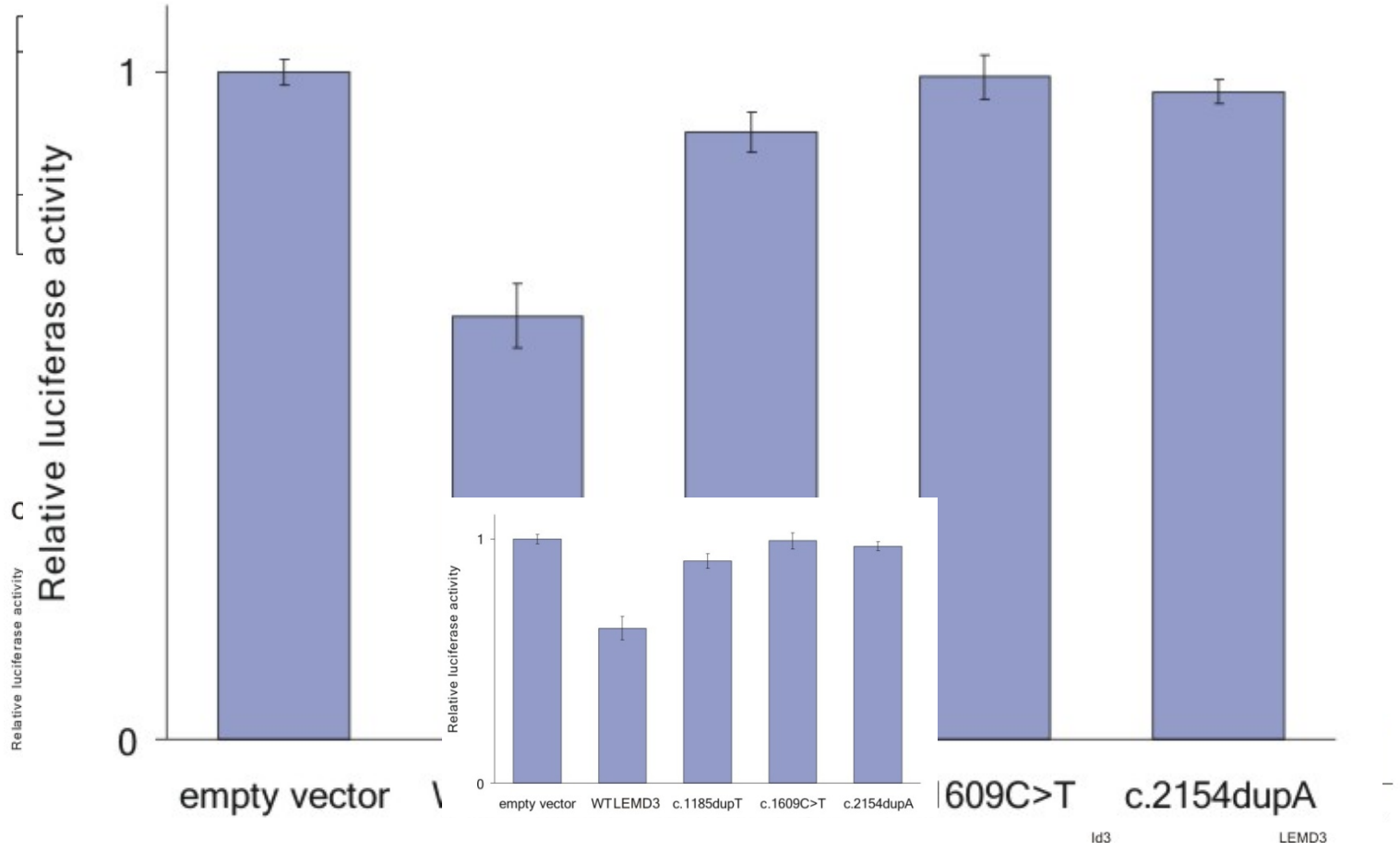
LEMD3 in BMP/TGFβ signaling



LEMD3 in BMP/TGFβ signaling



