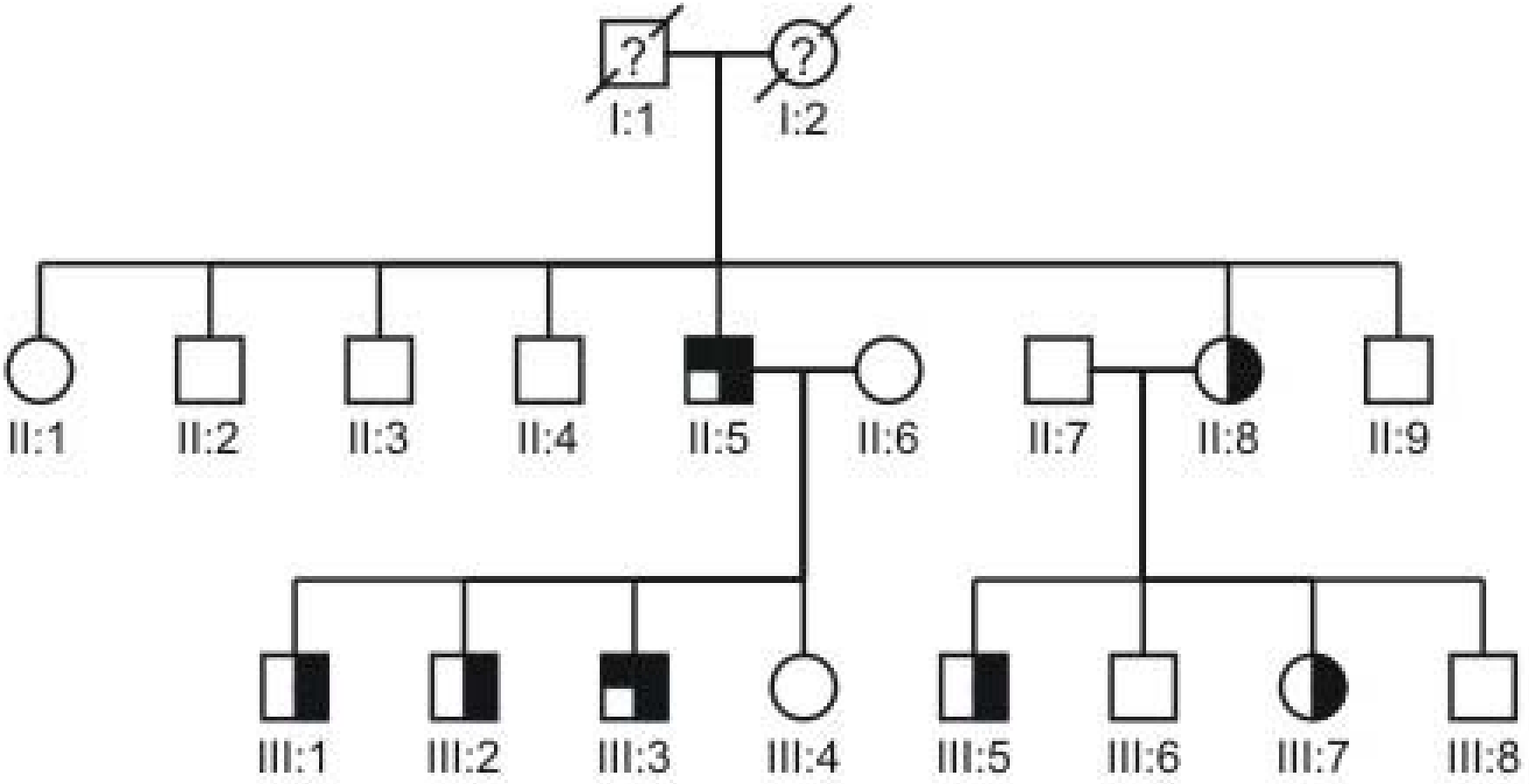
# The role of LEMD3 in the pathogenesis of melorheostosis

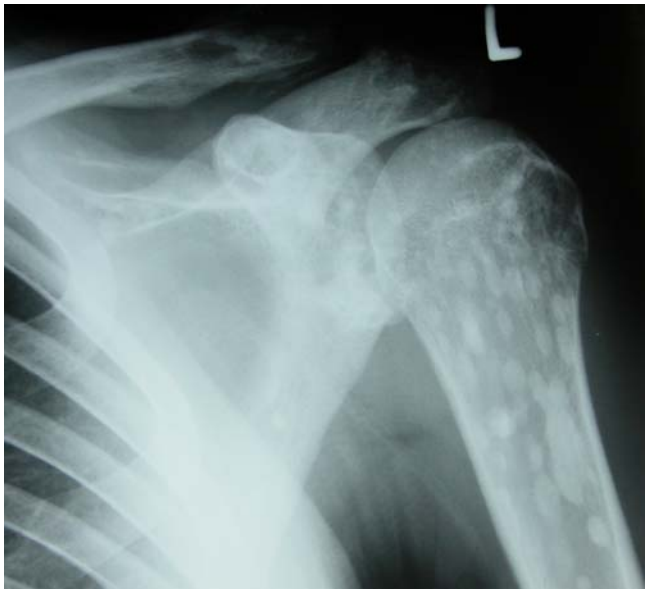
*Geert Mortier MD PhD*
*Center for Medical Genetics*
*Gent University Hospital*

