Analysis of the LEMD3 gene in individuals affected with melorheostosis

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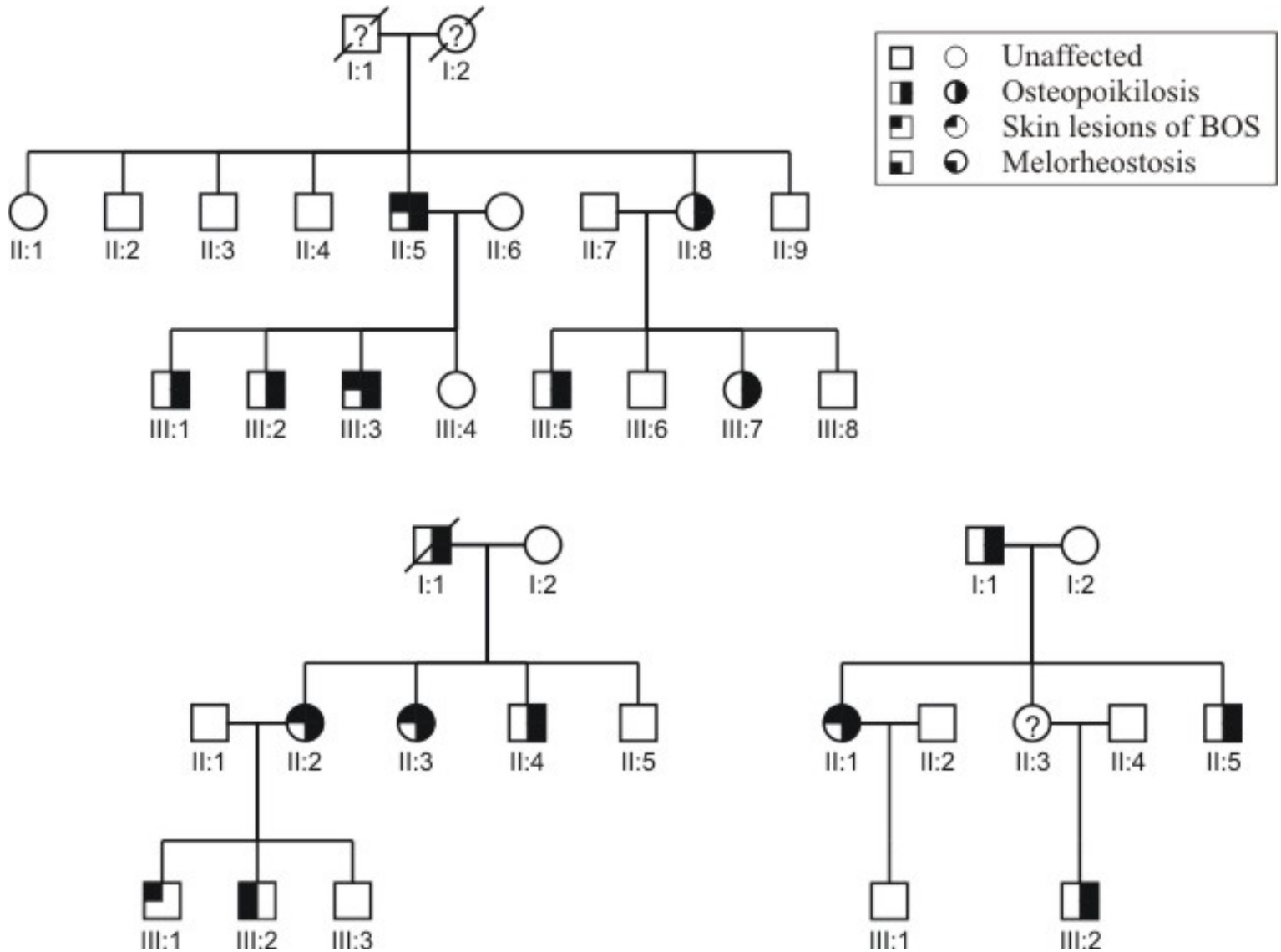
Genome search in three families



Family with melorheostosis

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*

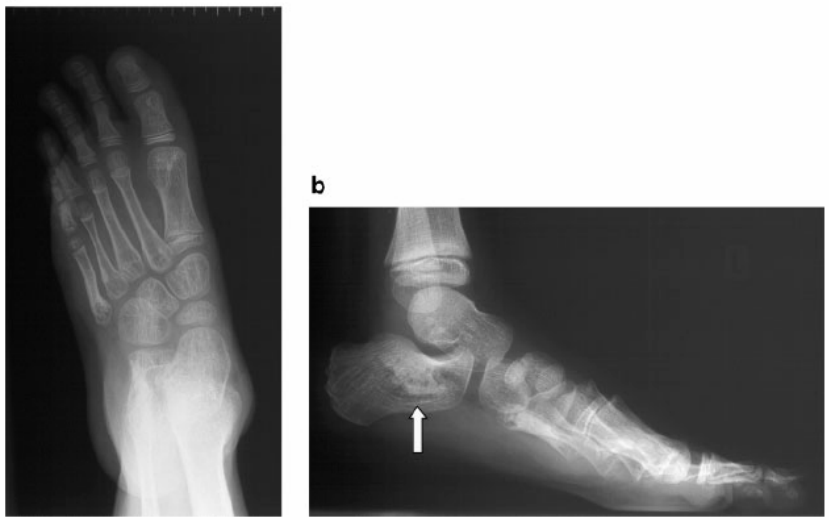


Fig. 3. Radiological appearance of the left foot of the proband at the age of 5 years. **a**: Typical sclerotic areas can be seen in the first metatarsal head, the proximal phalanx of the hallux, the fifth metatarsal, the phalanges of the fifth toe, and the basis of the fourth metatarsal. There is shortening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

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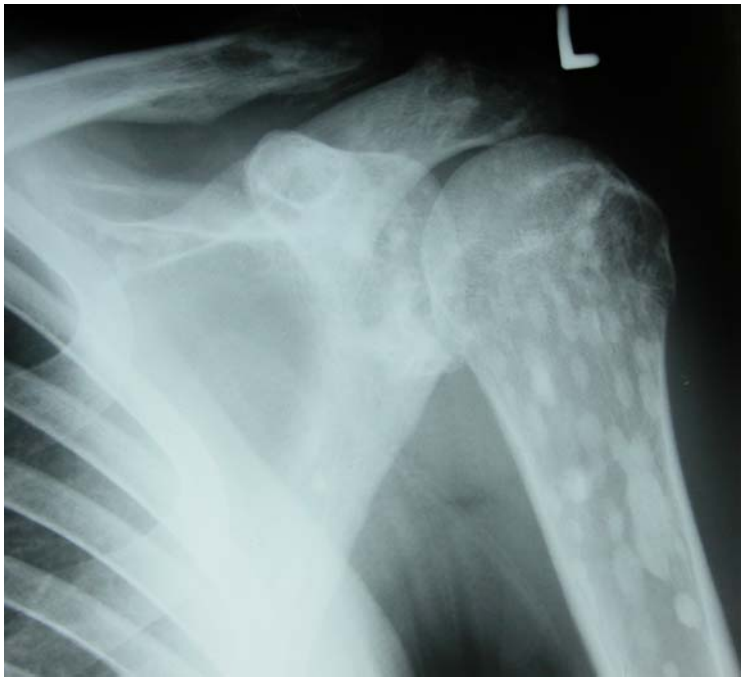
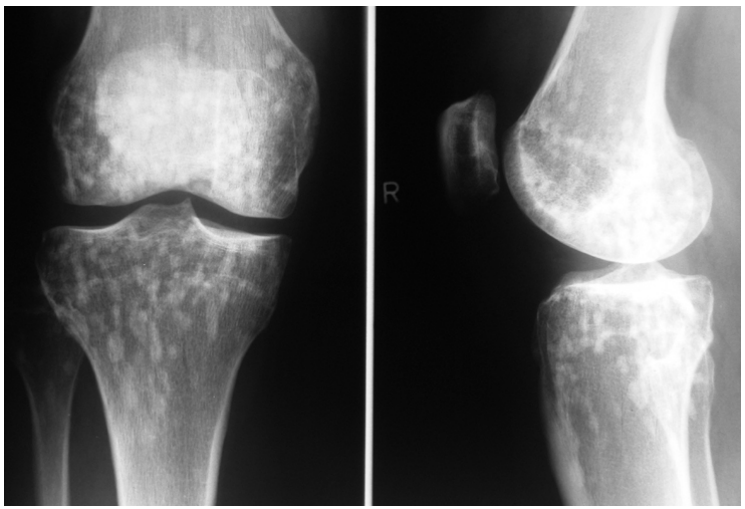
Osteopoikilosis