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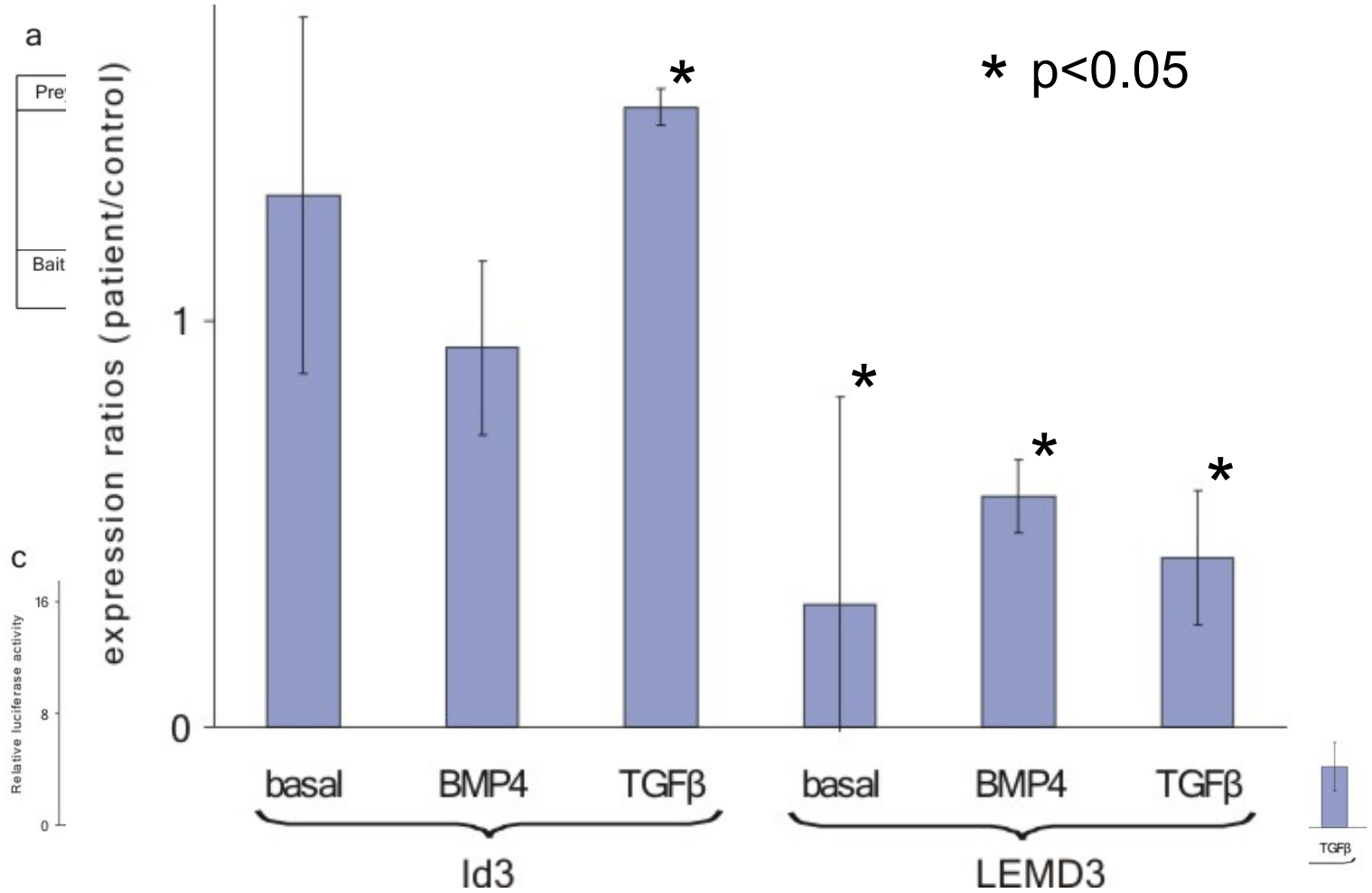
LEMD3 in BMP/TGFβ signaling