Center for Medical Genetics

# Osteopoikilosis

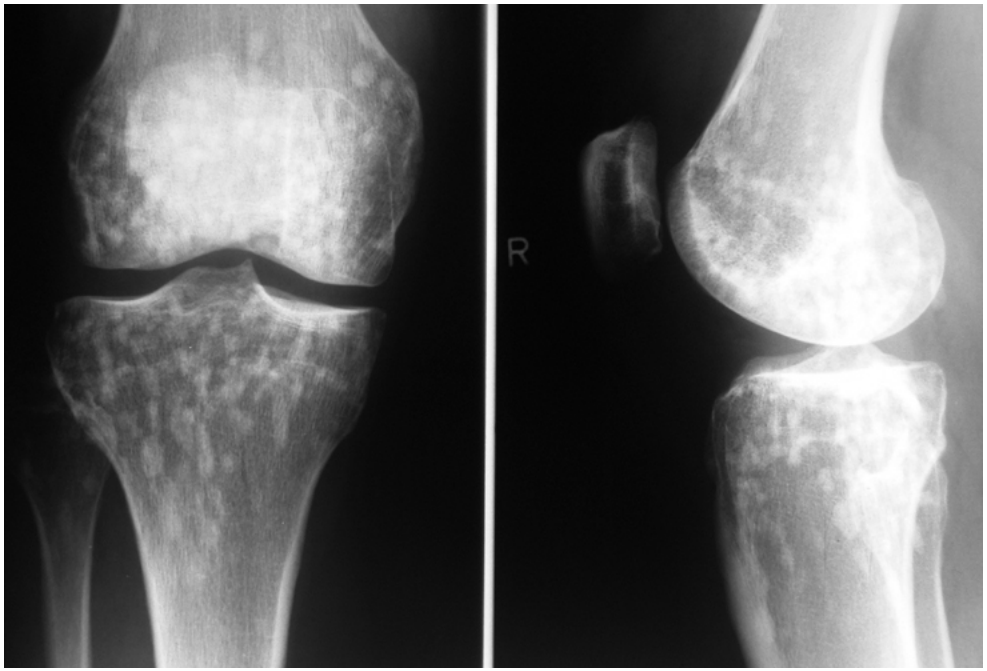


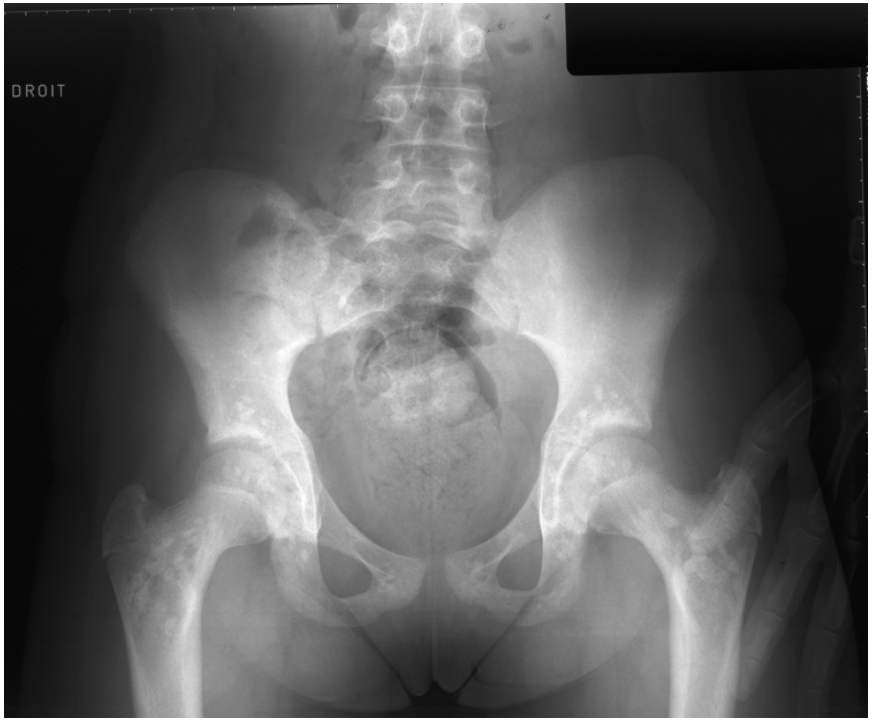
# Osteopoikilosis



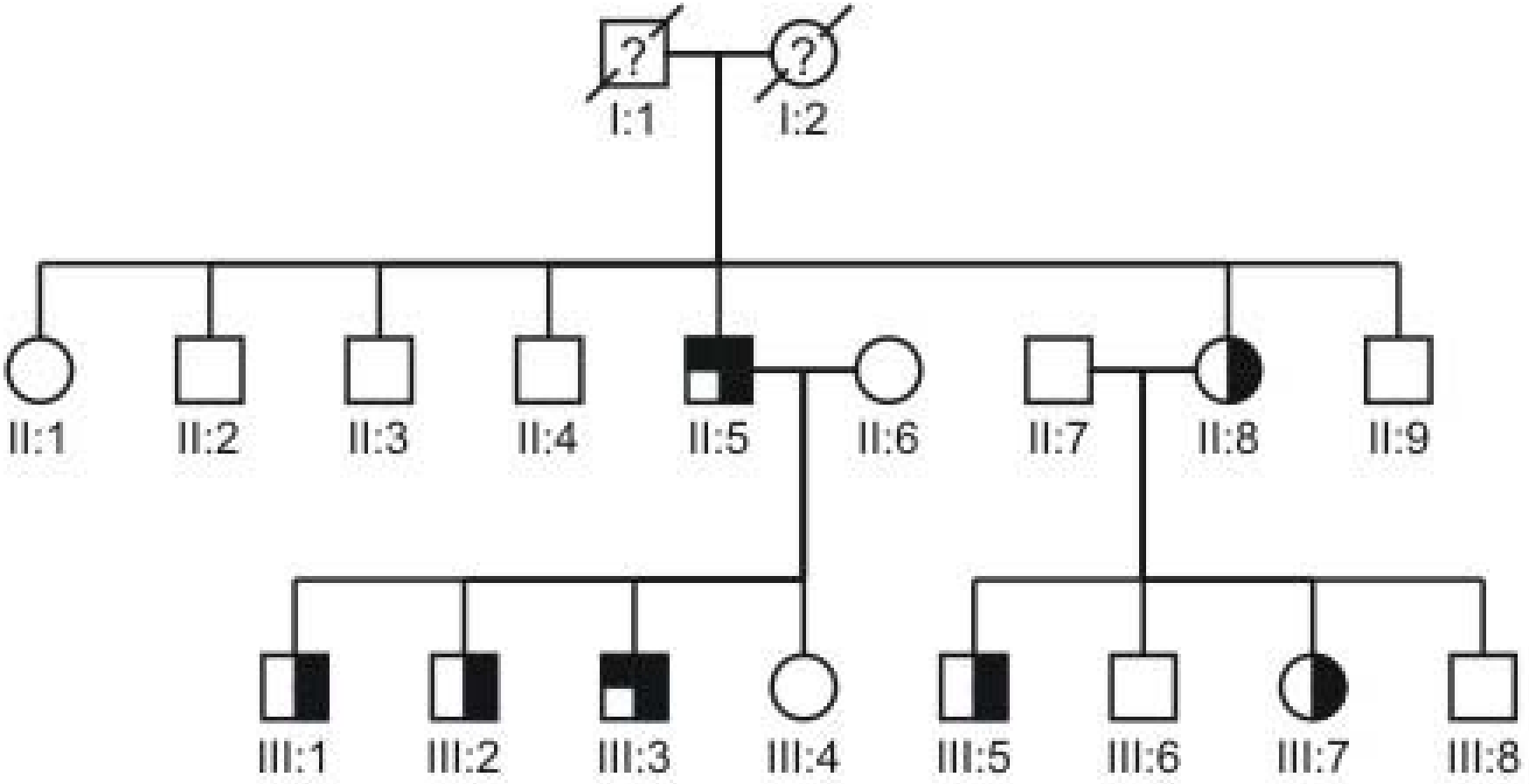
- sclerosing bone dysplasia
- autosomal dominant
- hyperostotic spots
- usually detected incidentally
- estimated prevalence: 1/20.000 - 1/50.000
- isolated or in association with other skin/bone lesions

# Osteopoikilosis



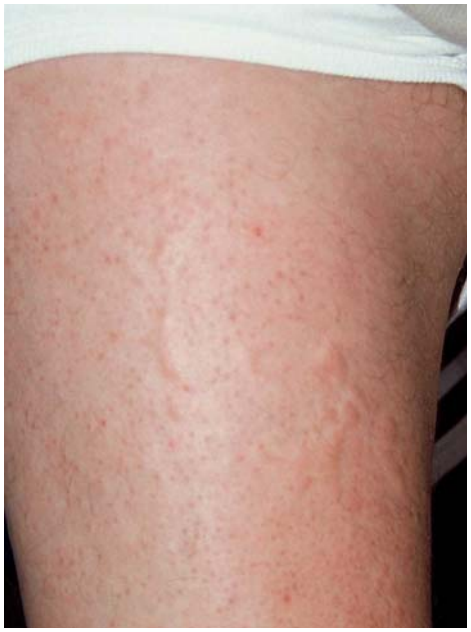



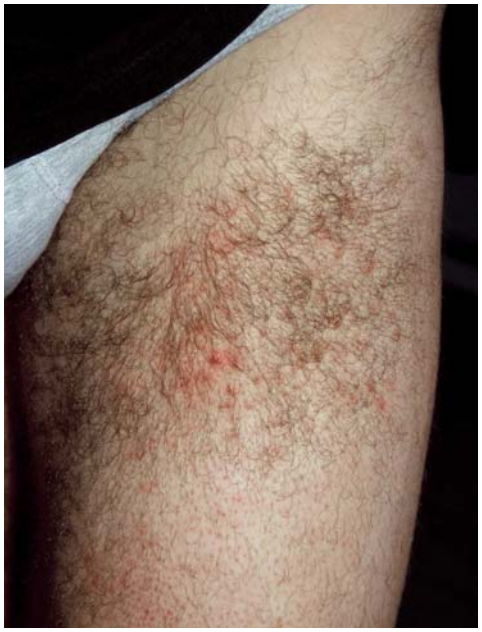
# Osteopoikilosis



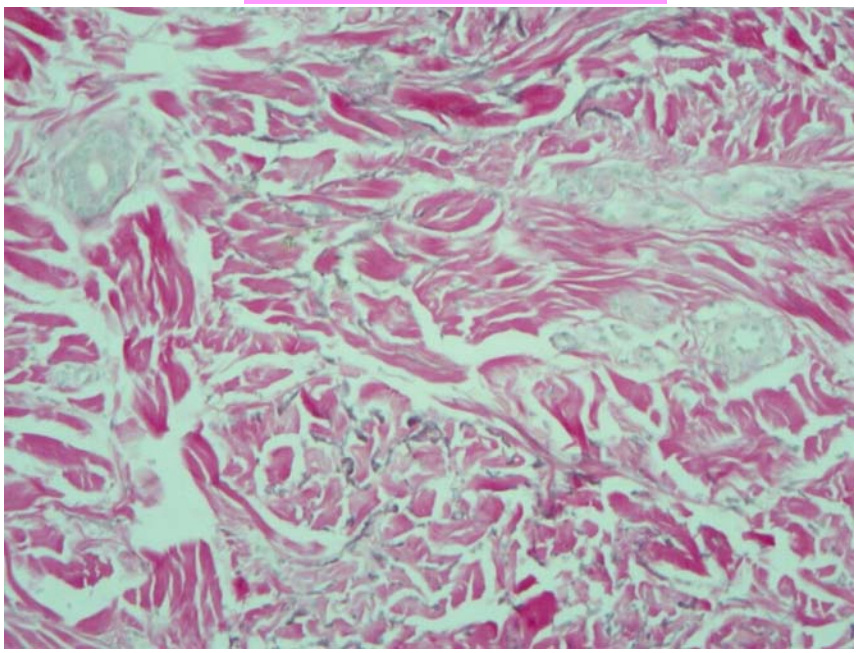
# Buschke-Ollendorff syndrome

BOS = osteopoikilosis + connective tissue nevi (elastic or collagenous type)