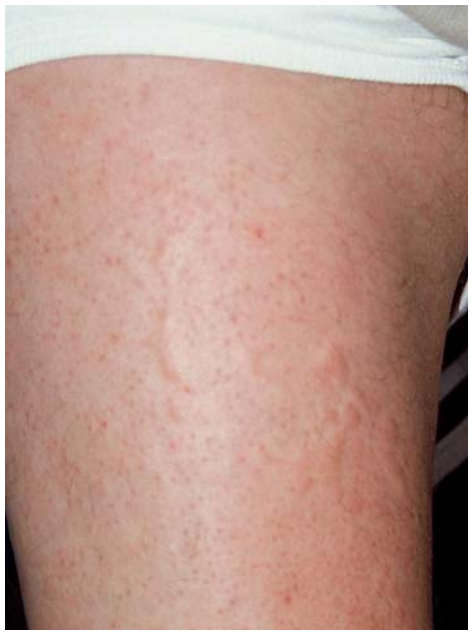




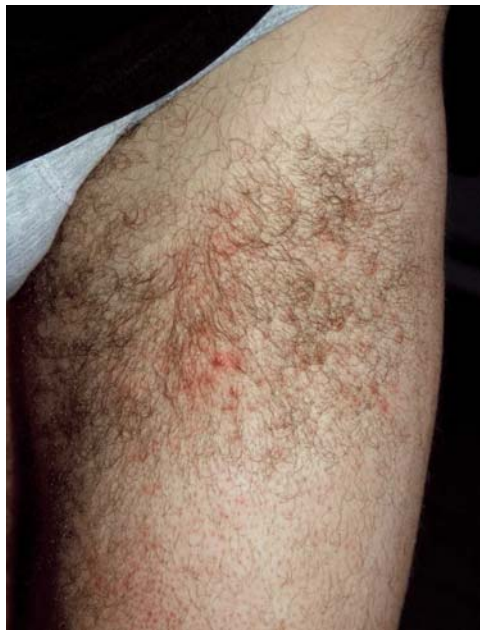
- Benign condition
- Autosomal dominant
- Hyperostotic spots
- Isolated or in association with other skin/bone lesions

Buschke-Ollendorff syndrome

BOS = osteopoikilosis + connective tissue nevi (elastic type)

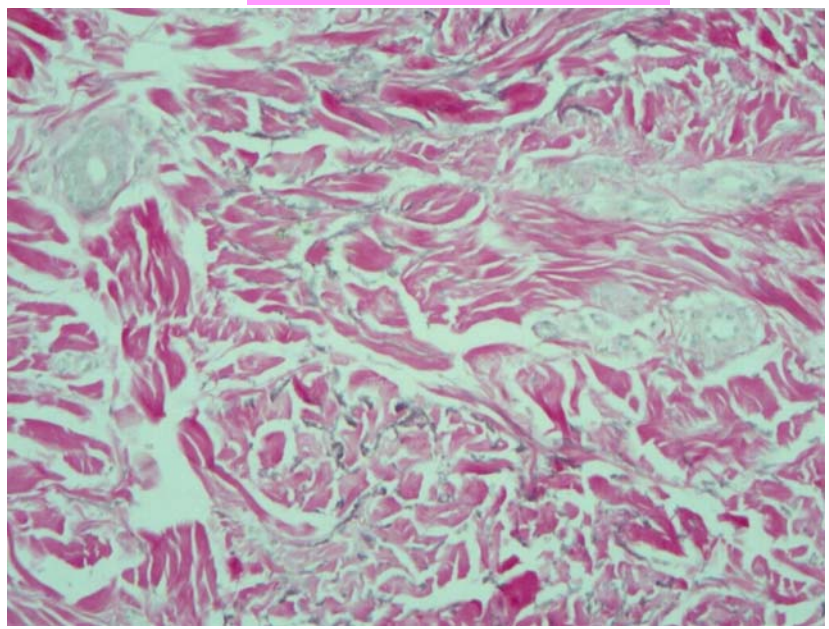


Widely disseminated, multiple, skin-colored to yellow, small papules (few mm in diameter)



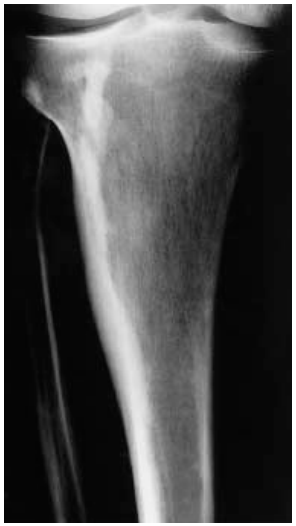
Localized, asymmetrically distributed, larger lesions (yellow plaques)