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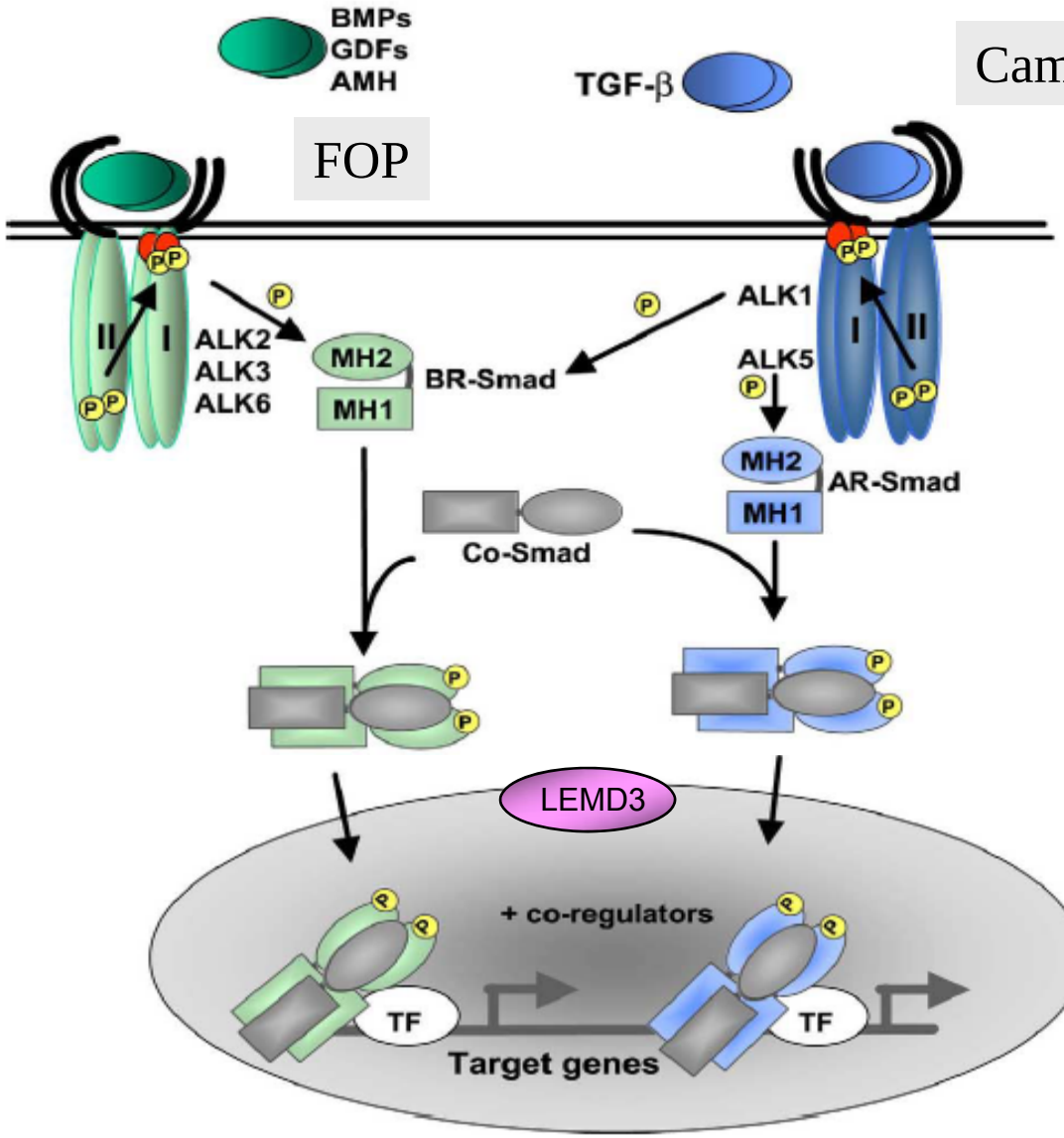
LEMD3: antagonist in the BMP and TGFβ pathway