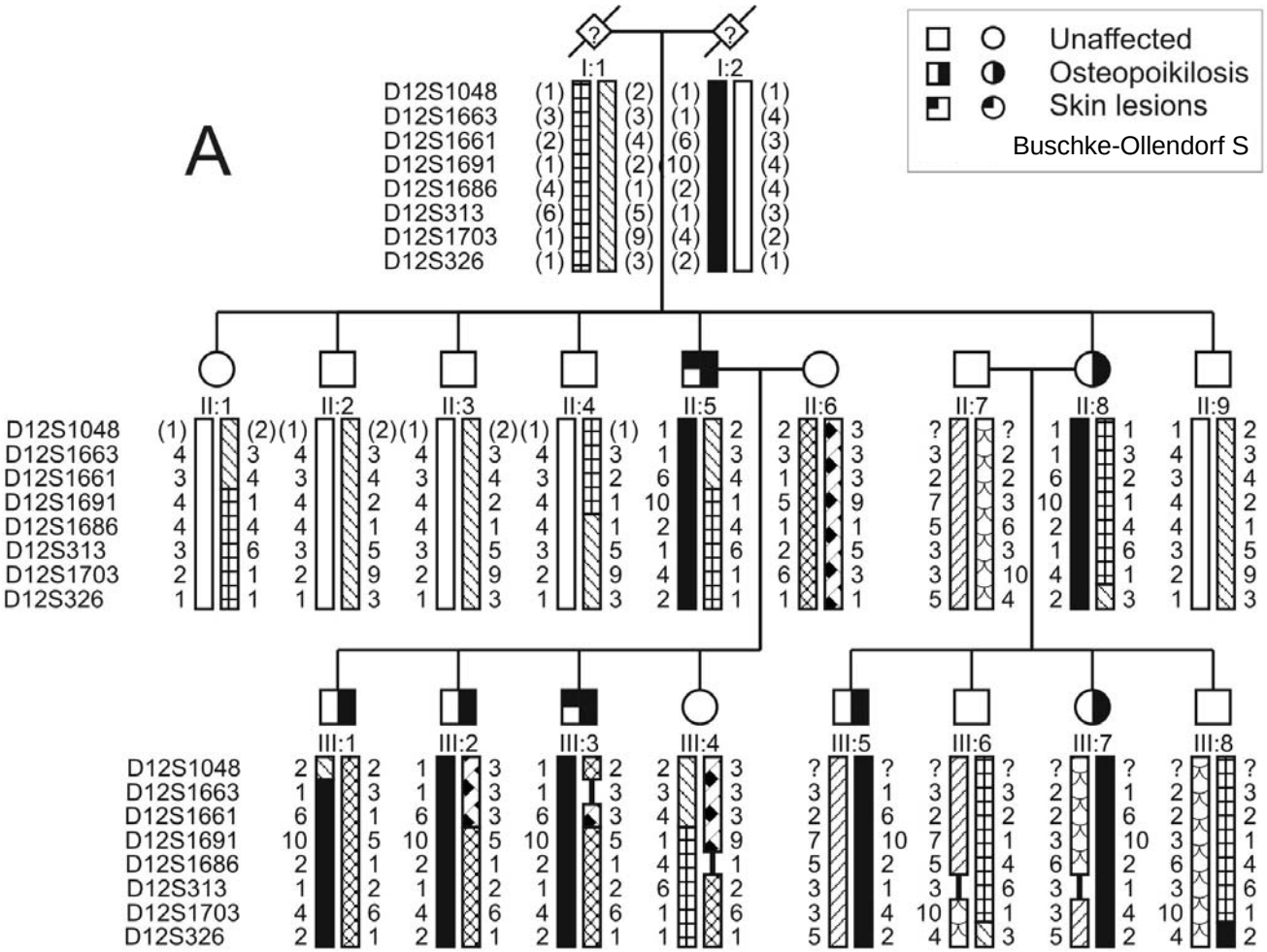


elastic-type nevus

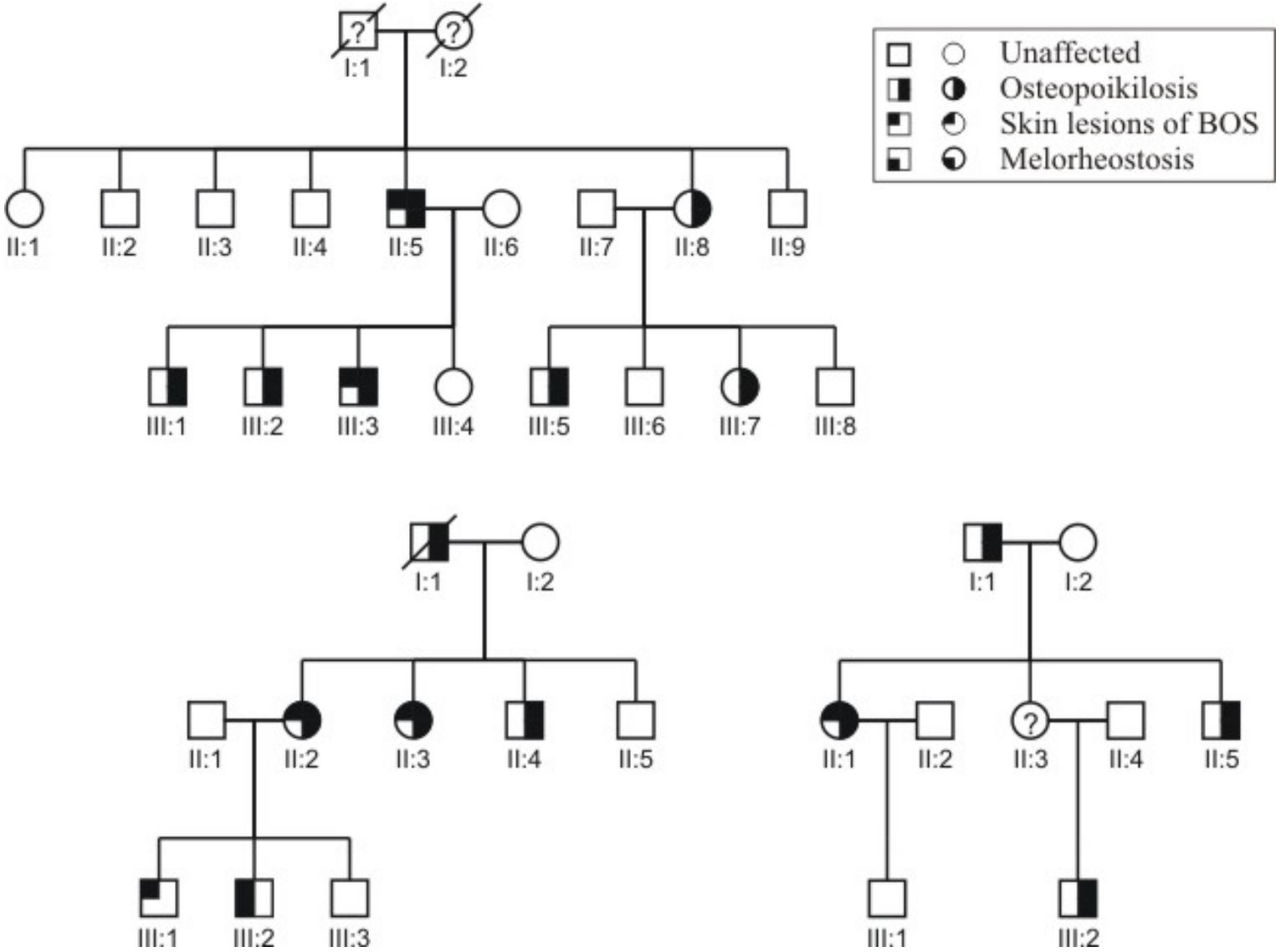


Light micrograph – Van Gieson – x100

# Osteopoikilosis



# Pedigrees




Center for Medical Genetics

Family B

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*

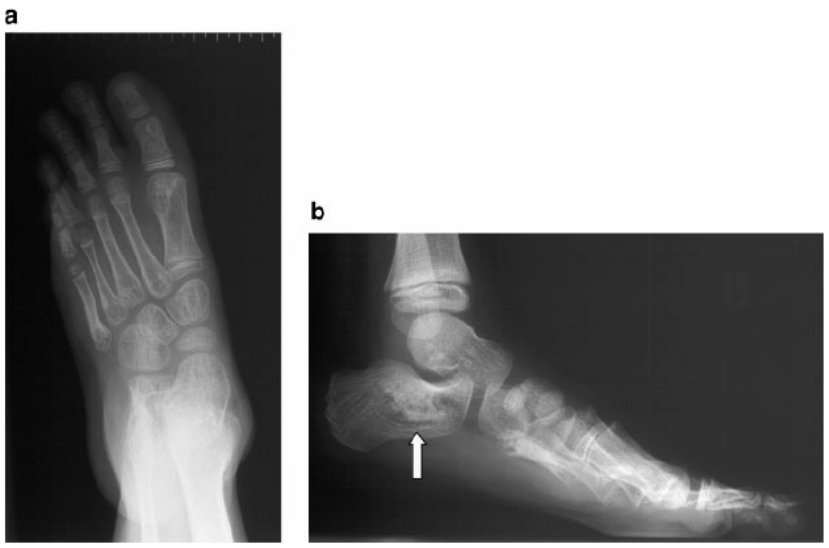
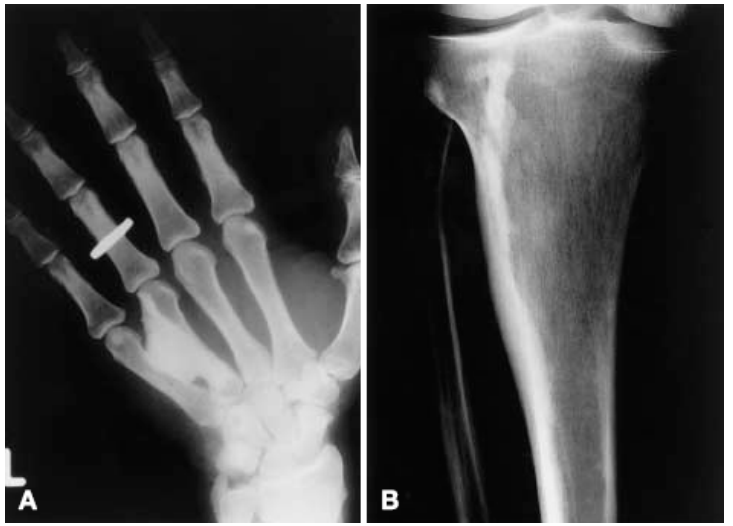
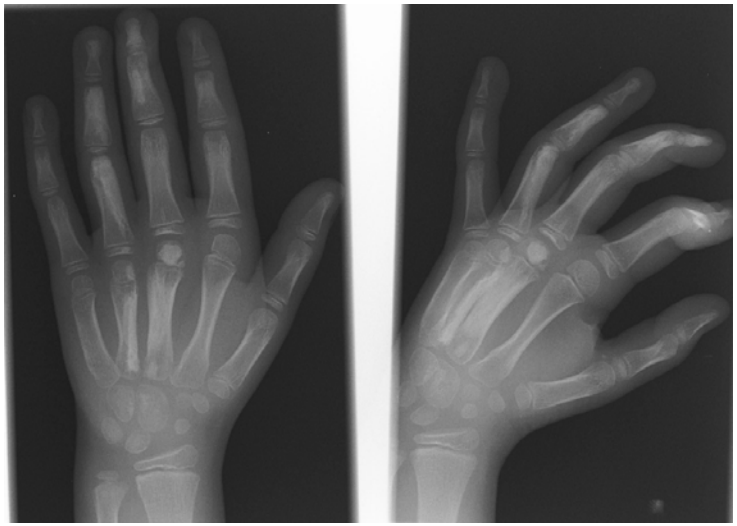