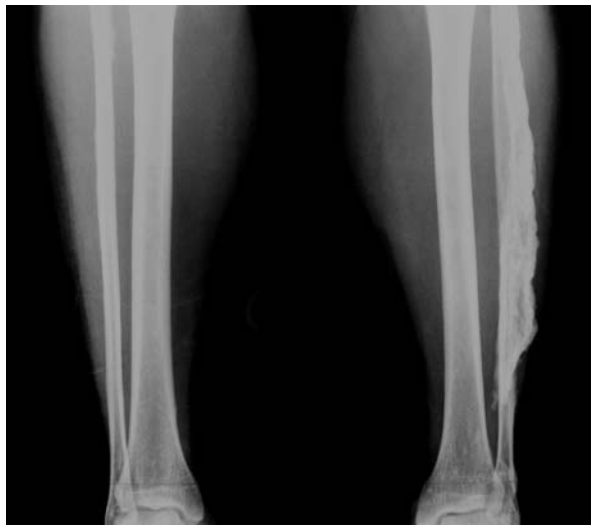
elastic-type nevus

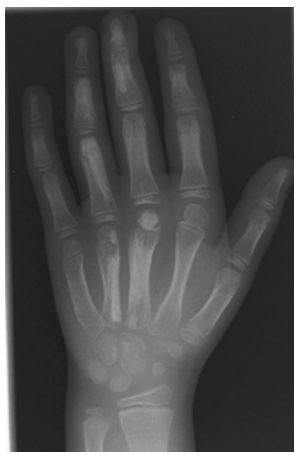


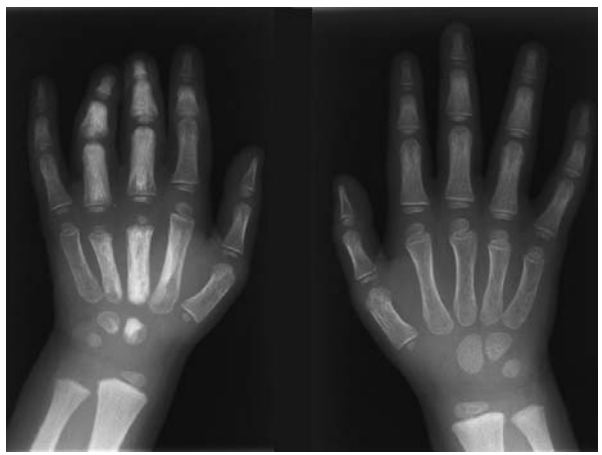
Light micrograph – Van Gieson – x100

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

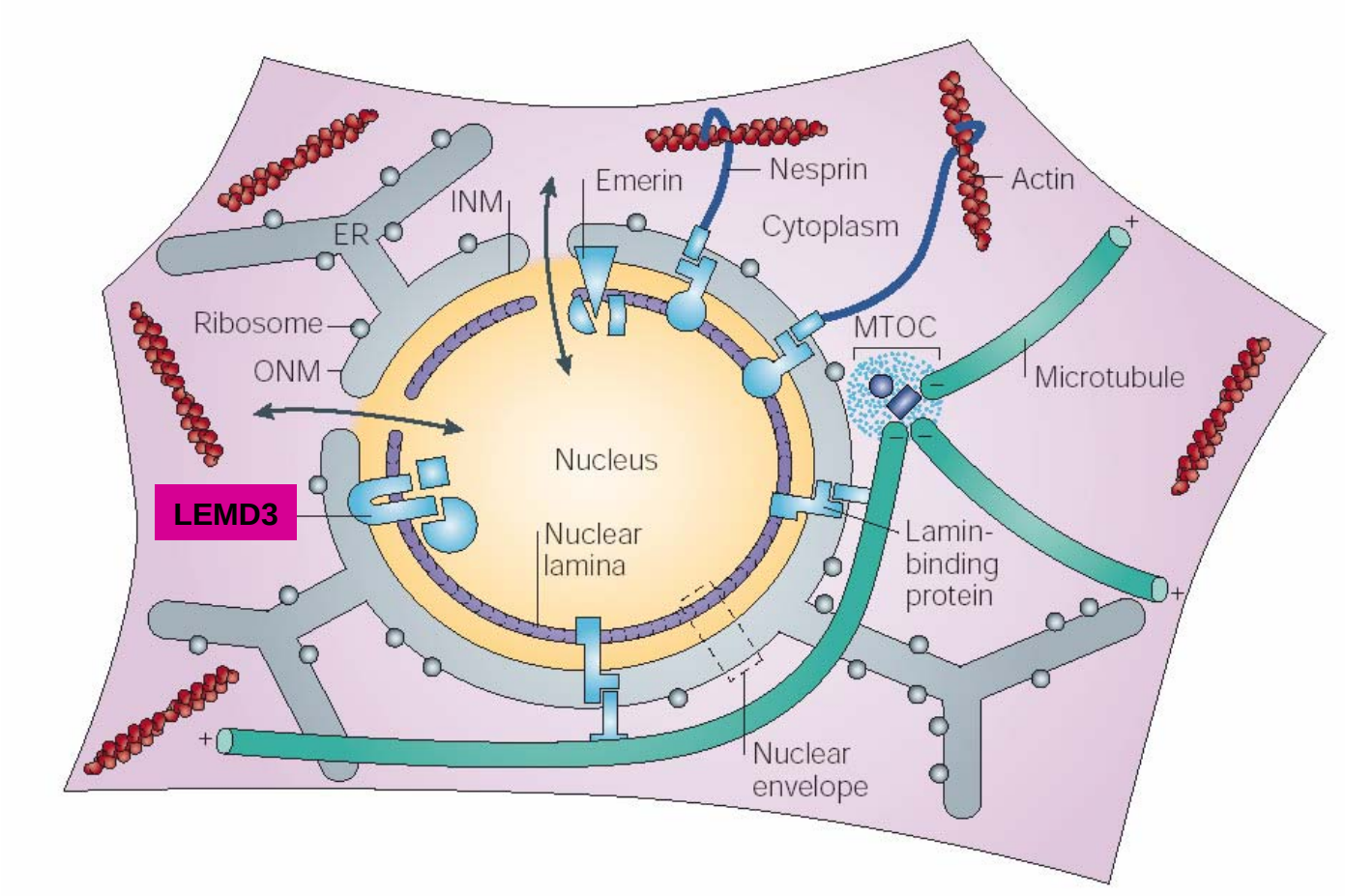
LEMD3

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]

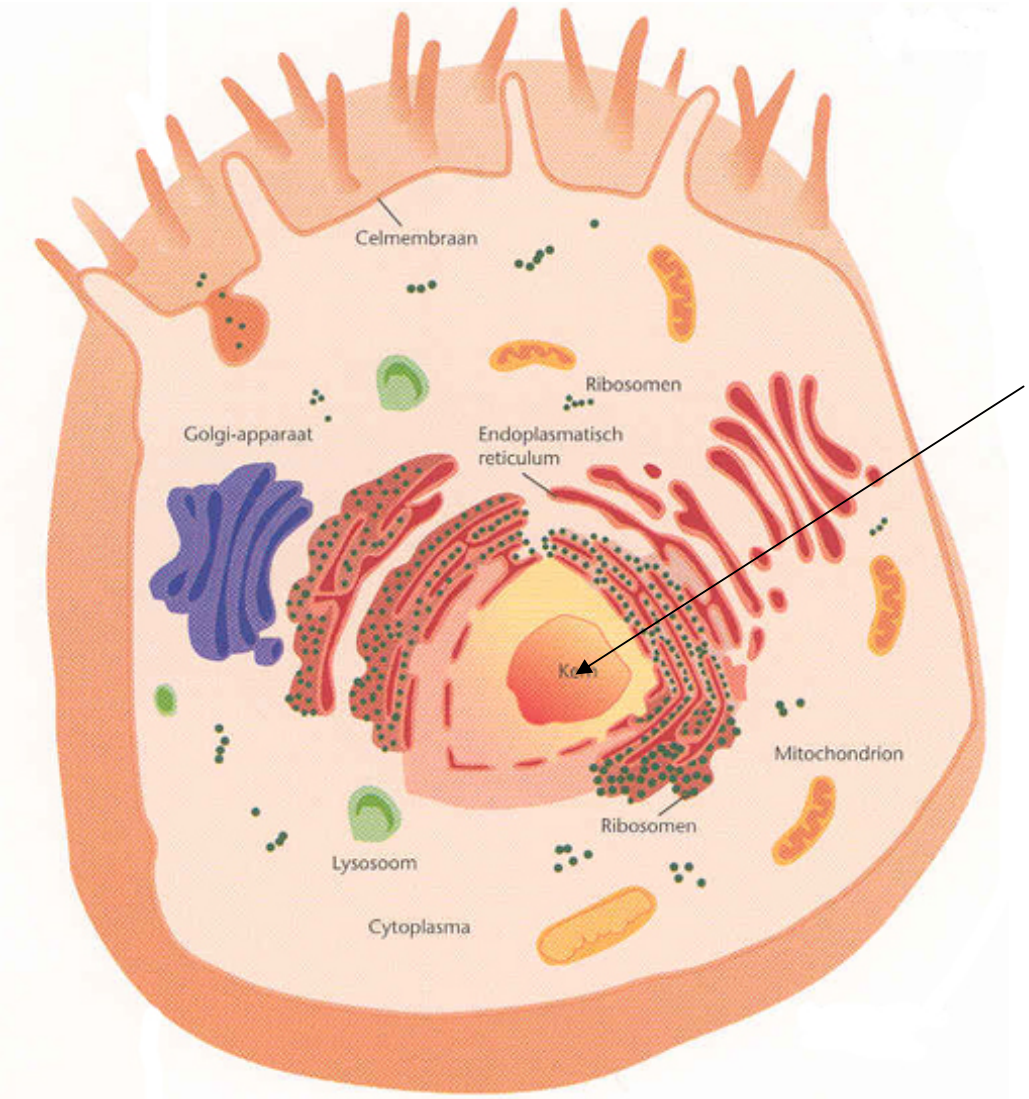
Nature Genetics Nov 2004; 36:1213

LEMD3: integral protein of the inner nuclear membrane



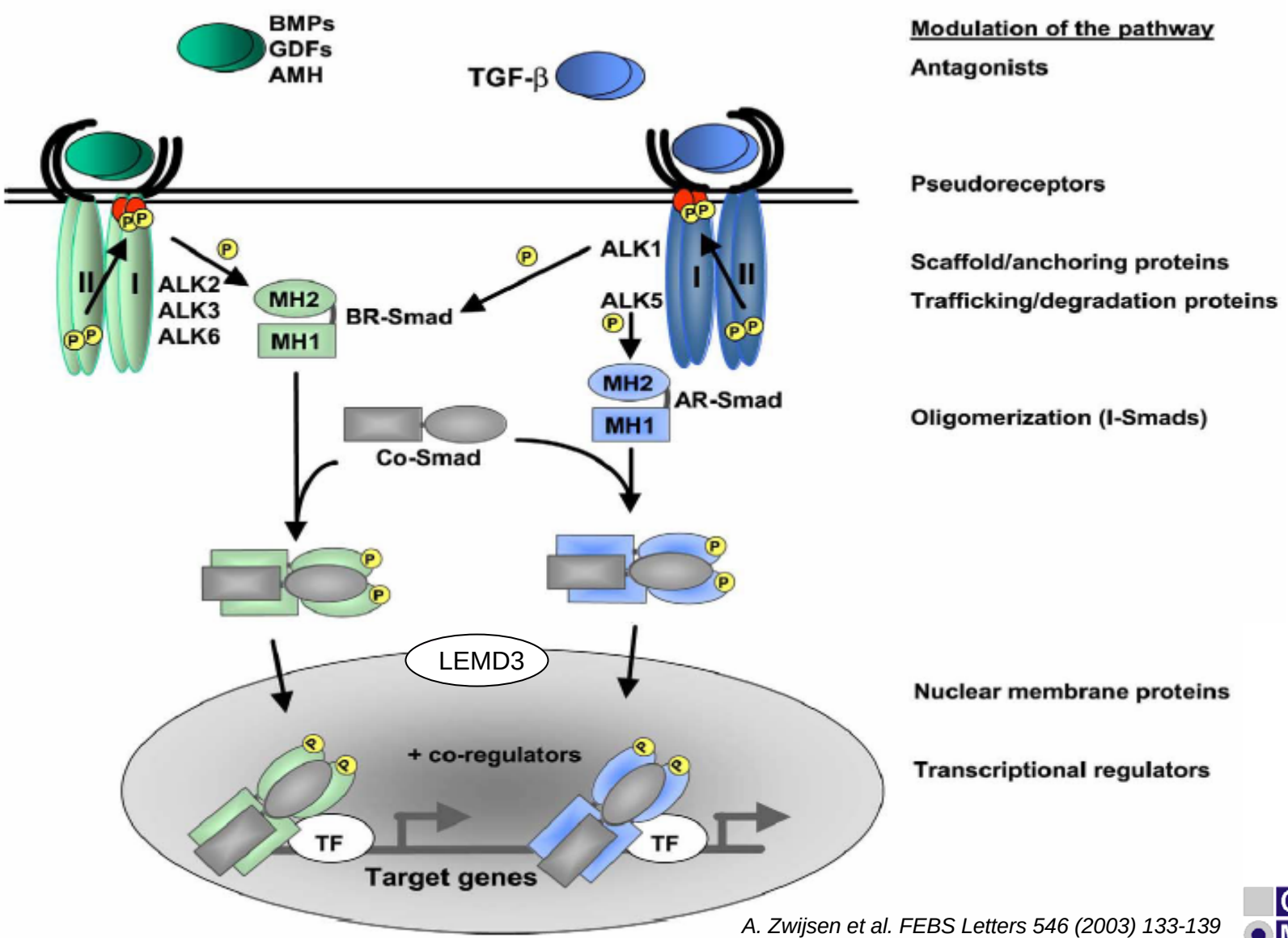
Adapted from Gruenbaum Y et al. Nature Rev Mol Cell Biol 6,21,2005