A. Zwijsen et al. FEBS Letters 546 (2003) 133–139

Analysis of LEMD3 in a larger series of patients

- Heterozygous loss-of-function mutations in 17/21 patients with OP/BOS
- Heterozygous loss-of-function mutations in 4/4 patients with melorheostosis who belong to a OP/BOS family
- Heterozygous loss-of-function mutations (germline) in only 1/30 patients with sporadic melorheostosis

Hellemans J et al. Hum Mutat 2006;27:290 and unpublished results

Family D0500261 (c.1963C>T;p.Arg655X)

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]

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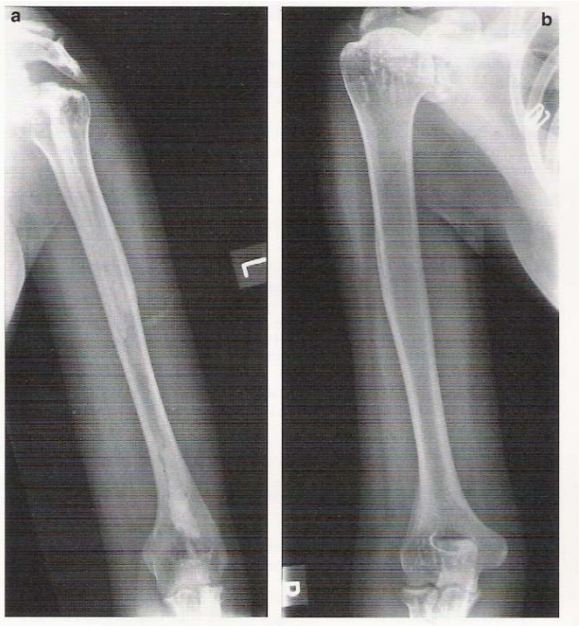
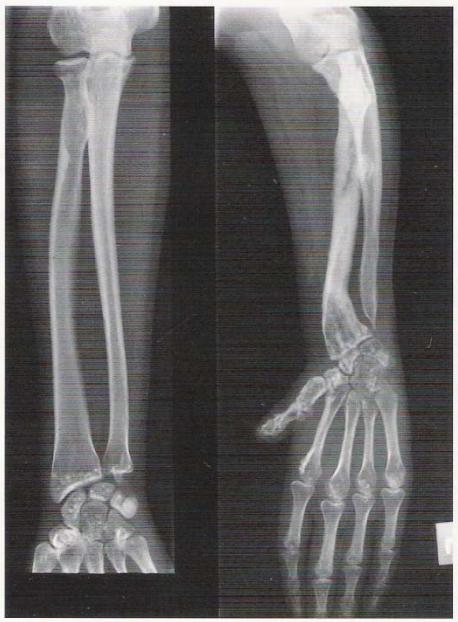
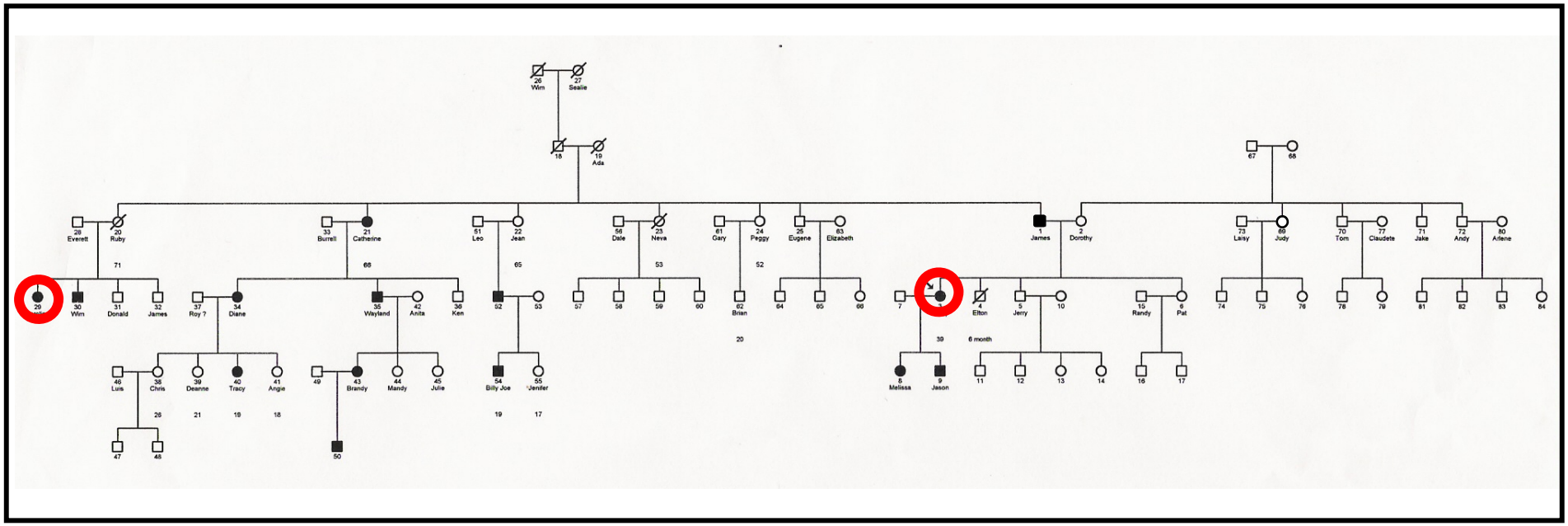




