Seltene Osteopathien
-
Rare bone diseases

Elena Gonzalez Rodriguez

CENTRE INTERDISCIPLINAIRE DE MALADIES OSSEUSES, CHUV

OSTEOPOROSE UPDATE 2025

Saturday 3 May 2025

canton de vaud

UNIL | Université de Lausanne
Faculté de biologie et de médecine

CHUV

1- « Definition » and related bone physiology

2- Why is it important to diagnose them

3- Signs and symptoms that should raise awareness, and what the general practitionner can do

4- Who to refer the patient: Swiss Groupment for Rare Bone Diseases (SG-BOND)

Rare bone diseases: « definition »

What are rare bone diseases?

RARE DISEASES

A rare disease is a disease who affects <1/2000 individuals

→ because of the high number of rare diseases (about 7000), total prevalence is high: 1/17 individuals

It includes both congenital and acquired diseases

Because of high phenotypic variability congenital diseases can manifest in adulthood

RARE BONE DISEASES:

- 5% of all birth defects

« Rare bone and non-inflammatory collagen diseases »

« Bone dysplasias »

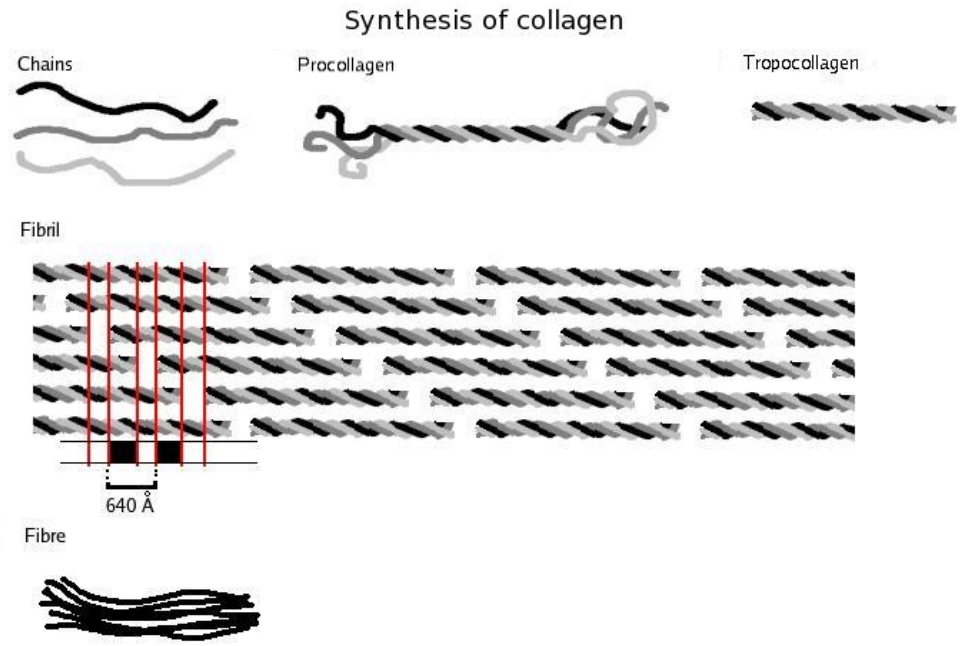
« Constitutional bone diseases »

Rare bone diseases develop due to alterations in bone components

Bone components: matrix

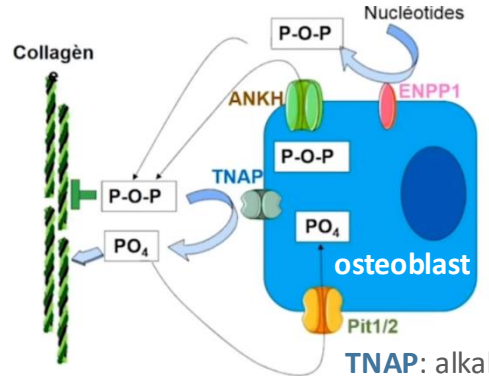
Organic - osteoid: 22%

- 90% type 1 collagen (2 alpha1 + 1 alpha2 chains)
- 10% non collagenic proteins (i.e. fibrilin)

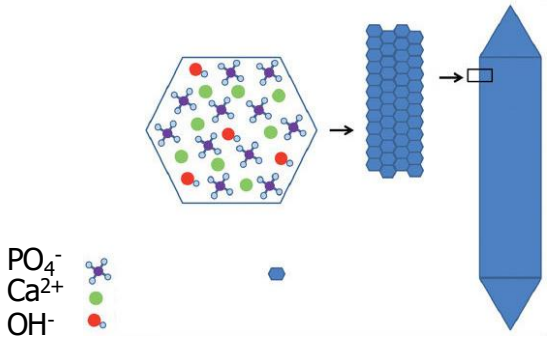


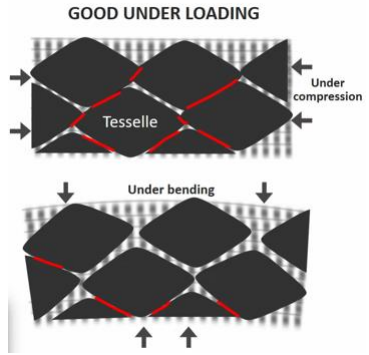
Inorganic – minerals : 69%

(mostly hydroxyapatite)