The cell



nucleus

LEMD3 function



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

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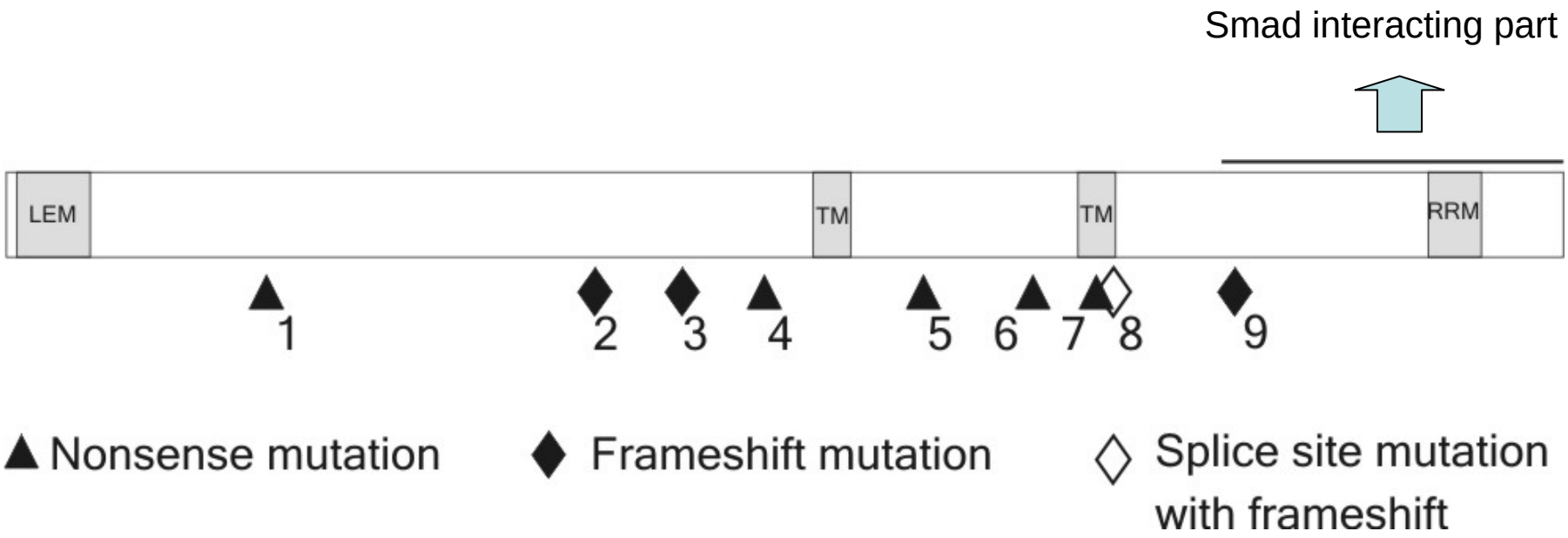
LEMD3 mutations



Analysis of LEMD3 in a larger series of patients

- group A: patients with osteopoikilosis, short stature and learning problems

n=3

- group B: patients with osteopoikilosis with(out) BOS skin lesions

n=15

- group C: patients with melorheostosis belonging to a family with OP/BOS

n=5

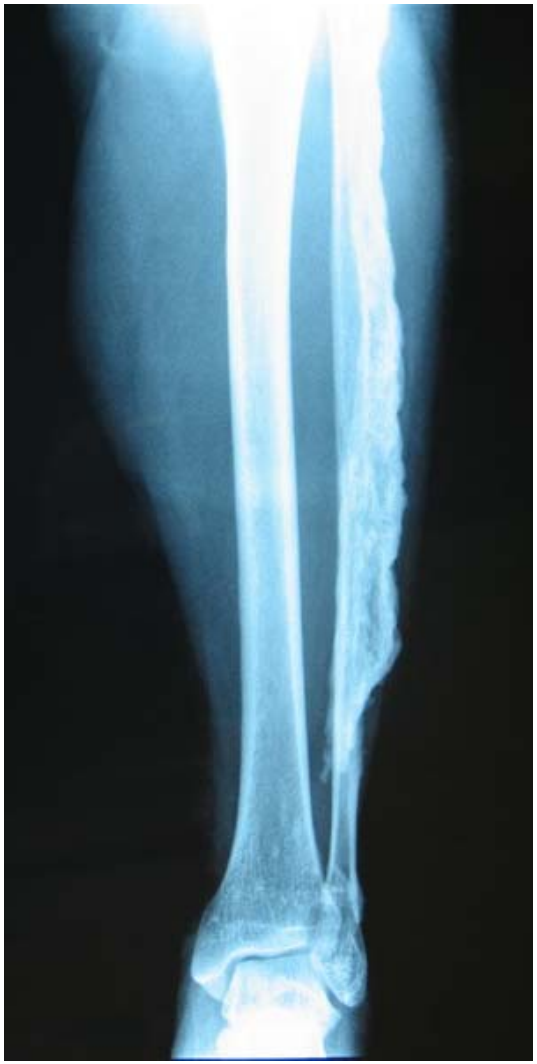
- group D: patients with melorheostosis (sporadic occurrence)

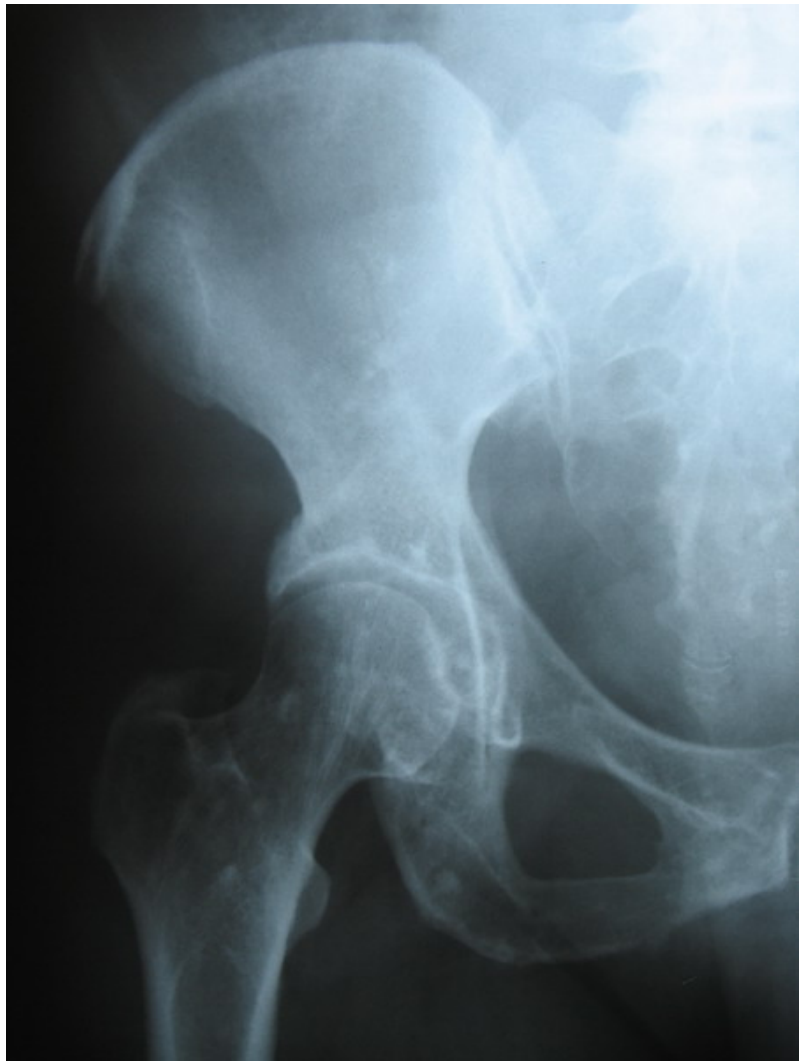
n=23

LEMD3 analysis

group	phenotype	nucleotide and residue changes	reference
A	osteopoikilosis, melorheostosis, short stature, MR	Not tested	Jurenka and Van Allen 1995
	osteopoikilosis, short stature, MR, ectopic kidney	microdeletion	Hellemans et al. 2004
	osteopoikilosis, short stature, MR	microdeletion	Hellemans et al. 2006
B	BOS	c.2134dupT; p.Met712fsX	Hellemans et al. 2004
	BOS	c.1185dupT; p.Gly395fsX	Hellemans et al. 2004
	osteopoikilosis	c.1033_1035delGGGinsC; p.Gly345fsX	Hellemans et al. 2004
	osteopoikilosis	c.1921+5delG; exon skip - frameshift	Hellemans et al. 2004
	osteopoikilosis	c.457C>T; p.Gln153X	Hellemans et al. 2004
	osteopoikilosis	c.1801G>T; p.Glu601X	Hellemans et al. 2006
	BOS	c.1323C>A; p.Tyr441X	Hellemans et al. 2006
	BOS	c.1873C>T; p.Arg625X	Hellemans et al. 2006
	BOS	c.1914dupA; p.Leu638fsX	Hellemans et al. 2006
	osteopoikilosis	c.2494-9A>G; splice site	Hellemans et al. 2006
	BOS	c.1873C>T; p.Arg625X	Hellemans et al. 2006
	BOS	c.2245C>T;p.Gln749X	Hellemans et al. 2006
	BOS	c.1707_1708delTG; p.Pro569fsX	unpublished
	osteopoikilosis	c.1813delA; p.Ile605fsX	unpublished
	osteopoikilosis	normal	Hellemans et al. 2006
C	melorheostosis (BOS in other relatives)	c.1609C>T; p.Arg537X	Hellemans et al. 2004, Debeer et al. 2003
	melorheostosis (BOS in other relatives)	c.830dupA; p.Lys277X	Hellemans et al. 2006
	melorheostosis (BOS in other relatives)	[c.1963C>T,c.2488C>T]; p.Arg655X	Hellemans et al. 2006, Butkus et al. 1997
	melorheostosis (BOS in other relatives)	c.2275_2278delGTTA; p.Val759fsX	unpublished
	melorheostosis (BOS in other relatives)	normal	unpublished
D	melorheostosis	c.1913T>A; p.Leu638X	Hellemans et al. 2006
	melorheostosis (22 patients)	normal	Hellemans et al. 2006 + unpublished