Family D0601651 (c.2275_2278delGTTA;p.Val759fs)



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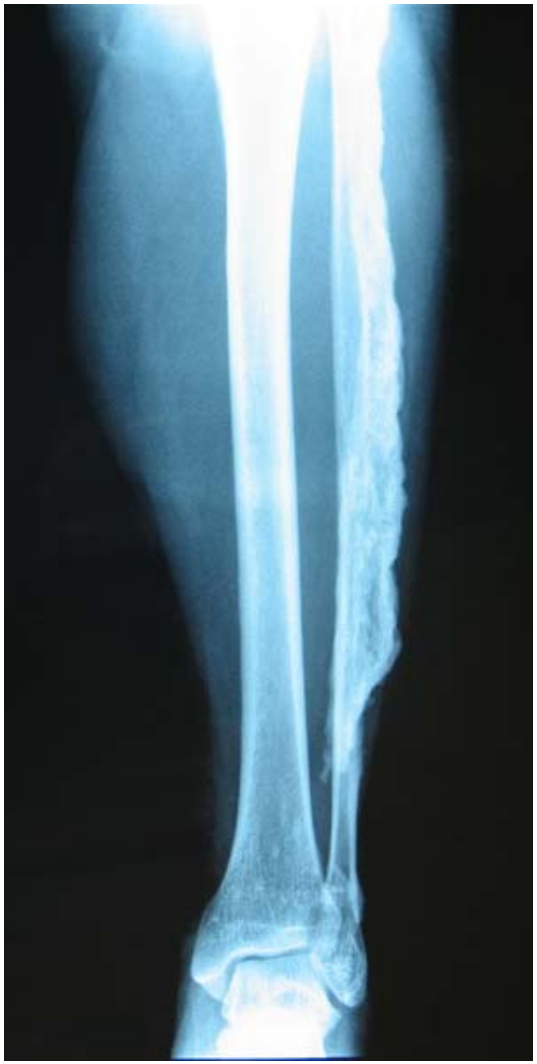
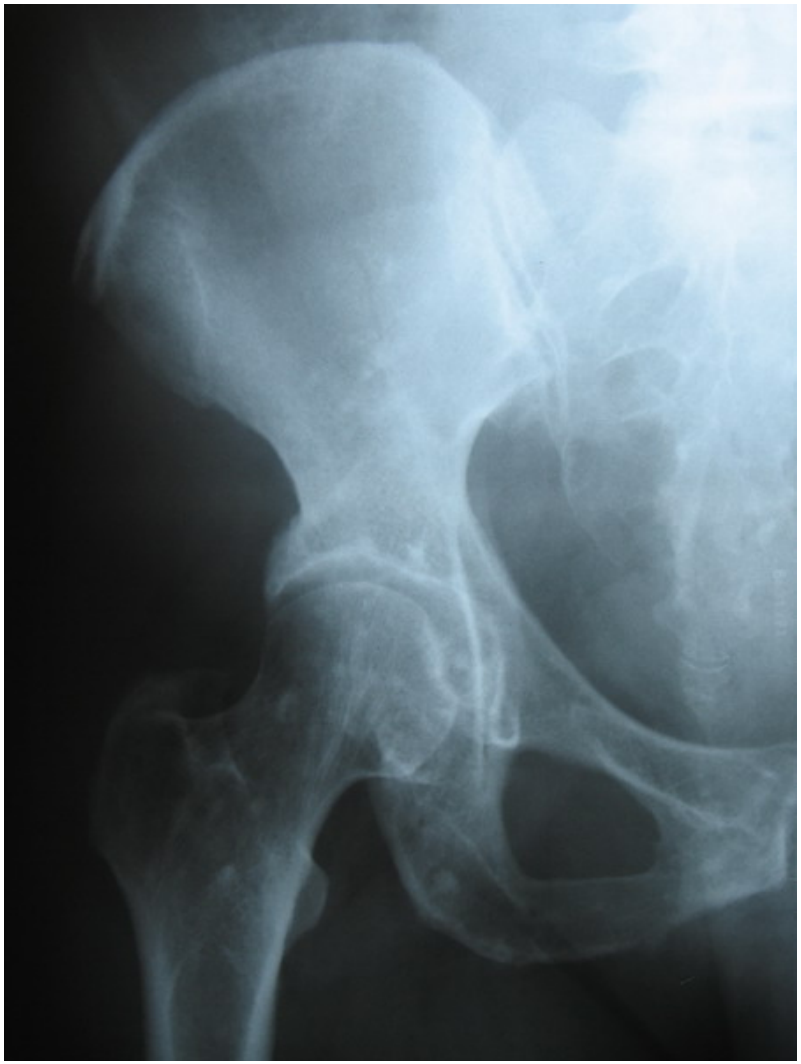
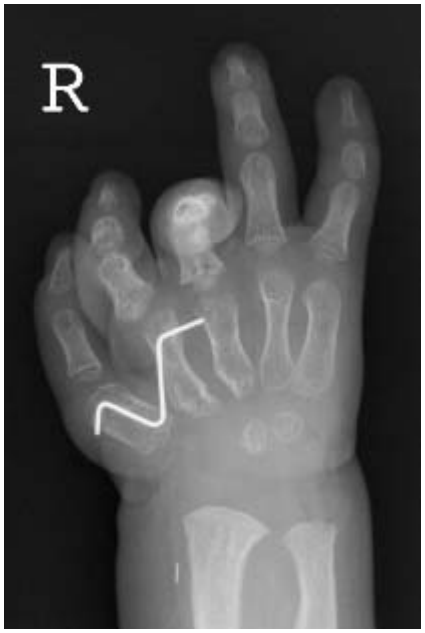