TNAP: alkaline phosphatase - ALP
P-O-P: pyrophosphate





Gives elasticity

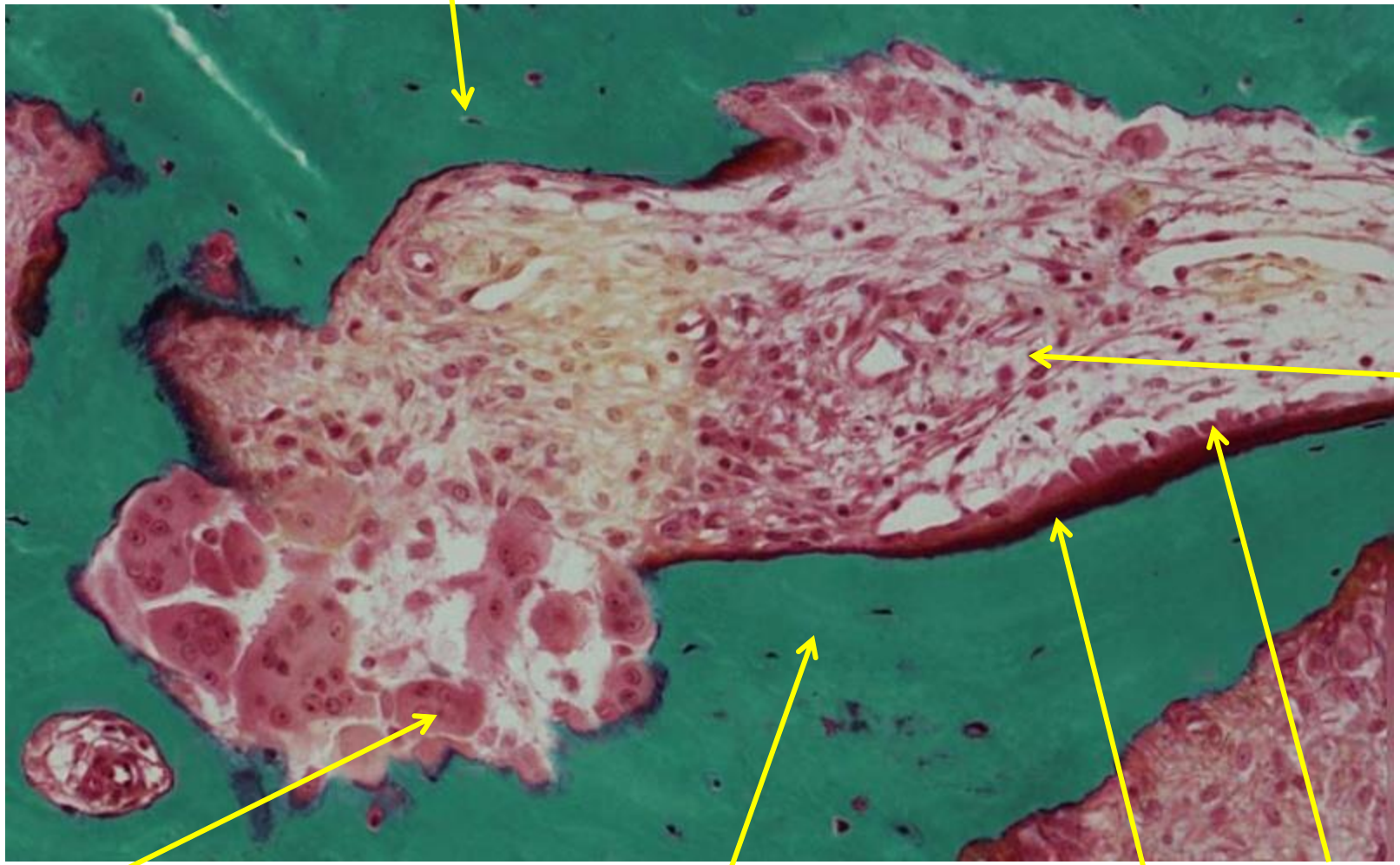
Gives resistance

Bone components: cells

Osteoclasts (1-2%): bone resorption

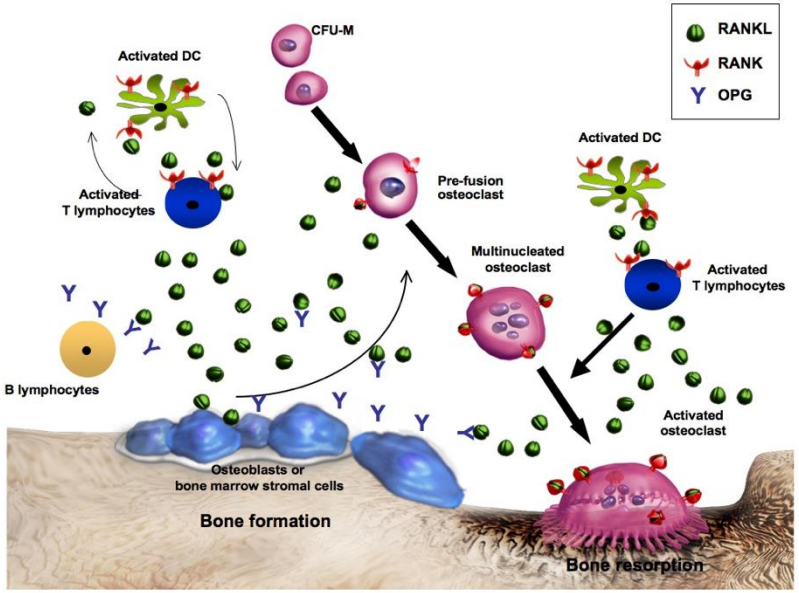
Osteoblasts (4-6%): bone formation → matrix production, secretion, maturation and mineralisation

Osteocytes (90-95%): forces and inflammation sensing, regulate remodeling, hormone secretion (FGF23 - phosphatonin)


Osteocytes
Vessels, blood cells, fat…
Osteoclasts
Mineralized matrix
Non mineralized matrix
Osteoblasts

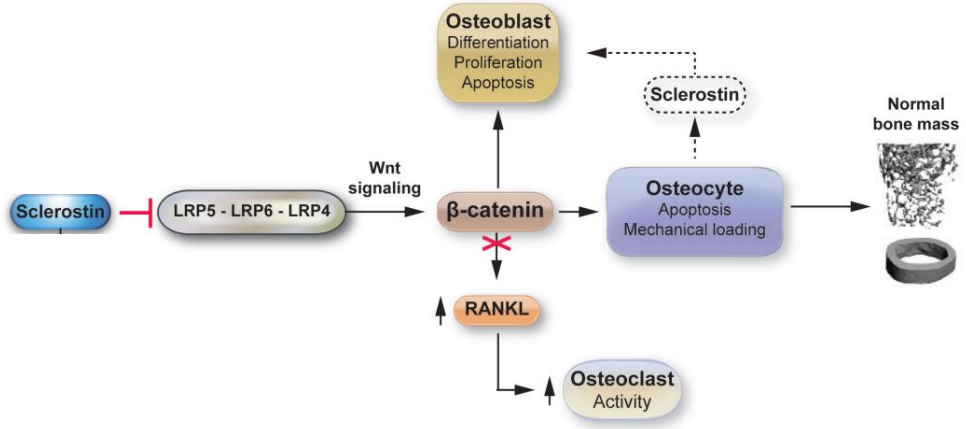
Bone remodelling regulation

Resorption regulation: RANKL



RANK : receptor activator of nuclear factor (transmembrain protein)
RANKL : receptor activator of nuclear factor ligand
OPG : osteoprotegerine (soluble protein)

Formation regulation: WNT



HORMONES 2014, 13(4):476-487

Very large number and variability of phenotypes

1- Congenital bone dysplasias with genetic origin

Nosology of genetic skeletal disorders: 2023 revision

Sheila Unger[1] | Carlos R. Ferreira[2] | Geert R. Mortier[3] | Houda Ali[4] | Débora R. Bertola[5,6] | Alistair Calder[7] | Daniel H. Cohn[8,9] | Valerie Cormier-Daire[10] | Katta M. Girisha[11] | Christine Hall[12] | Deborah Krakow[13] | Outi Makitie[14,15] | Stefan Mundlos[16] | Gen Nishimura[17] | Stephen P. Robertson[18] | Ravi Savarirayan[19] | David Sillence[20] | Marleen Simon[21] | V. Reid Sutton[22] | Matthew L. Warman[23,24] | Andrea Superti-Furga[1]