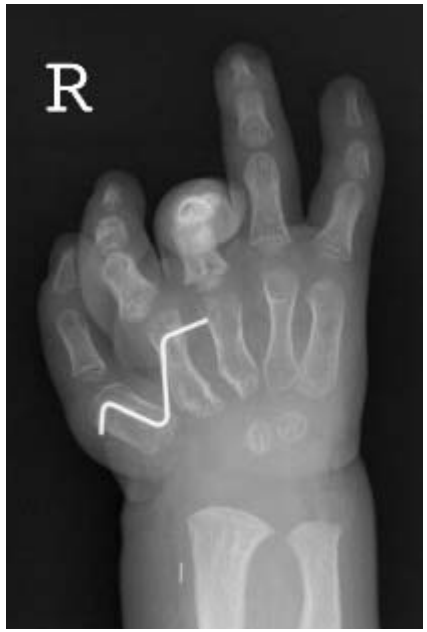
Group C – familial melorheostosis

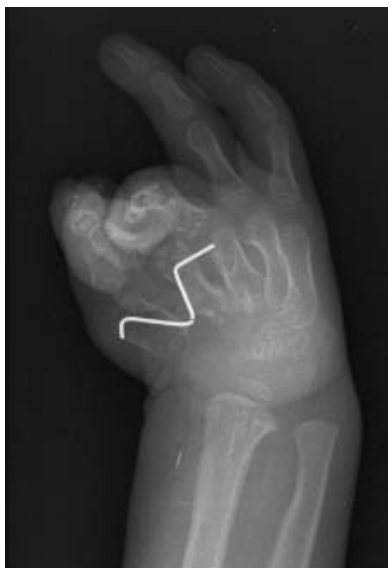


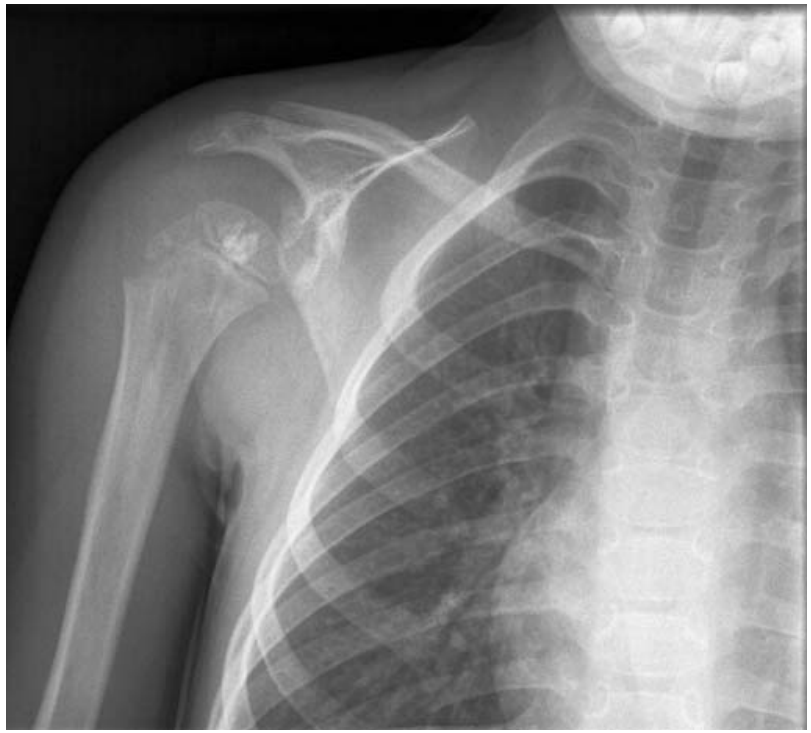


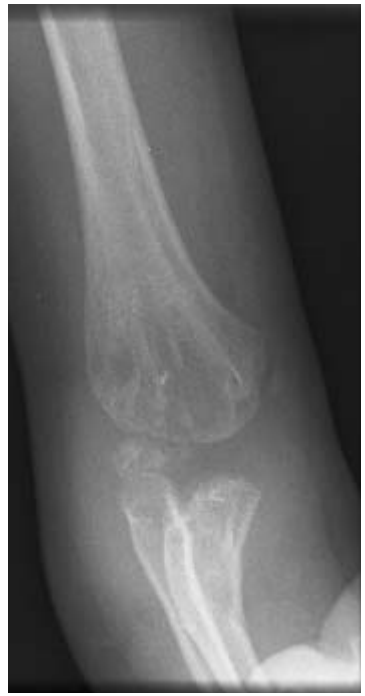
p.Val759fsX

Group D – sporadic melorheostosis

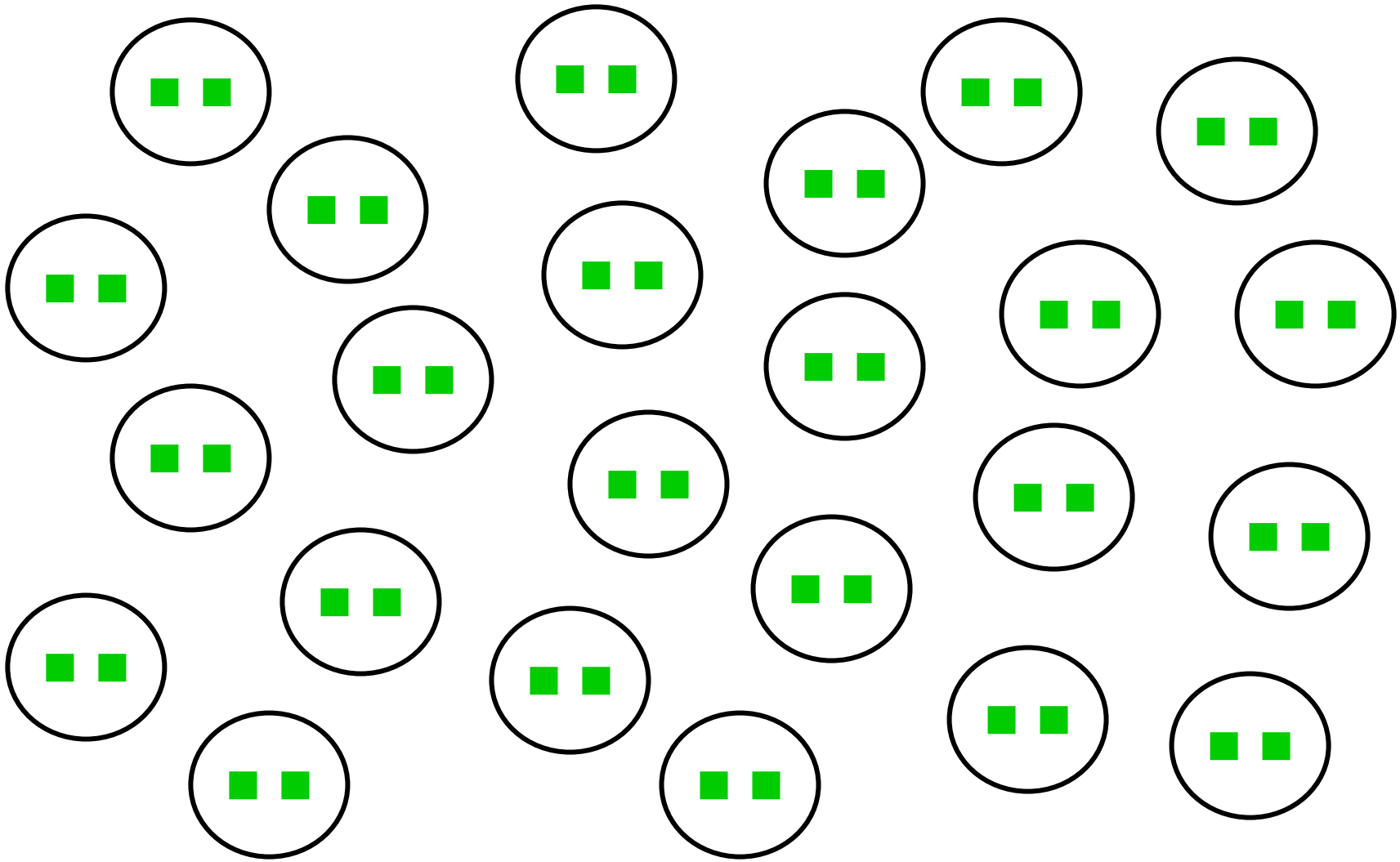






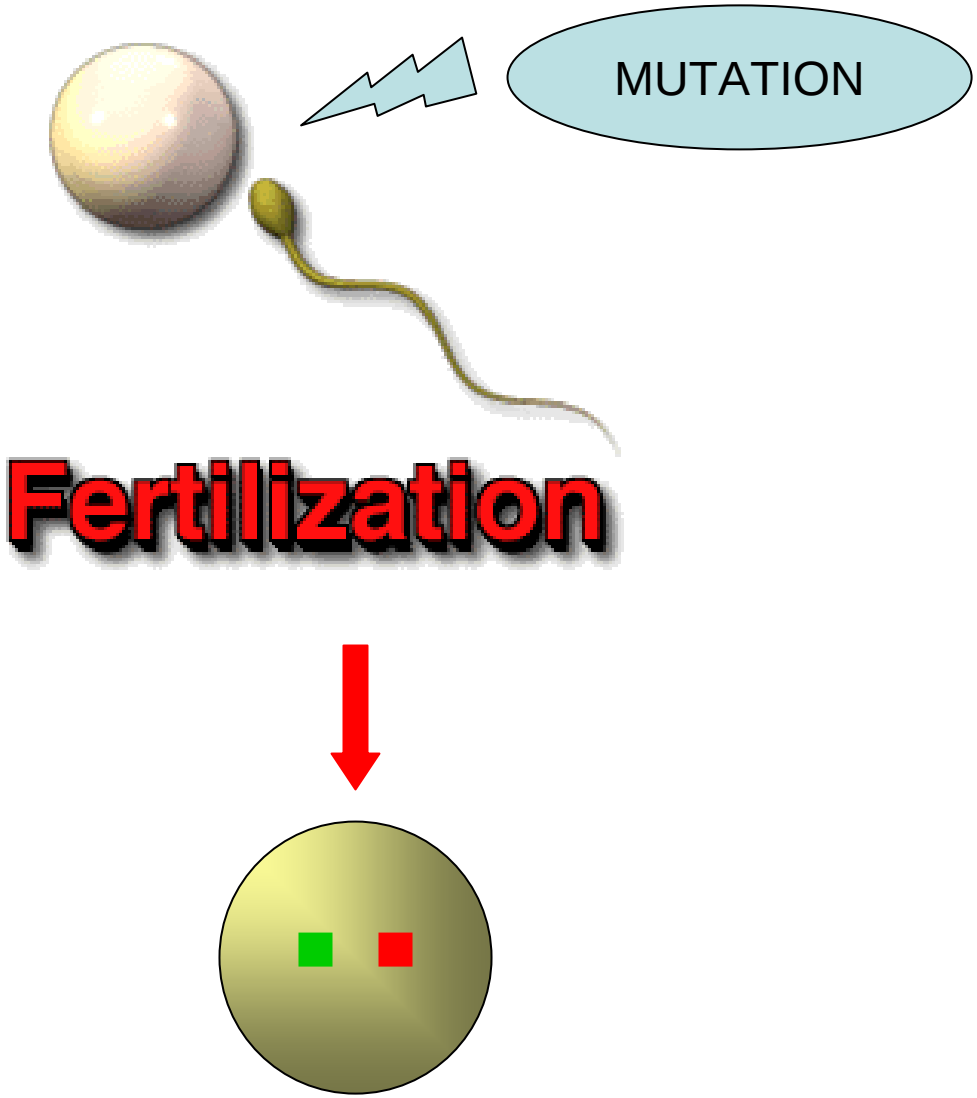


p.Leu638fsX

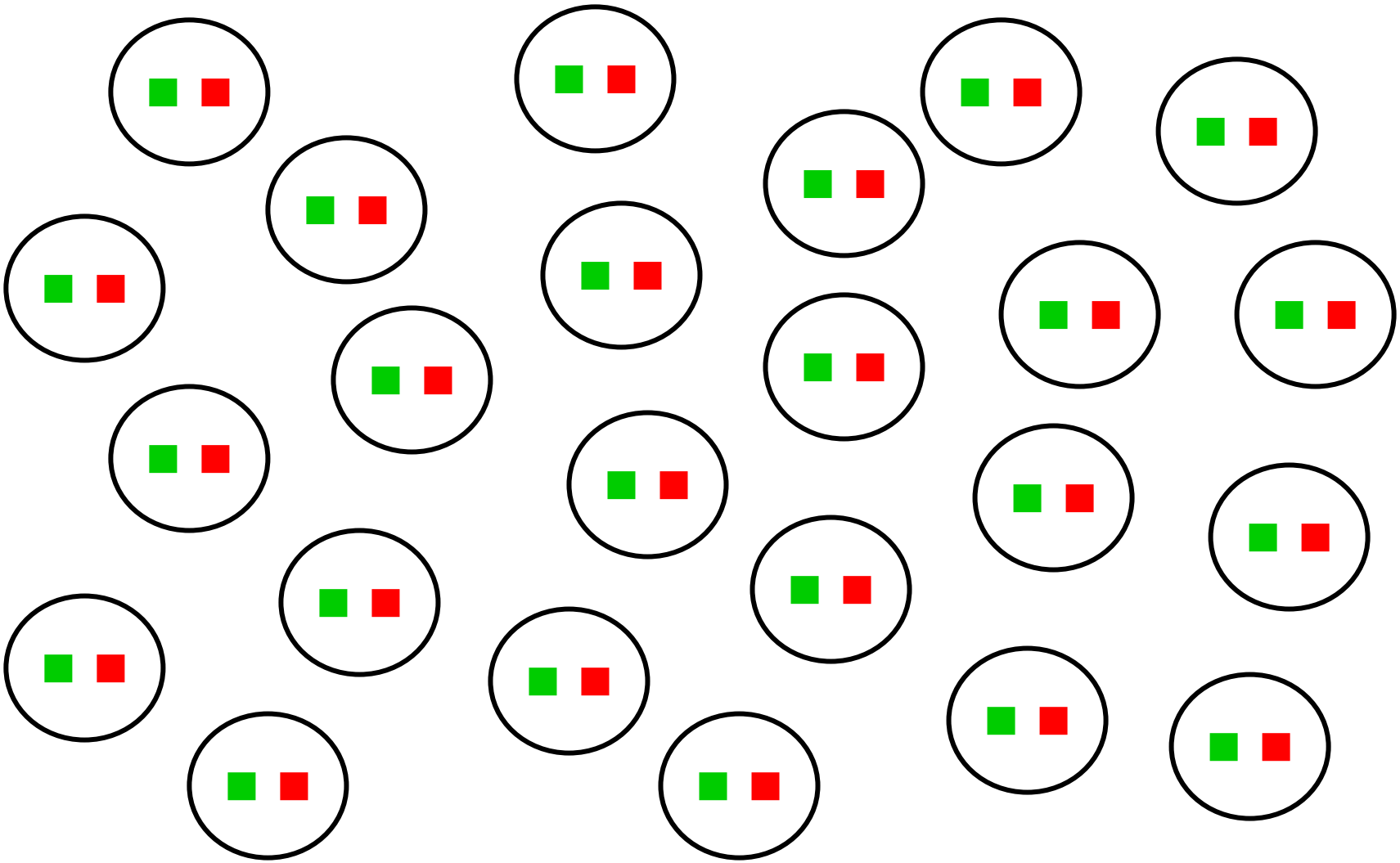