Fig. 3. Radiological appearance of the left foot of the proband at the age of 5 years. **a**: Typical sclerotic areas can be seen in the first metatarsal head, the proximal phalanx of the hallux, the fifth metatarsal, the phalanges of the fifth toe, and the basis of the fourth metatarsal. There is shortening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

Center for Medical Genetics

# Melorheostosis

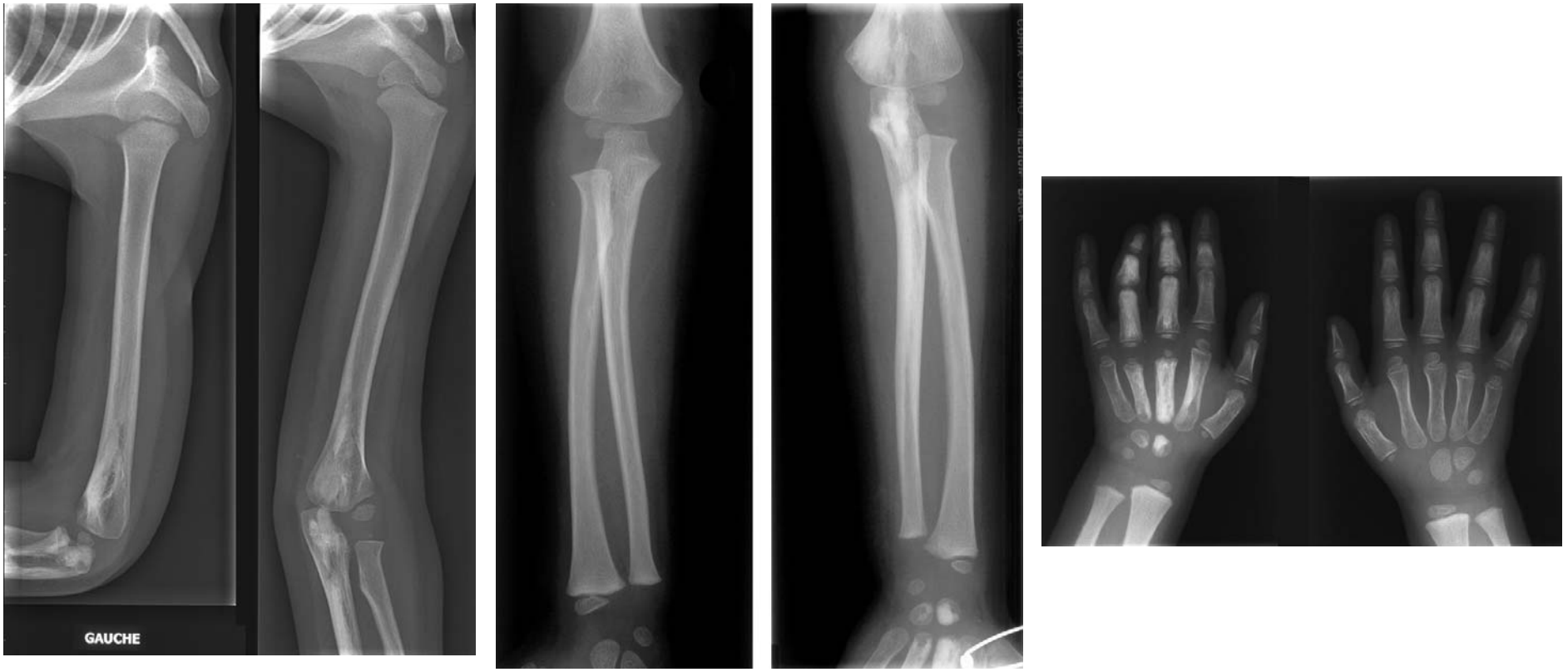


- joint contractures
- curving or shortening of limb(s)
- chronic pain, swelling of joints
- skin, subcutaneous tissue or muscle involvement
- irregular linear areas of increased radiodensity along the major axis of the tubular bones
- areas of osteophytic periosteal excrescences (dripping candle wax)
- ectopic bone formation
- sometimes round radiodensities

- no hereditary transmission

# Melorheostosis




Patient D0503242

# Linkage results

- Genome wide linkage analysis
- Linkage for two markers on chr. 12
- Region: D12S1048 – D12S313
- Combined maximum two-point LOD score of 6.691

| Marker | Position[a] | Family A Z at θ=0 | Family B Z at θ=0 | Family C Z at θ=0 | Families A to C Z at θ=0 |
|---|---|---|---|---|---|
| D12S1048 | 56.38 | -4.419 | | | -4.419 |
| D12S1663 | 56.38 | 3.744 | 1.764 | 0.602 | 6.110 |
| D12S1661 | 63.89 | 3.744 | 1.764 | 1.183 | 6.691 |
| D12S1691 | 72.20 | 3.744 | 1.764 | 1.183 | 6.691 |
| D12S1686 | 76.36 | 3.744 | 0.882 | 1.183 | 5.809 |
| D12S313 | 79.93 | 3.744 | 1.764 | -2.796 | 2.712 |
| D12S1703 | 81.05 | 3.744 | 1.764 | -2.796 | 2.712 |
| D12S326 | 86.40 | 2.443 | | | 2.443 |

[a] *Positions are given in centiMorgans according to the Marshfield map*

Center for Medical Genetics

# Unusual case

- 16-year-old girl
- normal pregnancy
- uneventful delivery
- small-for-date baby (W:2060 g at term)
- failure to thrive during infancy
- proportionate short stature

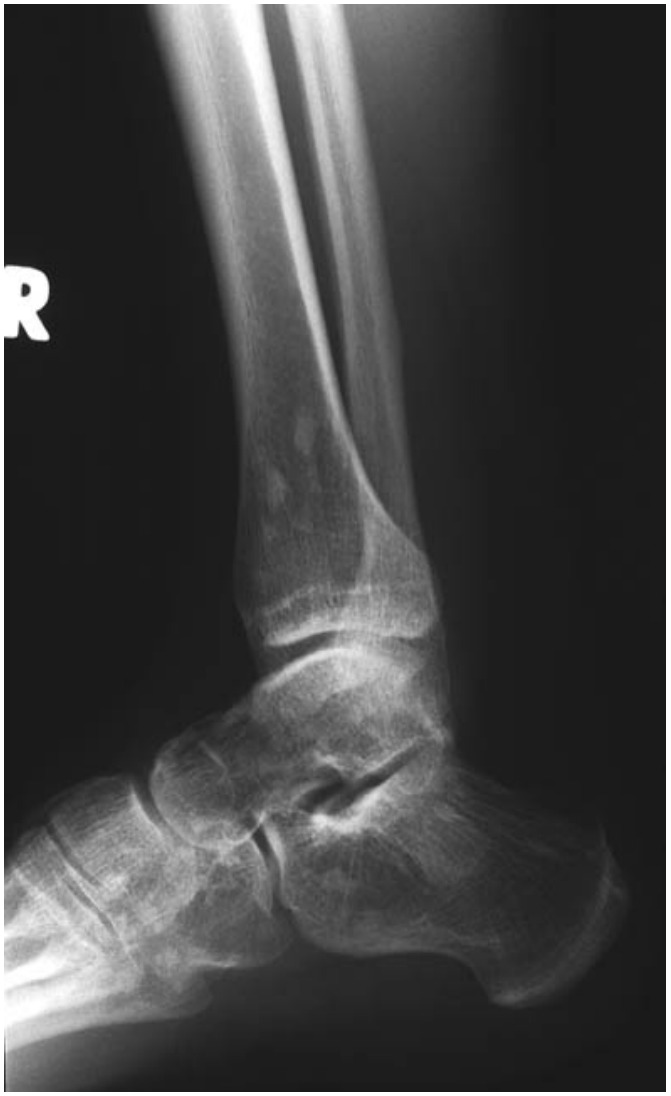
  measurements at age 16yrs:

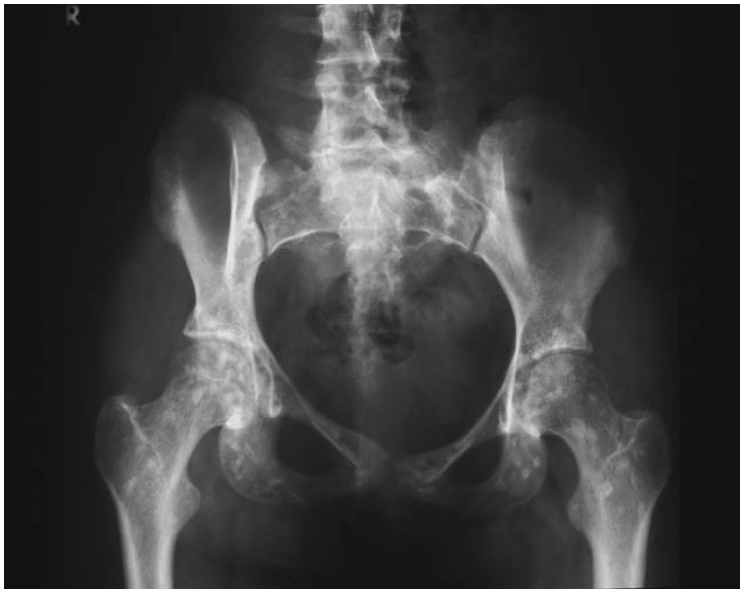
  - weight: 31.8 kg (P50 for 10 yrs)
  - height: 131.5 cm (P50 for 9 yrs)
  - OFC: 49 cm (P50 for 3 yrs)