Received: 22 December 2022 | Revised: 13 January 2023 | Accepted: 17 January 2023
DOI: 10.1002/ajmg.a.63132

- 771 diseases with 552 implicated genes
- Divided in 41 groups, classified by phenotype + affected gene (dyadic naming system)

→ « Osteogenesis imperfecta, progressively deforming (Sillence type 3), COL1A1-related »
→ « Marfan syndrome, FBN1-related »
→ « Achondroplasia, FGFR3-related »
→ « Neurofibromatosis type 1, NF1-related »

2- Congenital metabolic diseases (some overlapping)

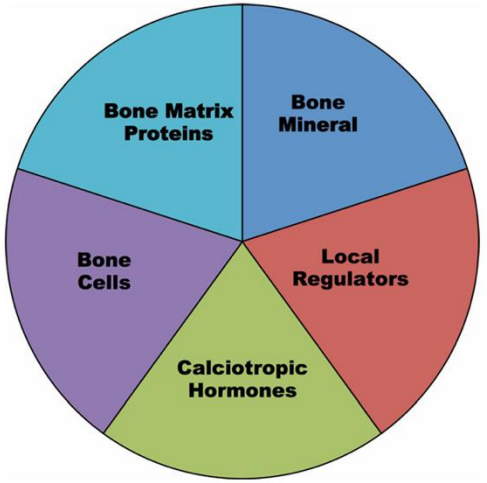
Review

Congenital Metabolic Bone Disorders as a Cause of Bone Fragility

Francesca Marini [1,2], Francesca Giusti [1], Teresa Iantomasi [1] and Maria Luisa Brandi [2,*]

Int. J. Mol. Sci. **2021**, 22, 10281. https://doi.org/10.3390/ijms221910281

Over 100 diseases
Includes congenital phospho-calcic diseases:
- Hypophosphatasia (low ALP)
- Vitamine D dependent and independent rickets



3- But not all are in these classifications…

- Tumor induced osteomalacia (paraneoplastic disease – FGF23 exces from mesenchymatous tumors)
- Fibrous dysplasia/McCune Albright syndrome (post-zygotic GNAS mutation- mosaic)

Most frequent

- Osteogenesis imperfecta

- Achondroplasia and hypochondroplasia

- Dyschondrosteosis (Leri-Weil syndrome: short stature and mesomelia)

- Fibrous dysplasia (rare: McCune Albright syndrom)

- Multiple exostosis

Other 50 can be seen once in clinical practice (out of specialized centers)

→ In many cases the disease is not diagnosed: small height, severe scoliosis, osteochondritis, precocious degeneratif arthritis, … lacking specialized management

Why is it important to diagnose them?

Why is it important to diagnose them?

1- Differential diagnosis

Bone fragility can be due to osteoporosis, a rare bone disease (i.e. osteogenesis imperfecta), osteomalacia…

2- Syndrome comorbidities

Collagen diseases can have cardiac, ocular, articular, teeth… abnormalities; others can degenerate on sarcomas

3- New treatments, treatment alternatives/contrindications

- New treatments: i.e. burosumab (anti-FGF23 antibody) for FGF-23 dependant hypophosphatemic rickets or osteomalacia

- Treatment depending on genetic variant (i.e. Osteogenesis imperfecta due to osteoblast mutations)

4- Genetic transmission

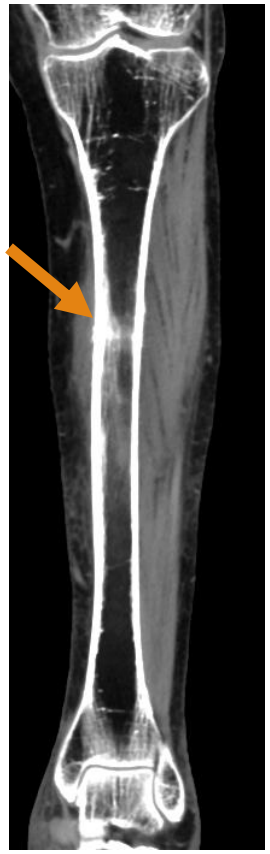
Counseling, siblings diagnosis

5- Quality of life

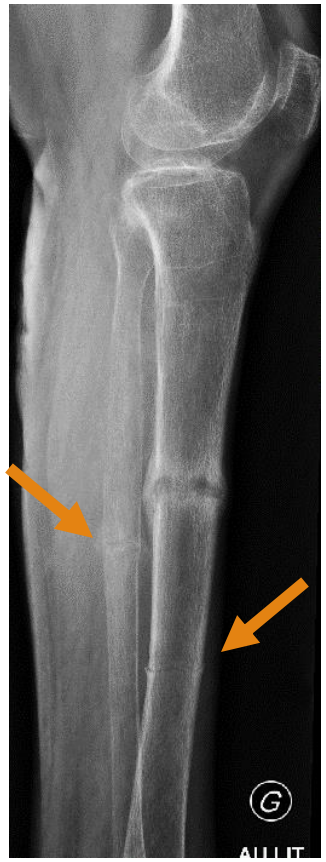
Important for the patients to know what they have, risks, how to manage (i.e. physical activity), insurances…