normal LEMD3 gene

Germline LEMD3 mutations



Germline LEMD3 mutations



normal LEMD3 gene

abnormal LEMD3 gene

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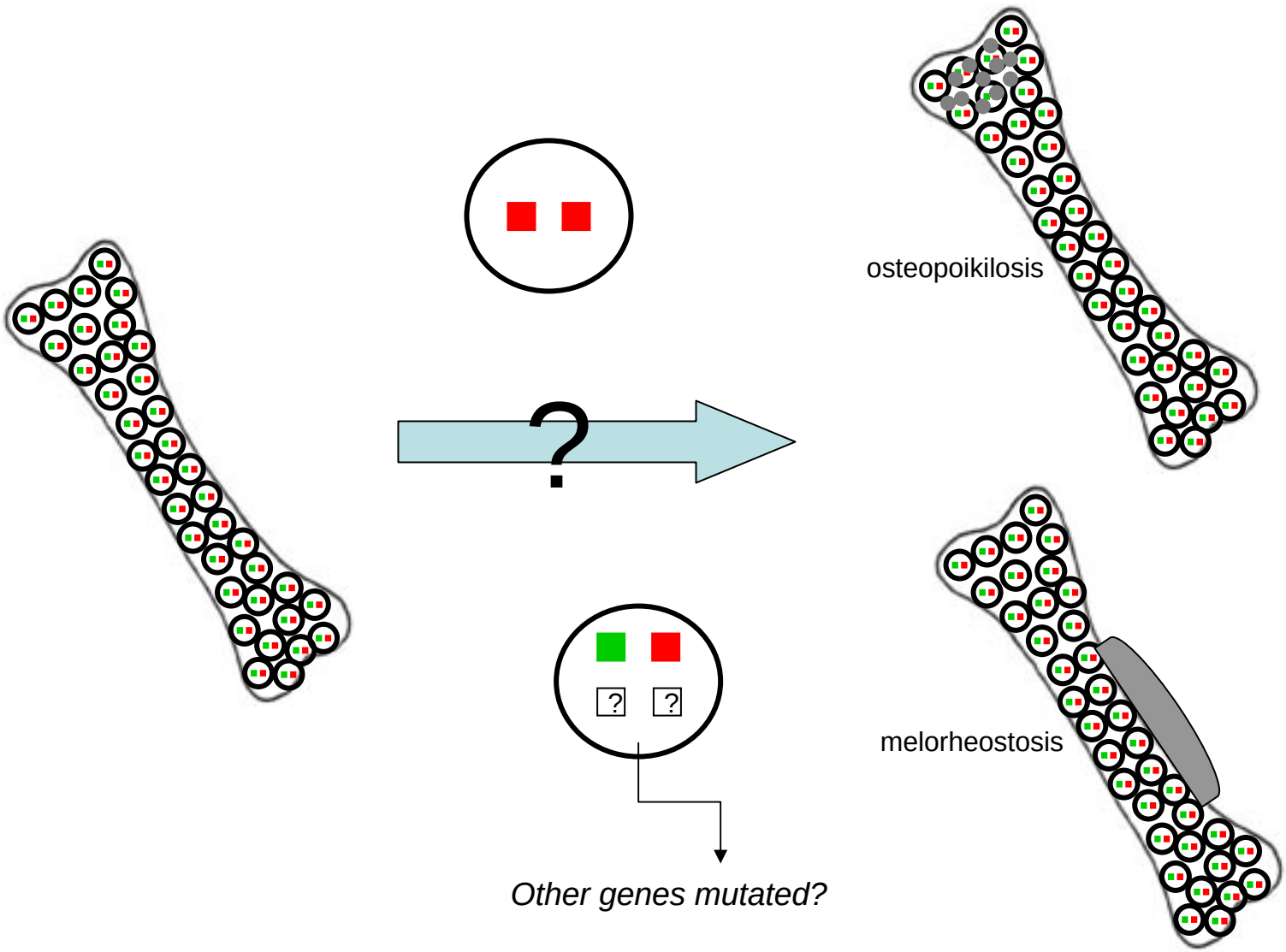
Germline LEMD3 mutations



normal LEMD3 gene

abnormal LEMD3 gene

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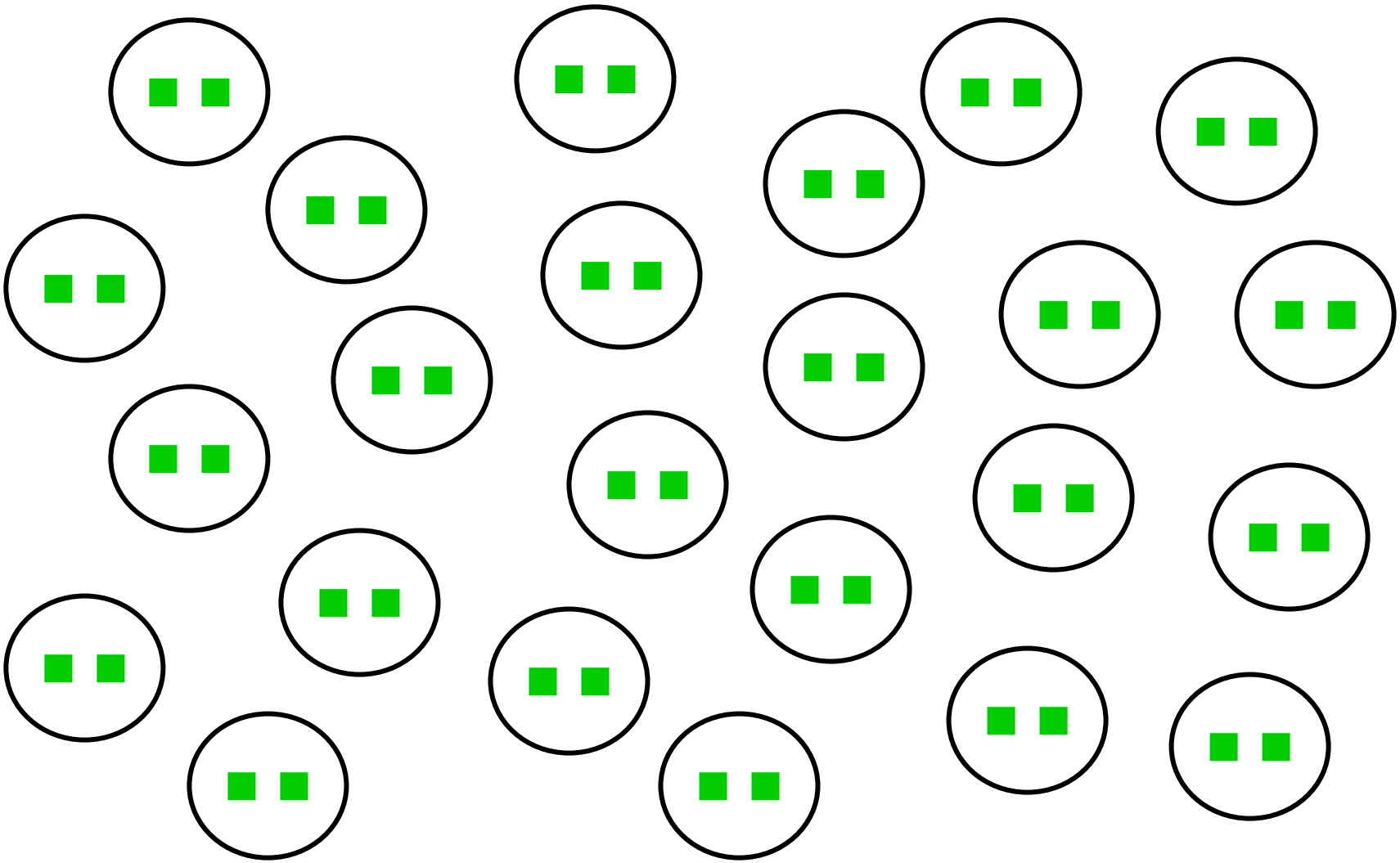