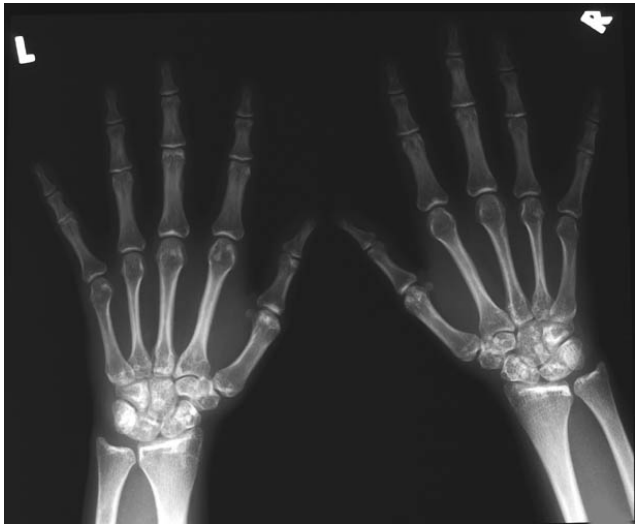
- mild cognitive impairment
- anomalies of position/shape of internal organs

  - ectopic kidneys
  - aberrant origin of renal arteries
  - malrotation of small bowel
  - midline positioned spleen; rectangular shaped liver

# Unusual case



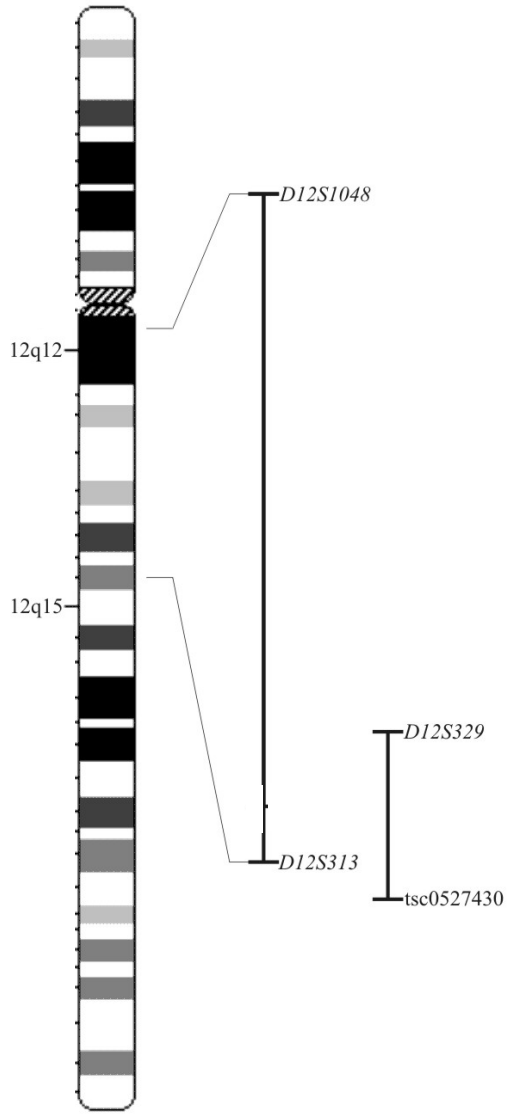



Center for Medical Genetics

# Syndromic form of osteopoikilosis

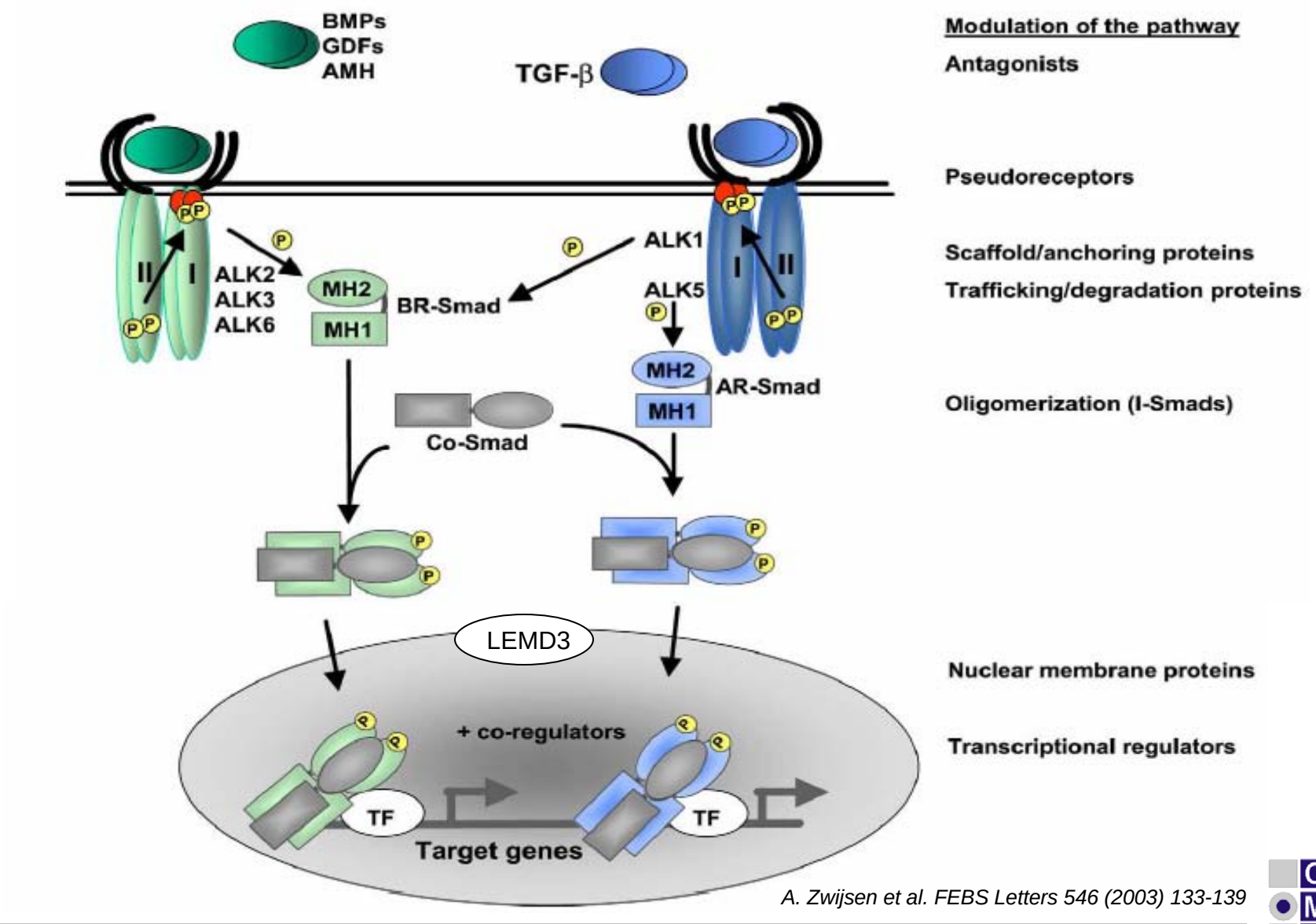
- Contiguous gene deletion syndrome?

# Linkage results




- Genome wide linkage analysis
- Linkage for two markers on chr. 12
- 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*