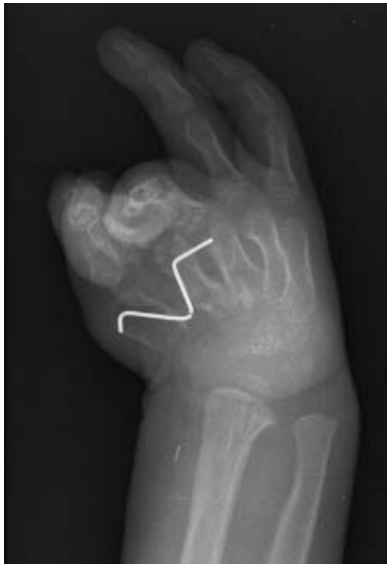
melorheostosis

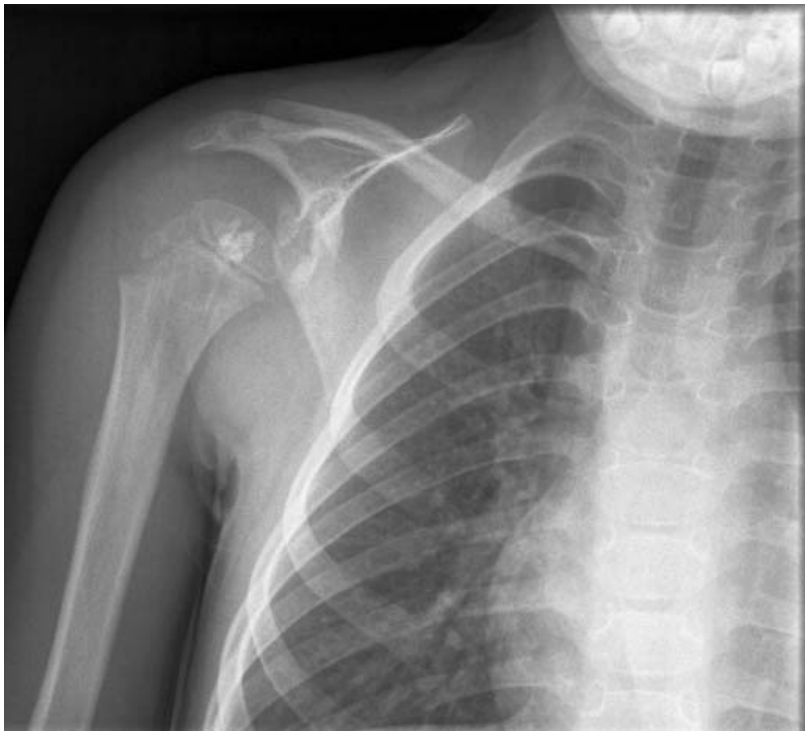


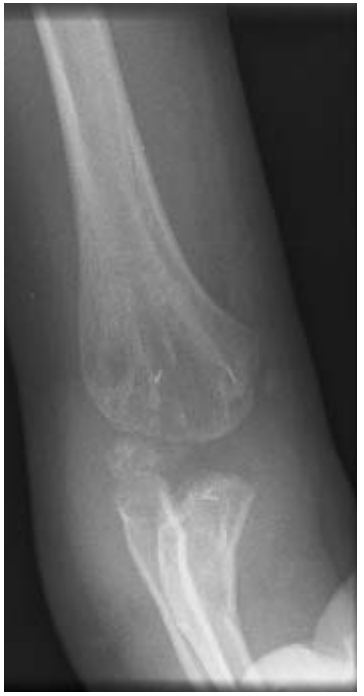
osteopoikilosis

Sporadic case with melorheostosis









Patient D0402645

Conclusions

- heterozygous inactivating mutations in LEMD3 cause:
  - osteopoikilosis
  - the Buschke-Ollendorff syndrome
  - rare “familial” forms of melorheostosis

- the cause of sporadic melorheostosis remains unknown
  - somatic LEMD3 mutations?
  - (somatic) defects in the BMP/TGFβ pathway?
  - polygenic?
  - non-genetic cause?

Fireside chat …

Short term goals

- need for samples of affected tissues
  - information on website of patient organisation
  - database of members
  - newsletters
- study of the natural history
- need for expert opinions and advice
  - centers of reference/excellence??
  - meetings with experts present
  - identify local physicians with interest
  - educate physicians

Acknowledgments

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Melorheostosis Association and the patients

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