Somatic mutations

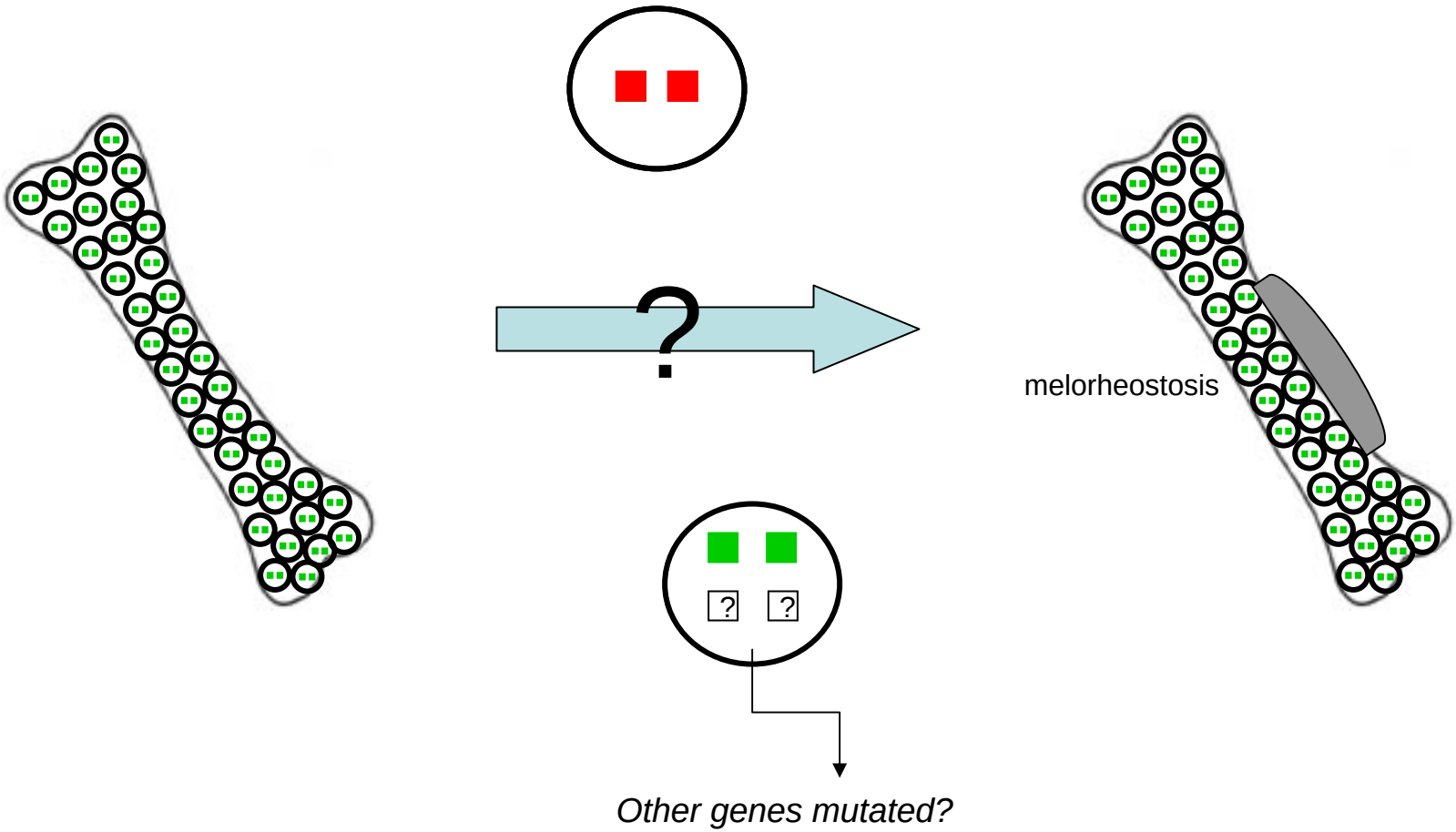
- Somatic *LEMD3* mutations responsible for the spotty, localized character of the lesions?
  → skin biopsy from:
  - elastic type nevus (BOS patient)
  - hard sclerodermic-like lesion (melorheostosis patient in BOS family)
- No LOH or allelic imbalance
- No second hit in *LEMD3*
- Only cDNA of wild type *LEMD3*