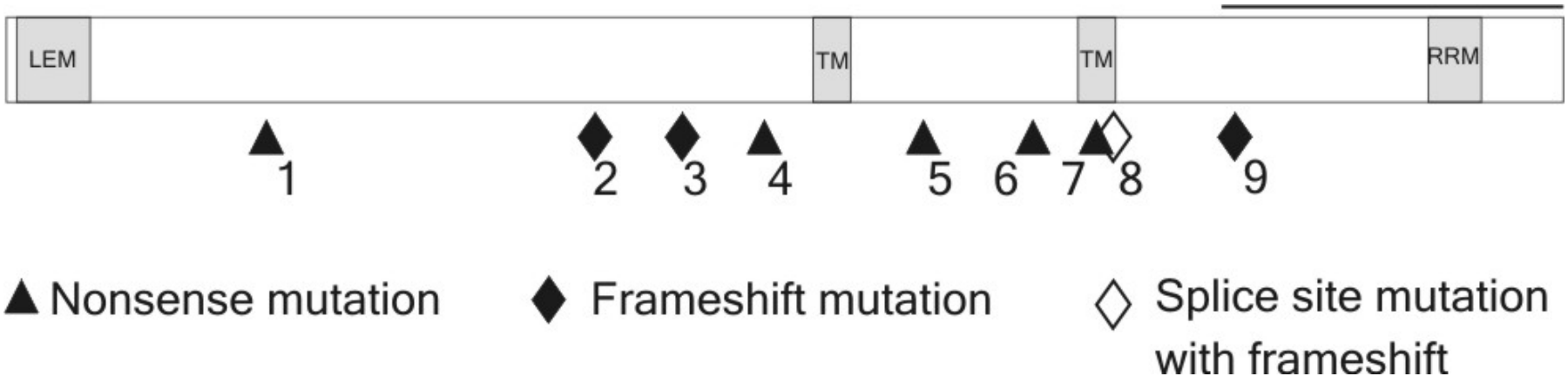
# LEMD3 function




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

Center for Medical Genetics

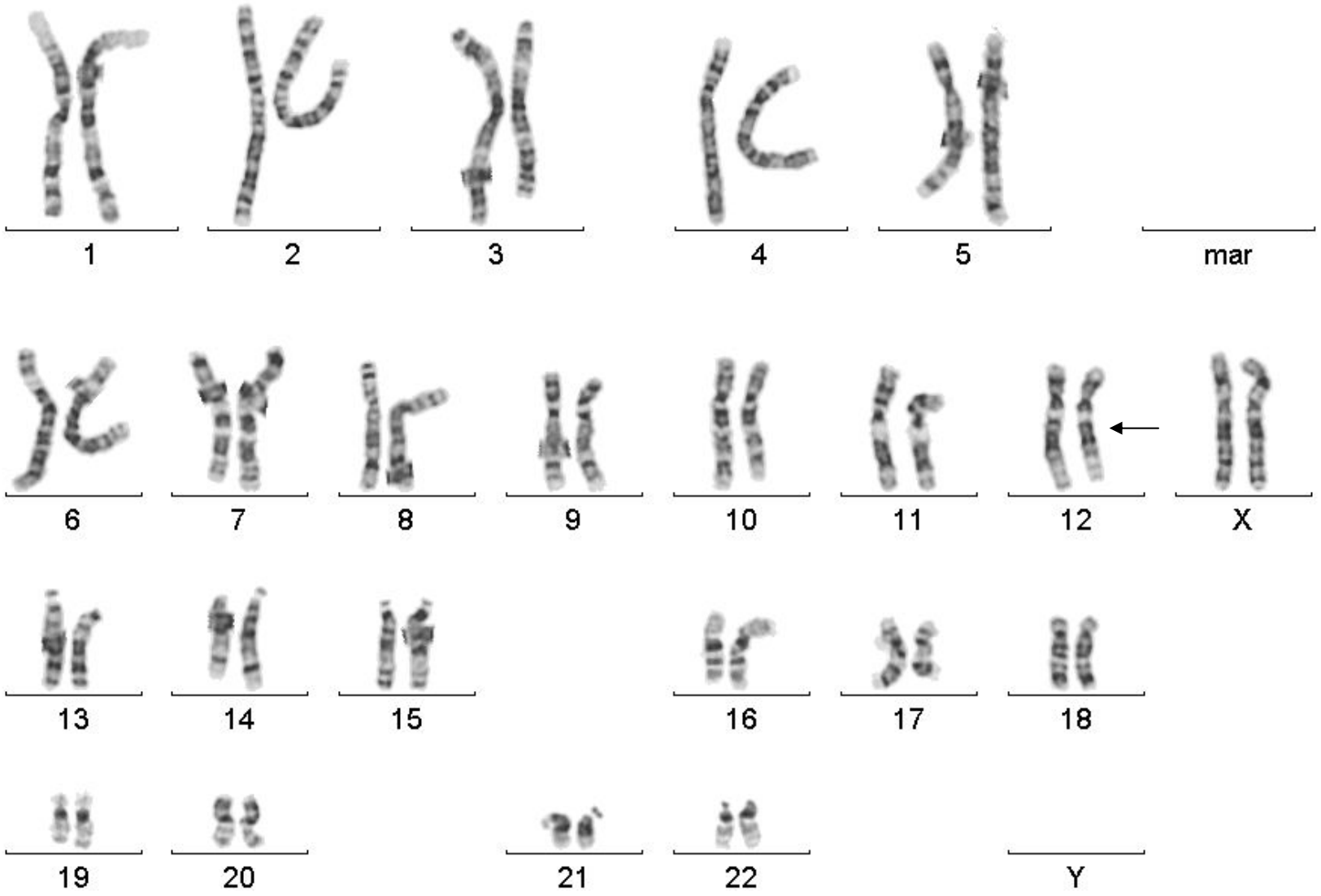
# *LEMD3* mutations




| Patient | diagnosis | LEMD3 mutation |
|---|---|---|
| Family A | BOS | c.2154dupA |
| Family B | OP + melo | c.1609C>T |
| Family C | BOS | c.1185dupT |
| G03-2881 | OP | c.1941+5delG |
| G03-2882 | OP | c.457C>T |
| G03-1885 | BOS | c.1033_1035delGGGinsC |
| G03-1858 | OP+MR+short stature | microdeletion |