Mme OK, 1938

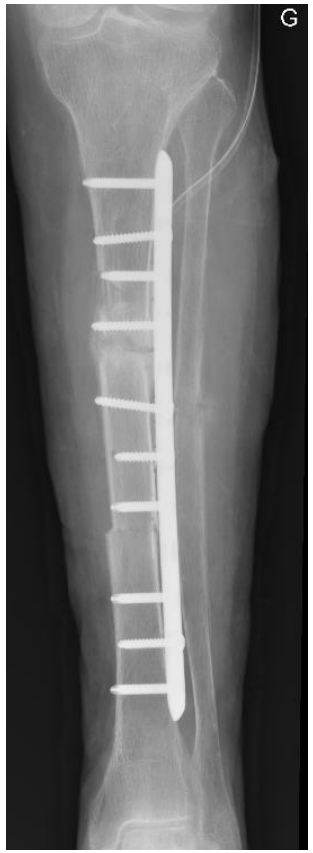
1- Differential diagnosis: fractures



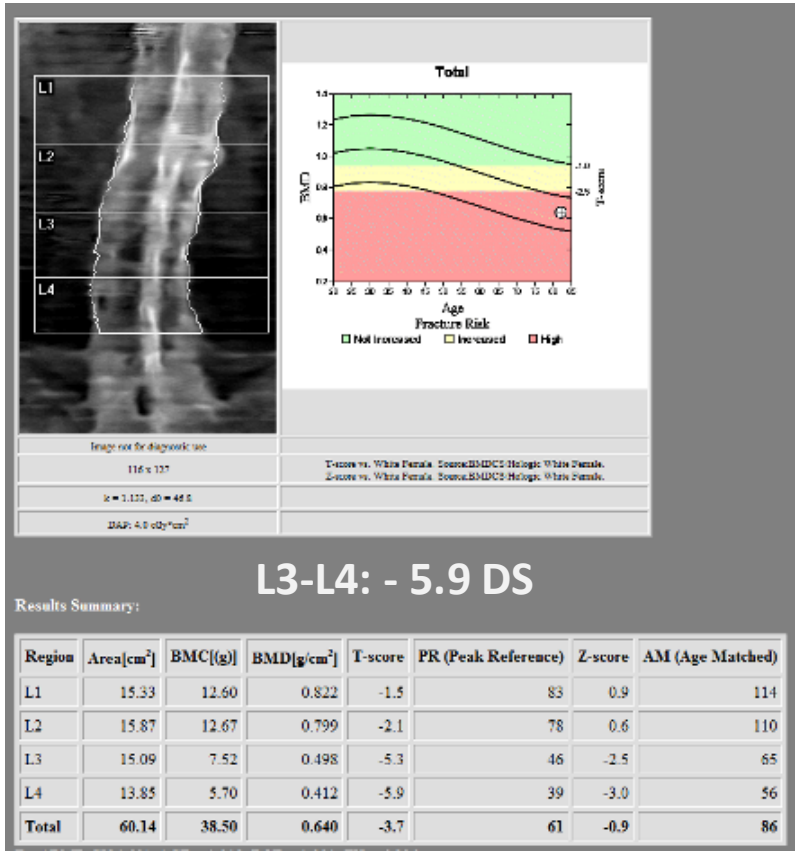
15.01.2020



27.05.2020



29.05.2020



L3-L4: - 5.9 DS

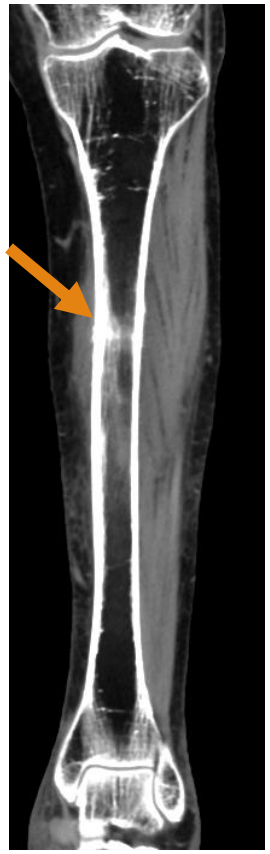
Results Summary:

Region	Area[cm²]	BMC[(g)]	BMD[g/cm²]	T-score	PR (Peak Reference)	Z-score	AM (Age Matched)
L1	15.33	12.60	0.822	-1.5	83	0.9	114
L2	15.87	12.67	0.799	-2.1	78	0.6	110
L3	15.09	7.52	0.498	-5.3	46	-2.5	65
L4	13.85	5.70	0.412	-5.9	39	-3.0	56
Total	60.14	38.50	0.640	-3.7	61	-0.9	86