Sporadic melorheostosis



normal LEMD3 gene

Sporadic melorheostosis



normal LEMD3 gene

abnormal LEMD3 gene

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Somatic mutations

- Somatic *LEMD3* mutations in melorheostosis patients without an identifiable germline mutation?
  → biopsies from skin and bone of 2 patients
- No somatic LOH or mutation in *LEMD3*

Conclusions (1)

- Heterozygous loss-of-function mutations in LEMD3 result in osteopoikilosis and Buschke-Ollendorff syndrome

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Conclusions (1)

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Conclusions (1)

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- Somatic defects in LEMD3 have not yet been identified in melorheostosis lesions

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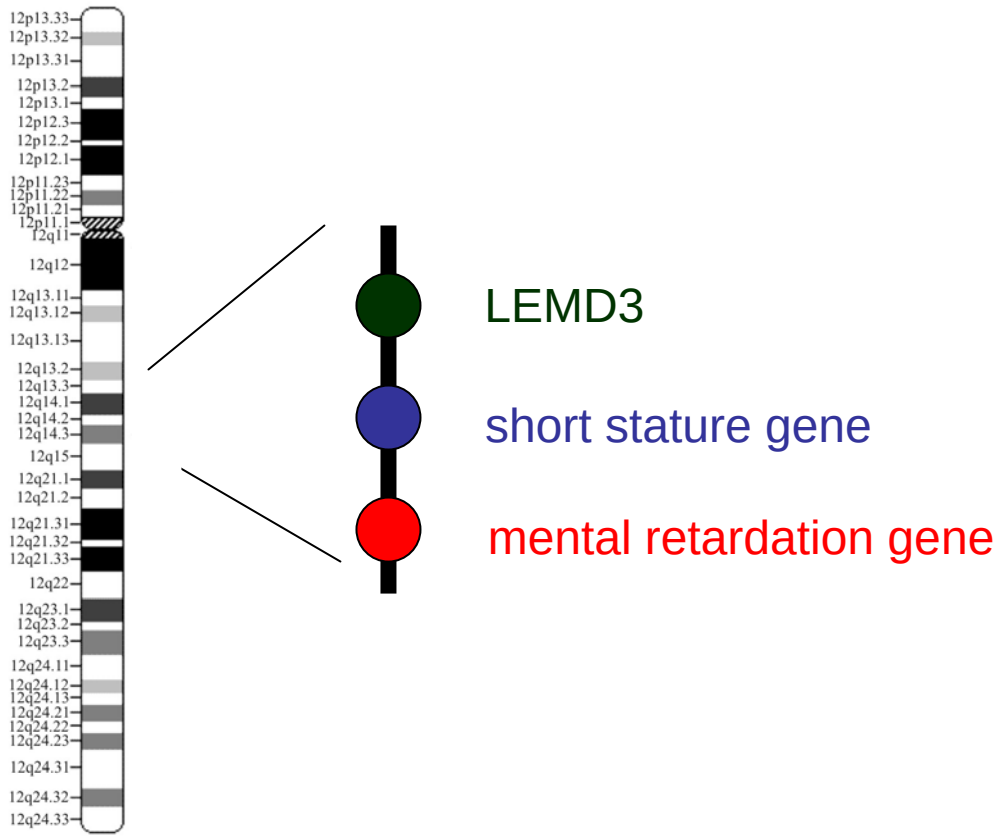
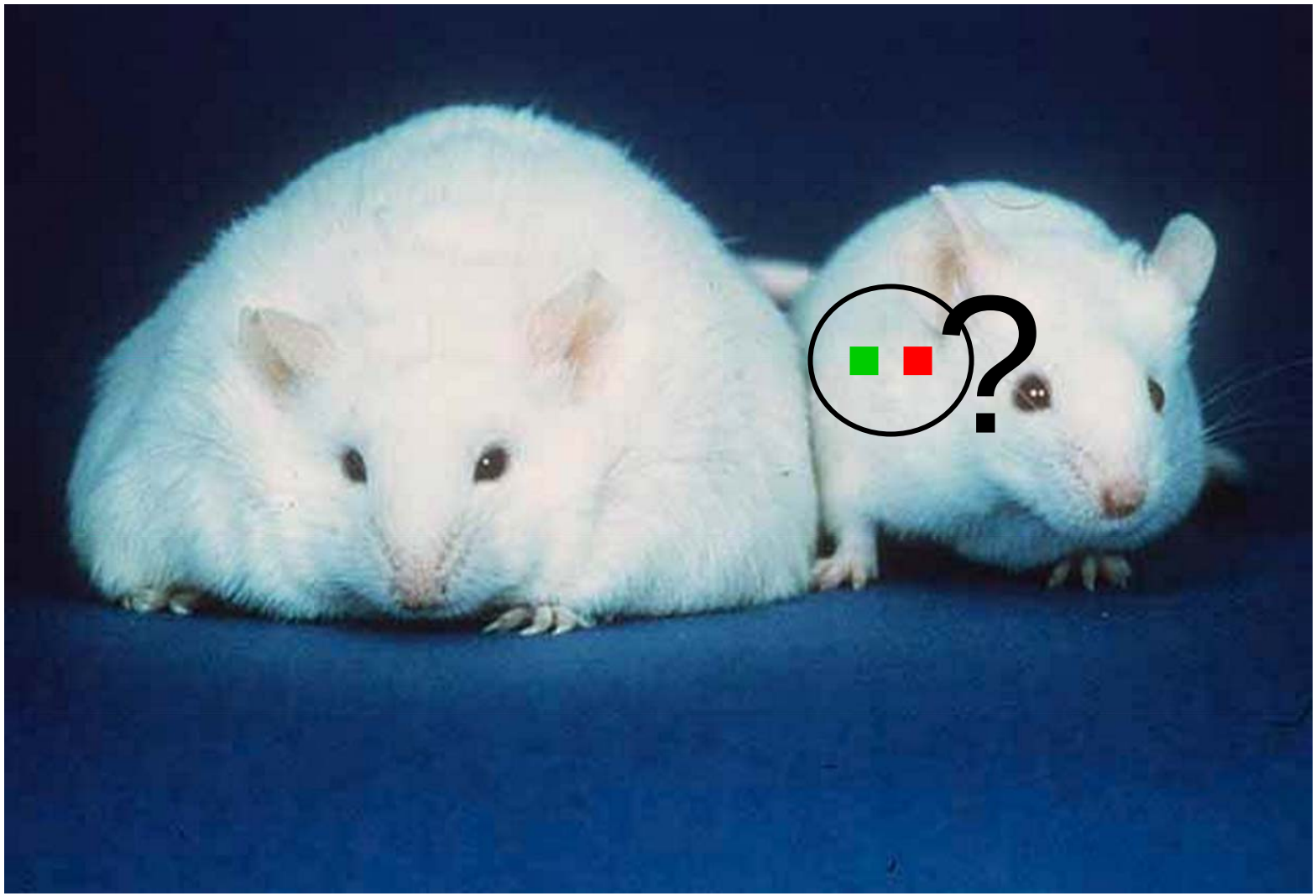
- Individuals with melorheostosis and osteopoikilosis (usually belonging to a family) have heterozygous LEMD3 mutations in the germline
- Individuals with melorheostosis (sporadic and isolated) do not have germline mutations in LEMD3
- Somatic defects in LEMD3 have not yet been identified in melorheostosis lesions
- The cause of sporadic, isolated melorheostosis remains to be unravelled

Conclusions (2)

- Microdeletions encompassing the LEMD3 gene result in a syndromic condition with osteopoikilosis, mental retardation and short stature



Heterozygous knock-out mouse: development of melorheostosis?



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