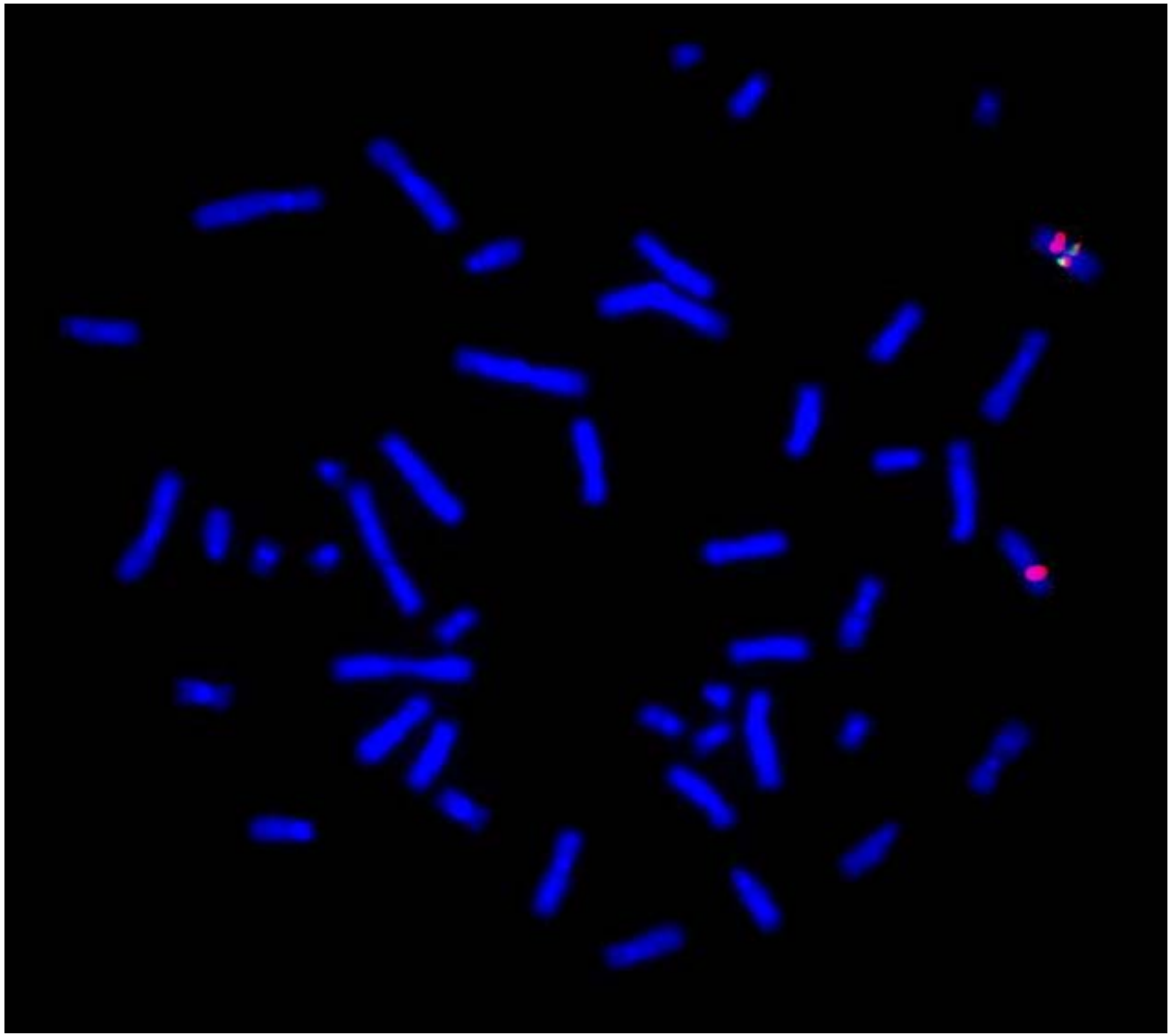
Center for Medical Genetics

# Microdeletion

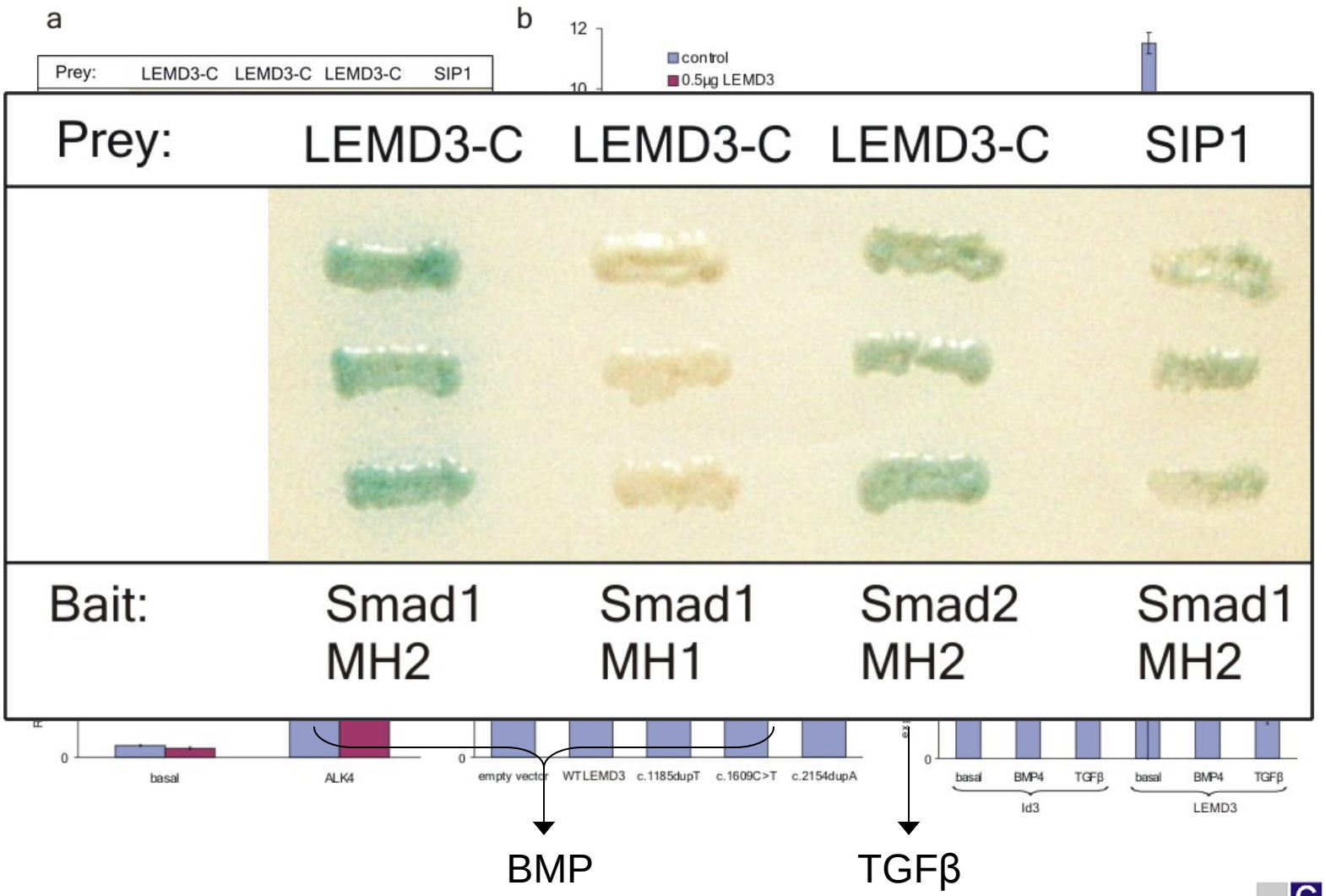



Center for Medical Genetics

# Microdeletion

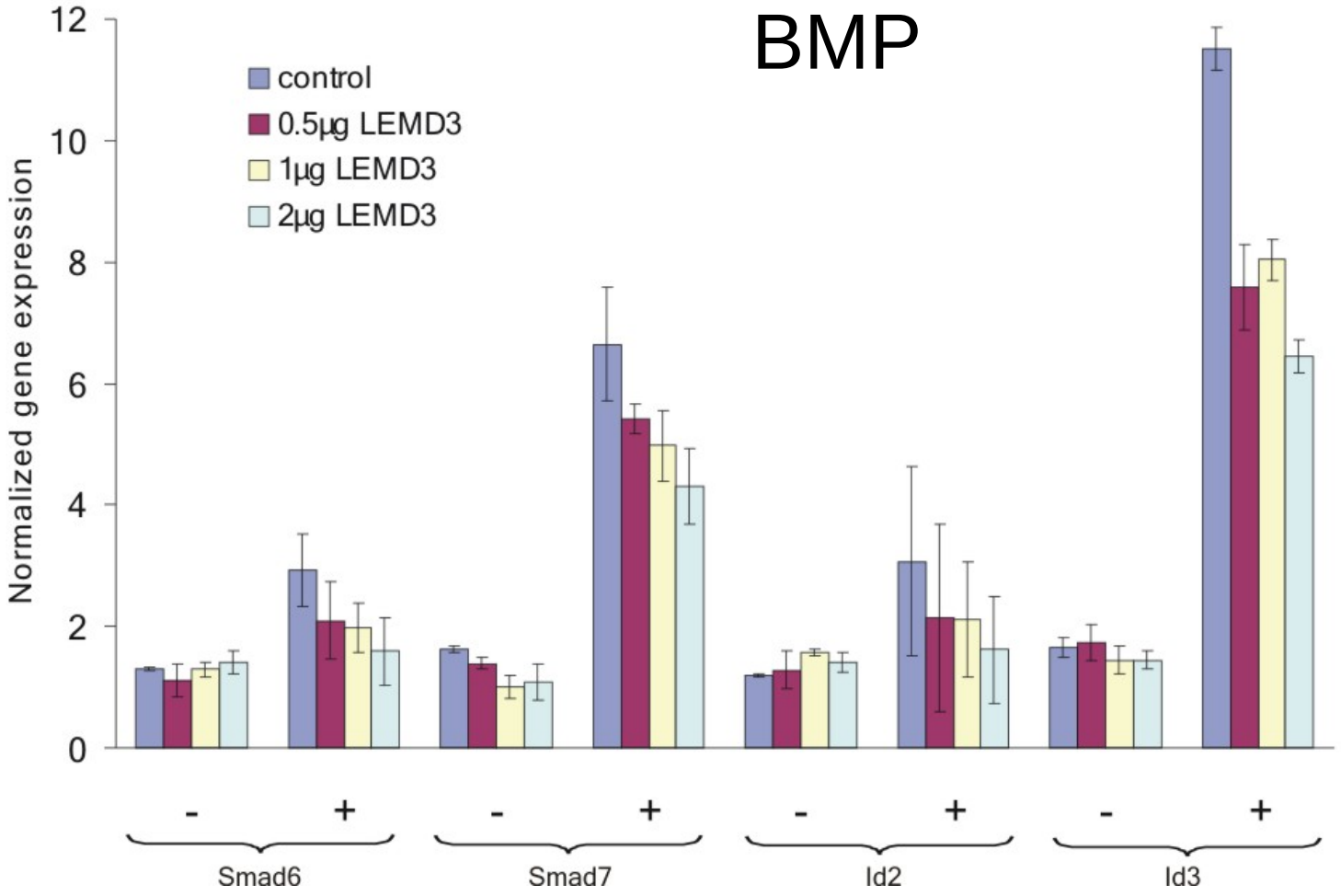


# LEMD3 in BMP/TGFβ signaling

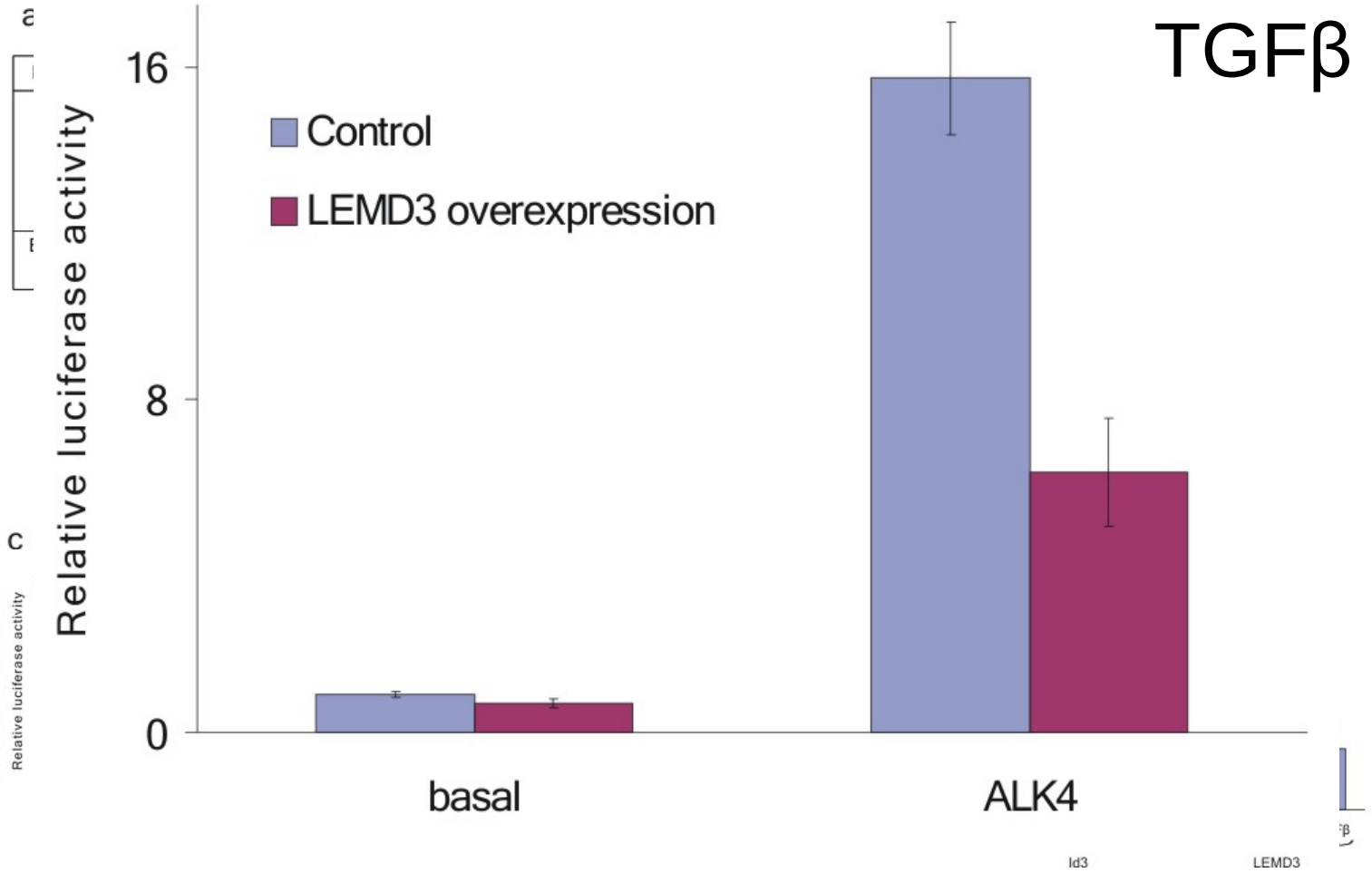



Center for Medical Genetics

# LEMD3 in BMP/TGFβ signaling

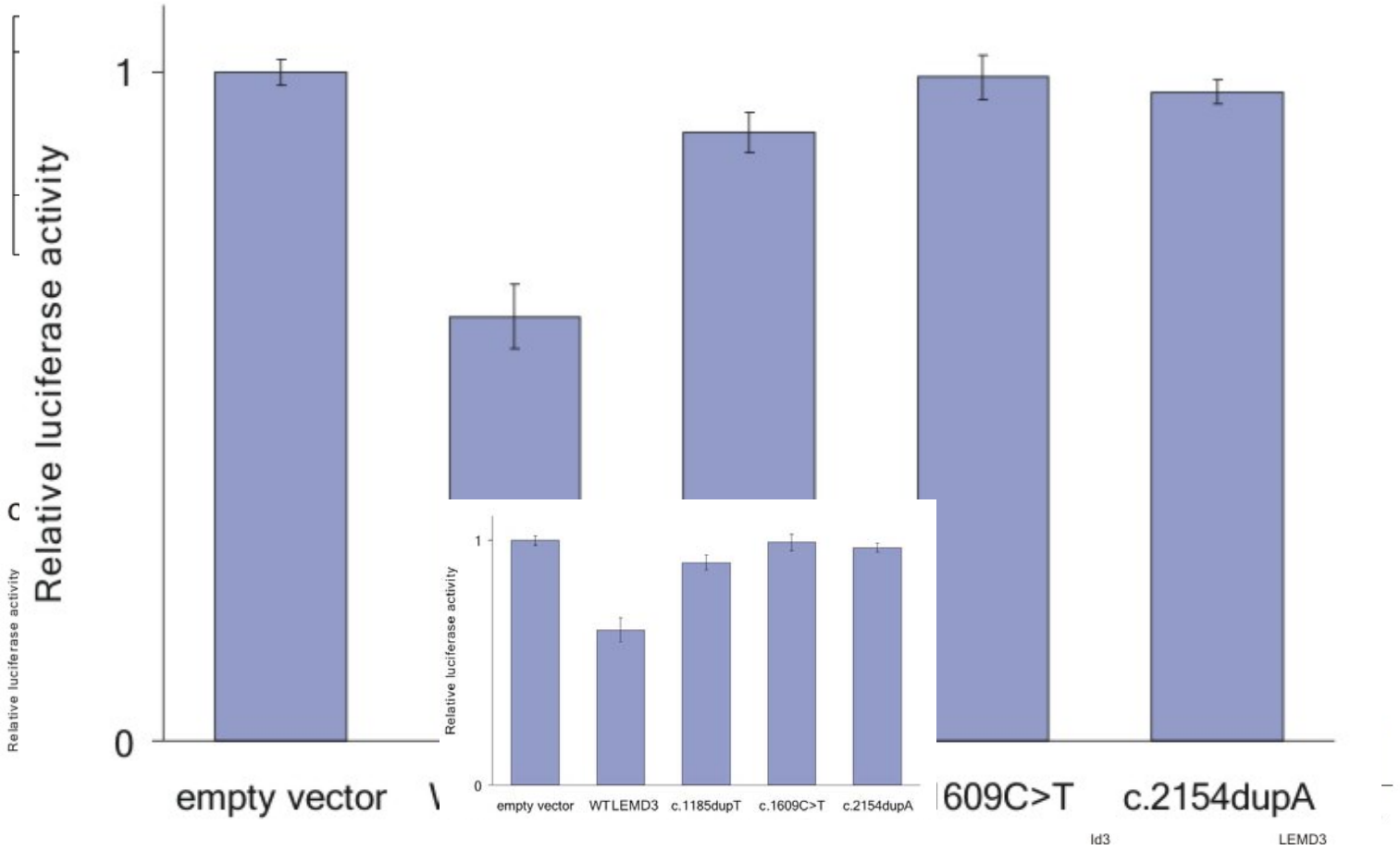


# LEMD3 in BMP/TGFβ signaling



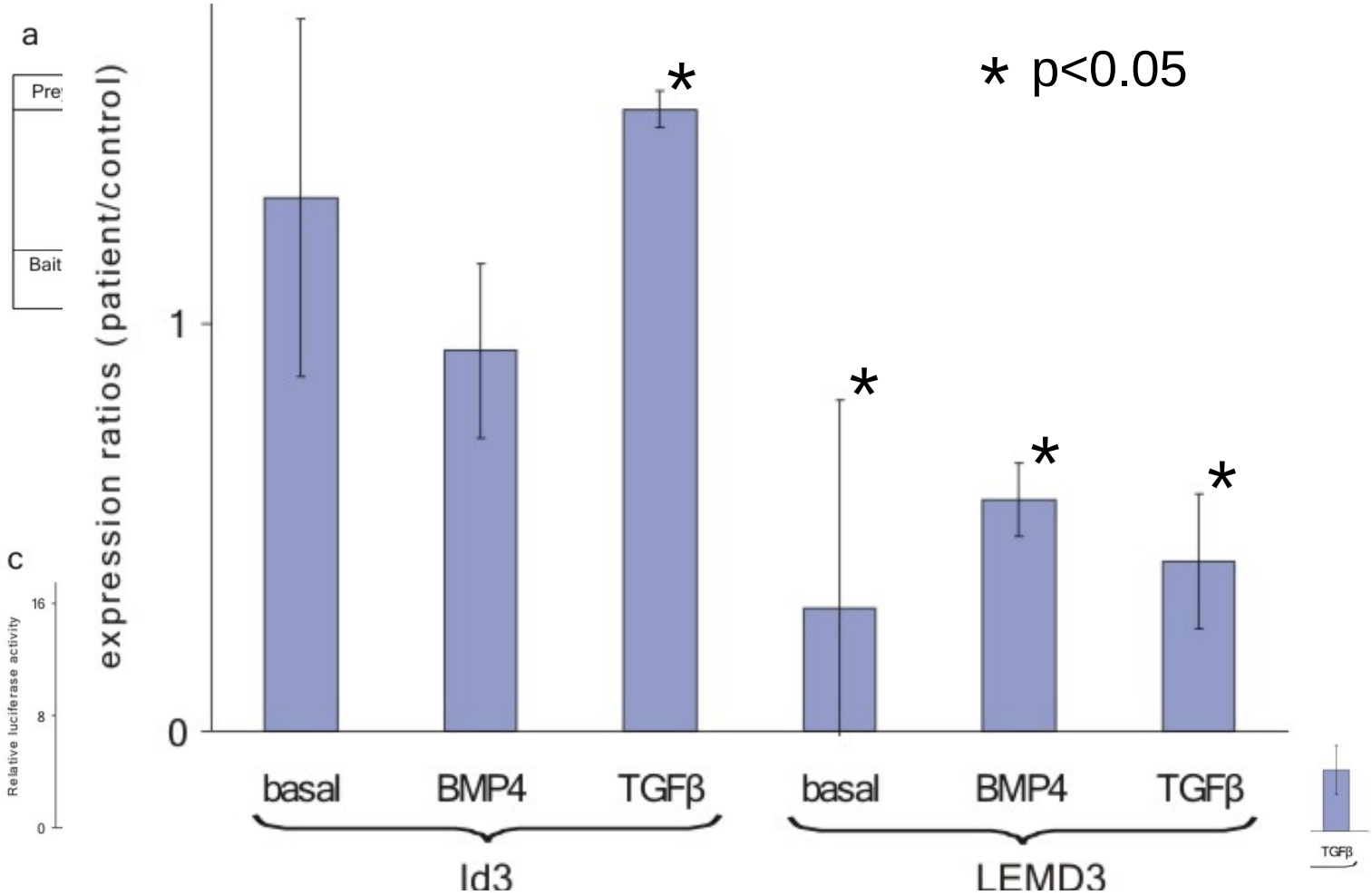

Center for Medical Genetics

# LEMD3 in BMP/TGFβ signaling




Center for Medical Genetics

# LEMD3 in BMP/TGFβ signaling




Center for Medical Genetics

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]

Nature Genetics Nov 2004; 36:1213

1) Loss of function mutations in *LEMD3* can result in
   - osteopoikilosis
   - Buschke-Ollendorff syndrome
   - melorheostosis

1) Human LEMD3
   - binds to the MH2 domain of BMP and TGFβ specific Smads
   - inhibits both the BMP and TGFβ signaling pathways

# Follow-up study

Screening a larger series of patients

| Group | patient | disorder | mutation |