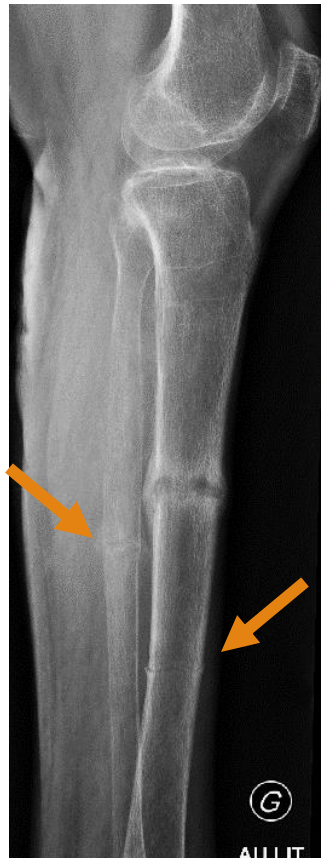
19.10.2020

Zoledronate perfusions 03.2021 & 03.2022

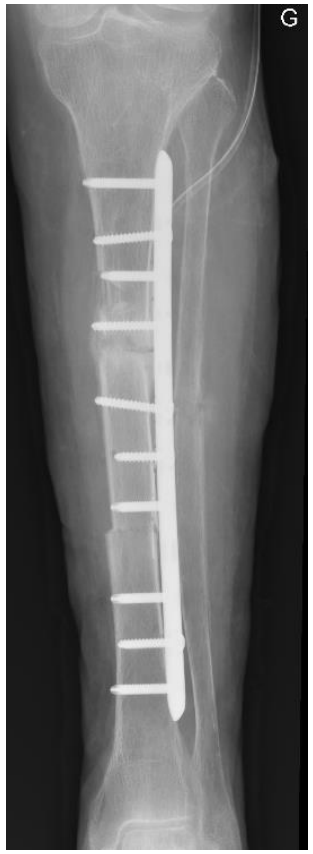
Mme OK, 1938



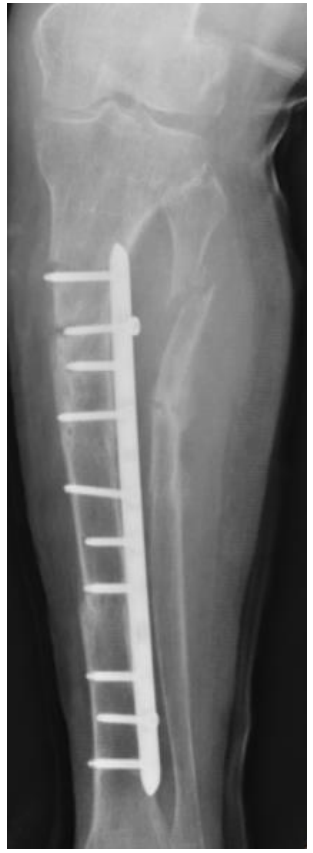
15.01.2020



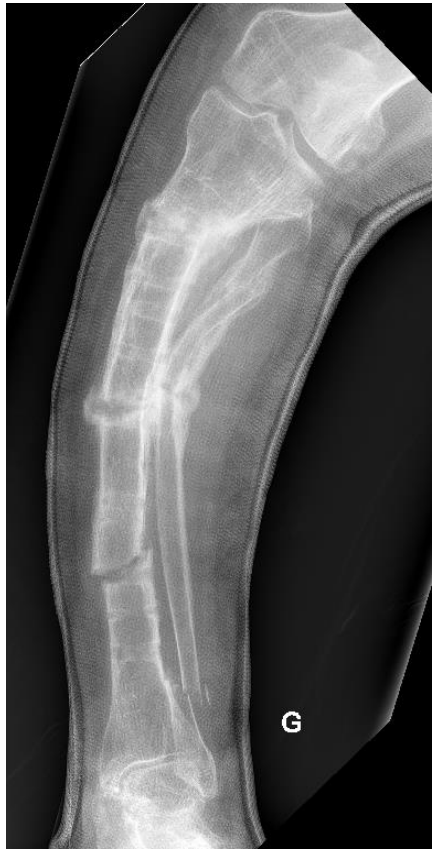
27.05.2020



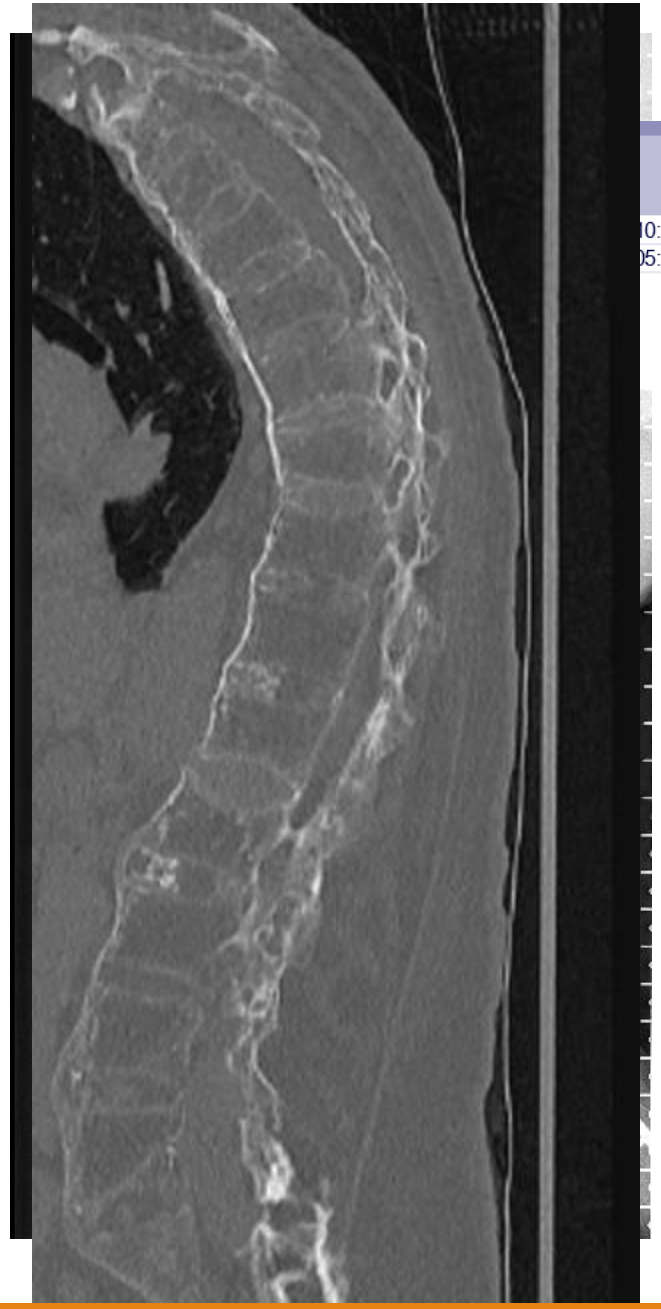
29.05.2020



16.07.2021



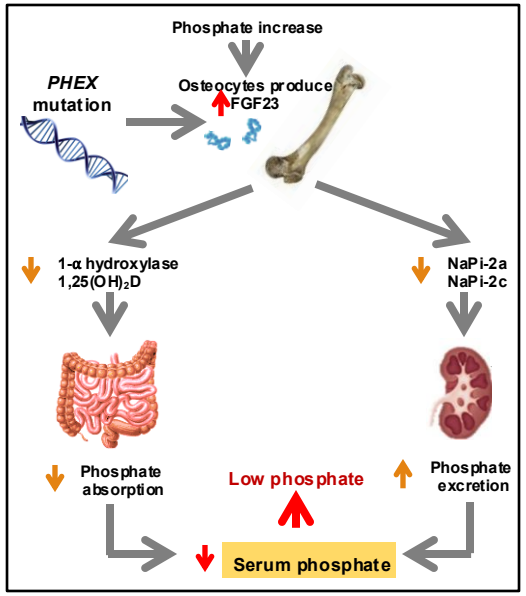
20.06.2022



	Calcium corrigé sg (2.10 - 2.50) mmol/l	Phosphate sg (0.80 - 1.40) mmol/l	Phosphatase alcaline sg (36 - 120) U/l	Gamma-GT sg (6 - 42) U/l	25-OH Vitamine D (D3+D2) sg (8.8 - 44.2) µg/l
10:00	2.51 ▲H	0.38 ▲▲L	314 ▲H	77 ▲H	
05:26	2.52 ▲H	0.45 ▲▲L	291 ▲H	74 ▲H	25.1 ▲

Renal phosphate loss: TmP (maximal P resorption rate): 0.30 (norm: 0.80-1.35)

			Auftragsnummer: 97159798 R Probenabnahme: *10.06.22 10:00* Auftragseingang: *14.06.22 12:25* Auftragsabschluss: *22.06.22 14:29*
Analyse	Einheit	Referenzber.	
Blut: Ca-P-Metabolismus			
FGF-23	pg/mL	10 - 50	95.3



Razzaque MS. ***Nat Rev Endocrinol* 2009**;5:611–619
Martin A *et al*. ***Physiol Rev* 2012**;92:131–155

Anamnesis:

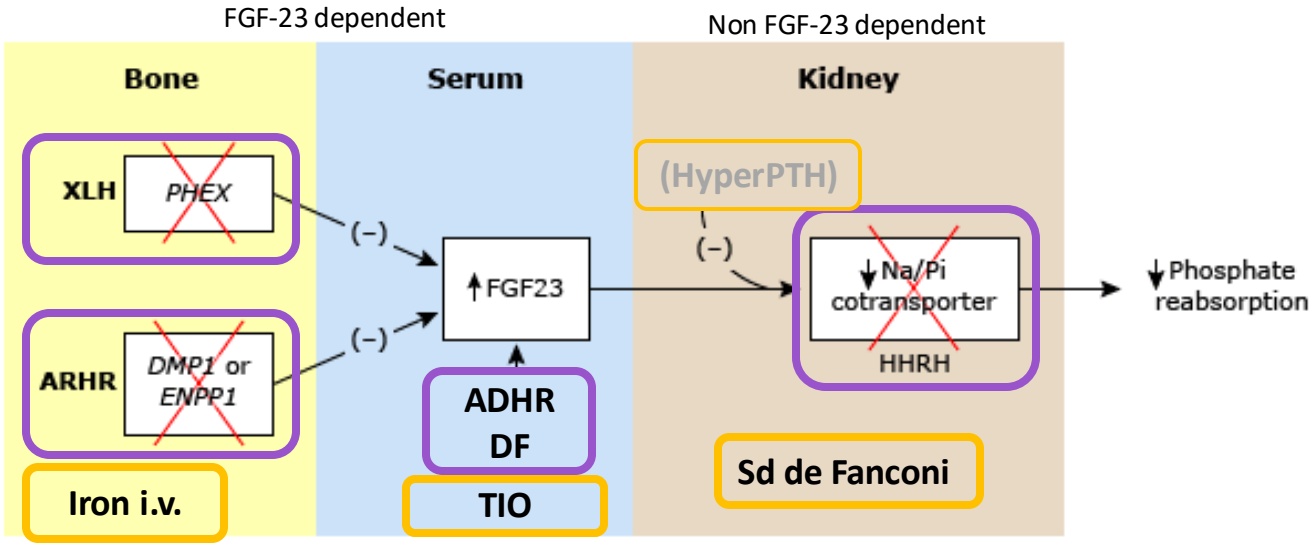
- Her father had rickets
- A 60 years-old nephew has rickets and multiple surgeries
- Her theet broked and necrotized around 13-14 years old
- She as a severe DISH

PROBABLE DIAGNOSIS: X-LINKED HYPOPHOSPHATEMIC RICKETS

- Rickets/osteomalacia
- Spontaneous dental abcesses
- Enthesopathies

ATTITUDE (10.06.2022): stop calcium; introduction of phosphate and calcitriol

Etiology of chronic hypophosphatemia in the adult



Congenital, systemic:

- XLH: X-linked hypophosphatemic rickets (dominant), 80%
- ARHR: autosomal recessif hypophosphatemic rickets
- ADHR: autosomal dominant HR, FGF-23 variants
- HHRH: hypophosphatemic hypercalciuric rickets

Congenital, mosaic:

- DF: dysplasie fibreuse/McCune Albright (mosaic), post-zygotic GNAS variants (most frequent bone tumor)

Acquired:

- Osteomalacia due to iron perfusion (FGF-23 dependent)
- TIO: tumor induced osteomalacia (FGF-23 dependent)
- Acquired renal fanconi syndrome (i.e. adefovir, tenofovir disoproxil)
- (HyperPTH: hyperparathyroïdie primaire)

(Genetic analysis confirmed XLH diagnosis for Mme OK at 80 years old)

Freely adapted from UpToDate®

2- Syndrome comorbidities: Osteogenesis imperfecta

90% due to COL1A1 AND COL1A2 autosomal dominant variants
Over 40 genes result in Osteogenesis Imperfecta (OI) and/or Bone Fragility and/or Familial Osteoporosis

Guillaume Bats, humorist

Type I collagen forms the matrix of many different tissues: bone, skin, tendons, cornea, blood vessel walls, teeth…

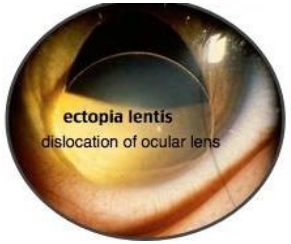
VERY HIGH PHENOTYPIC VARIATIONS EVEN IN THE SAME FAMILY

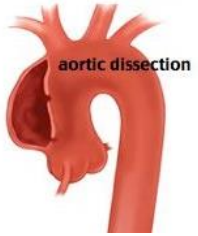
- **Bone fragility: « glass bone disease »**
- Low height
- Scoliosis, pectum excavatum/carinatum
- Respiratory insufficiency: deformities + pulmonary tissue modifications
- Hearing loss of mixed origin
- Myopia
- Cardiac valves abnormalities
- Easy bruising
- Joints hyperlaxity
- Arnold-Chiary malformation (posterior fossa of the skull) / C1-C2 instability

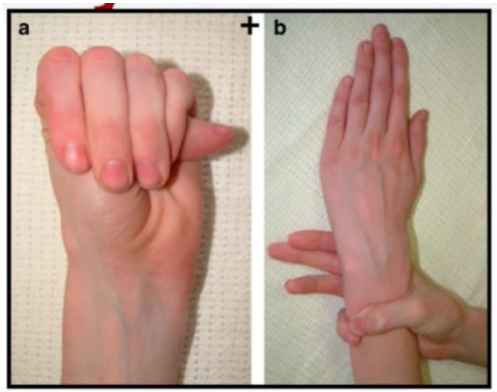
Sillence DO. *Calcif Tissue Int*. **2024**; 115:873–890

Osteogenesis imperfecta

Marfan syndrome (fibrillin)



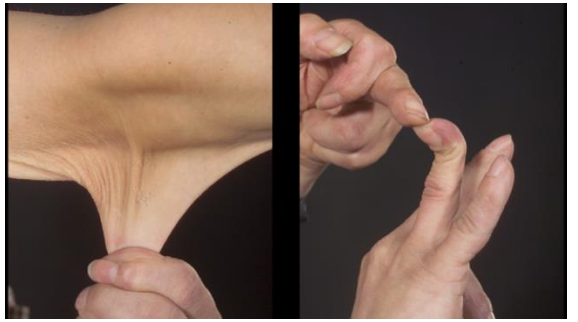




Arachnodactily

Hyperlaxity/hypermobility: matrix proteins

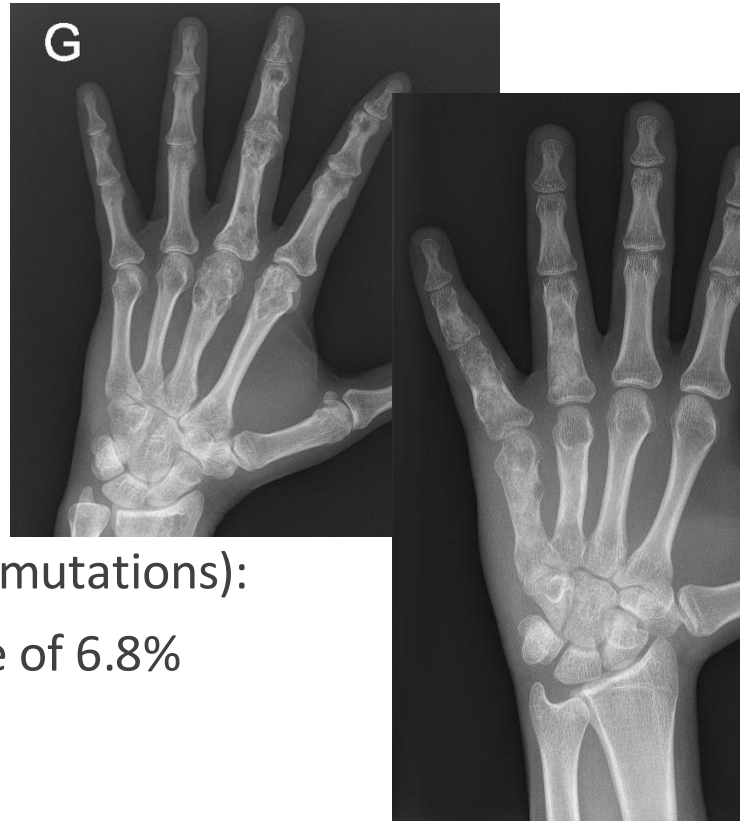
- Osteogenesis imperfecta
- Marfan syndrome
- Genetic Ehlers-Danlos syndrome



2- Sarcoma degeneration

Fibrous dysplasia: 1-2% of craniofacial lesions, probably long bones also. Mainly osteosarcoma.

→ one case in a femur diagnosed at CHUV (femoral amputation)



Hereditary multiple exostoses or diaphyseal aclasia (osteochondromas):

- <5% of transformation, higher (up to 25%) in pelvis/trunk lesions

→ one case in the pelvis diagnosed at CHUV (deceased)

Multiple enchondromatosis (Ollier & Mafucci diseases; mosaic IDH1 & IDH2 mutations):

- 30-50% develop chondrosarcomas in adulthood, with disease-mortality rate of 6.8%
- higher risk of gliomas, ovarian mesenchymal tumours, others.

Horvai & Unni. *J Orthop Sci.* **2006**; 11:412–423
Sharif et al. *Skeletal Radiol.* **2021**; 50:1941-1962
Sharif et al. *Skeletal Radiol.* **2022**; 51:747-762

3- New treatments

ALREADY AVAILABLE

- Burosumab for **FGF-23 dependent hypophosphatemia**
  → humanized antibody binding and blocking FGF-23

- Asphotase alpha for **hypophosphatasemia** (low alcaline phosphatase)
  → hormone replacement

- Vosireotide for **achondroplasia** (in children)
  → C-type natriuretic peptide analogue

- Palopegtériparatide for **hypoparathyroidism**
  → hormone replacement

- Palovarotene for **fibrodysplasia ossificans progresiva** (FOP)

ONGOING CLINICAL STUDIES

- Garetosmab, Zilugisertib, Andecaliximab, Fidrisertib, Saracatinib... for **FOP**

- Sestrusumab & romosozumab (anti-sclerostin antibodies), and fresolimumab (anti-TNF alpha antibody) for **osteogenesis imperfecta**

- INZ-701 (hormone replacement) for autosomal recessif **hypophosphatemic rickets with ENPP1 pathogenic variant**

- Efzimfotase alfa (hormone replacement) for **hypophosphatasemia**

- Ivosidenib (IDH1 inhibitor) for **Ollier disease** (multiple enchondromatosis)

…

3- Treatment depending on genetic variant

M AG, 1960: clinical diagnosis of osteogenesis imperfecta in a familial context:

- of 7 siblings, two brothers severly affected (wheel chair, blue sclera/multiple fractures), one sister died of Arnold-Chiari malformation, probable consanguinity

- no genetic analysis

Treatments:

2000-2005: alendronate

2006-2016: pamidronate

2016-2018: tériparatide

2018-2020: zoledronate 1/year

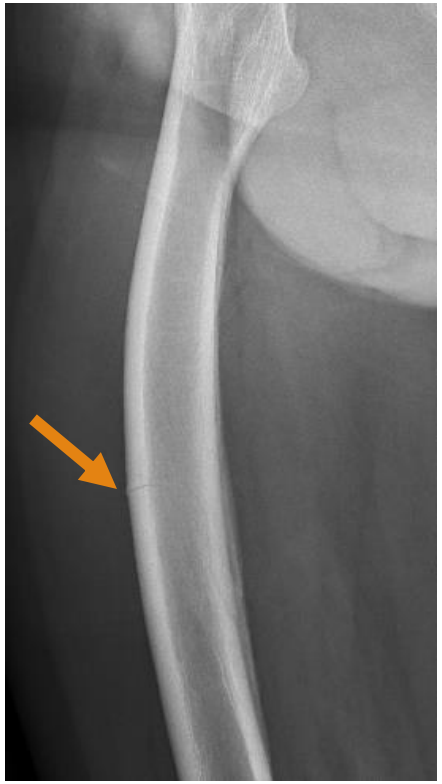
2020-2023: zoledronate 2/year (last 07.2023)

Examen densitométrique (Hologic Discovery, version 13.3) du 07.02.2019.

	BMD	T-score	Evolution 02.2024	
Colonne lombaire :				
L1-L2-L3-L4 :	0.689 g/cm²	-3.7 DS	-4,0 DS	-3,5 %
Fémur proximal gauche :				
Col :	0.582 g/cm²	-2.6 DS	-2,3 DS	
Hanche totale :	0.743 g/cm²	-1.9 DS	-2,1 DS	-3,3 %
Tiers distal du radius droit:	0.687 g/cm²	-2.5 DS	-1,8 DS	-5,3 %