|---|---|---|---|
| | 04g3557 | OP | c.1801G>T |
| | 04g3867 | BOS | c.1323C>A |
| **A** | 04g3934 | BOS | c.1873C>T |
| | D0501606 | BOS | c.1914insA |
| | 04g3820 | OP? | no mutation |
| | D0500261* | OP+melo | c.1963C>T |
| **B** | D0503238 | OP+melo | c.830dupA |
| | D0503122 | *OP+melo?* | c.2494-9A>G |
| | D0402645 | melo | c.1913T>A |
| **C** | 9 other patients | melo | no mutation |

* Butkus CE et al Am J Med Genet 1997;72:43

# Conclusions

- loss-of-function mutations in LEMD3 do result in OP or BOS

- loss-of-function mutations in LEMD3 are found in families with OP and melorheostosis

- majority of sporadic patients with melorheostosis do NOT have a germline mutation in LEMD3

  - germline mutation outside the analysed region?
  - somatic mutations in LEMD3?
  - is haploinsufficiency for LEMD3 just a predisposing factor?

Center for Medical Genetics

Gent University Hospital

Center for Medical Genetics

Gent

Center for Medical Genetics


University of Gent

Center for Medical Genetics

Brugge

Center for Medical Genetics


Lissewege


Center for Medical Genetics