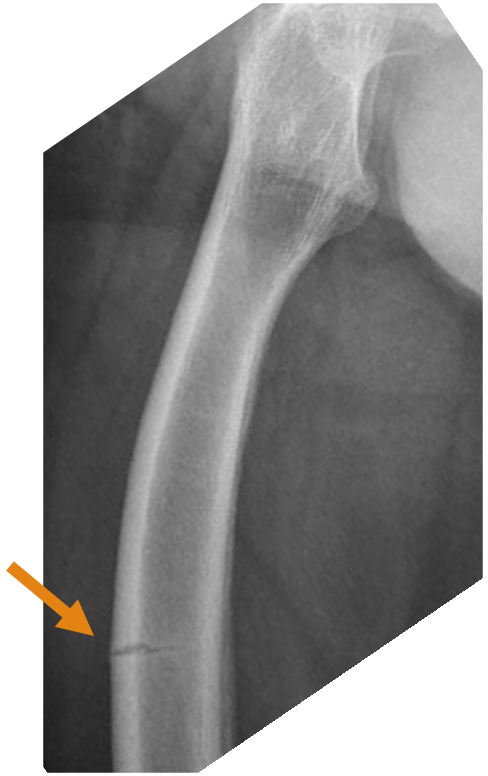
TBS iNsight™ de L1-L4 : 1.167

Atypical femoral fracture due to long bisphosphonate treatment



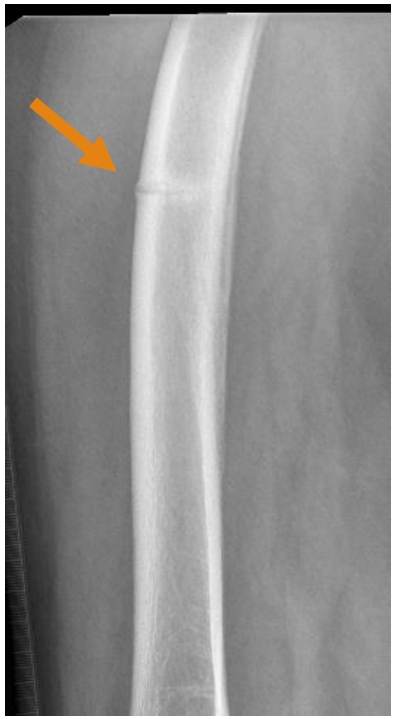
05.2023

Pain after forced mouvement and fall



06.2023

Hospitalized until 10.2023 (immobilisation, readaptation)



01.2024

Unable to walk (pain after 5 minutes)

One brother benefited in 2023 of a genetic testing:
- Homozygous for a WNT1 variant
- Heterozygous for a CREB3L1 variant

→ Later same mutations found in the patient

→ Both necessary for **osteoblast** function

→ Bisphosphonates **inhibit** osteoclasts, and secondarily osteoblasts

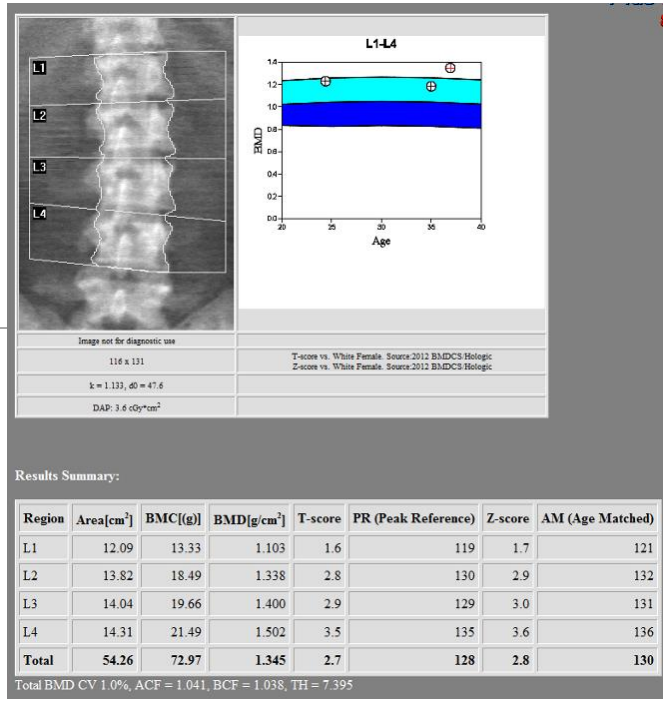
→ Studies in WNT1 patients show no/little effect of bisphosphonates

→ Anabolic agents should be prefered in this patients

Signs and symptoms that should raise awareness

AND WHAT THE GENERAL PRACTITIONER CAN DO

Clinical history



Region	Area[cm²]	BMC[(g)]	BMD[g/cm²]	T-score	PR (Peak Reference)	Z-score	AM (Age Matched)
L1	12.09	13.33	1.103	1.6	119	1.7	121
L2	13.82	18.49	1.338	2.8	130	2.9	132
L3	14.04	19.66	1.400	2.9	129	3.0	131
L4	14.31	21.49	1.502	3.5	135	3.6	136
Total	**54.26**	**72.97**	**1.345**	**2.7**	**128**	**2.8**	**130**

Total BMD CV 1.0%, ACF = 1.041, BCF = 1.038, TH = 7.395

Suspect a rare bone disease with increased fragility if fractures occur:

- young patients
- multiple fractures since infancy
- vertebral fractures: before menopause/50 yo, pregnancy/lactation vertebral fractures
- unusual sites: atypical femoral fractures, osteomalacic fractures

Low bone density (without cause)**/high bone density** (ostepetrosis and hypoP rickets-XLH)

→ perform a complete anamnesis of fractures since infancy

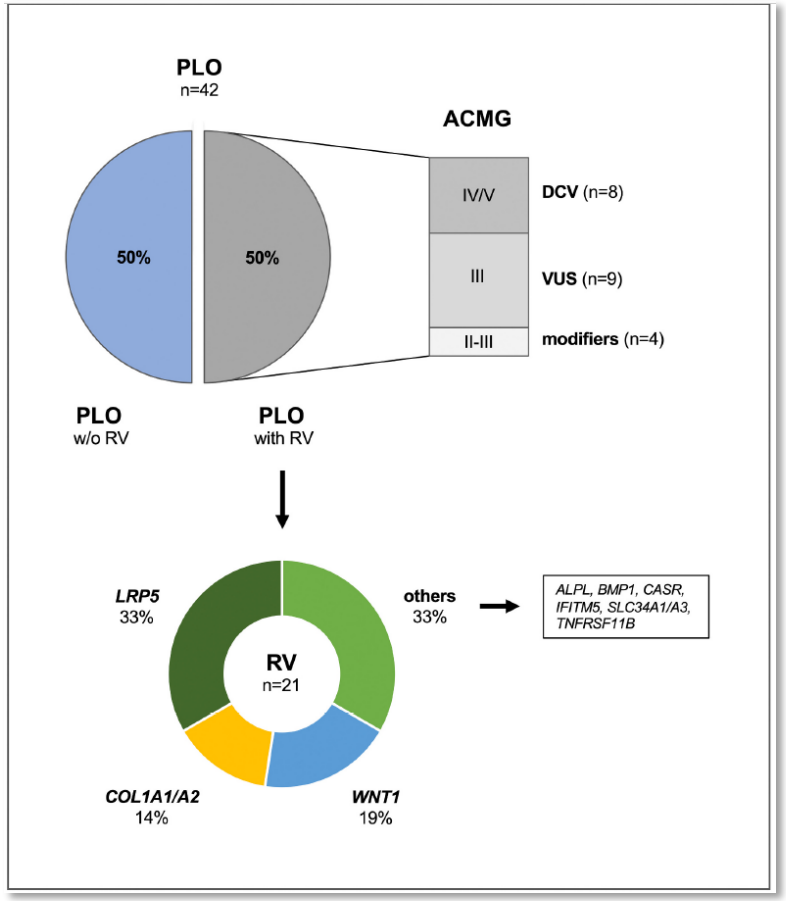
→ perform a familial anamnesis of fractures and eventual consanguinity

→ exclude secondary causes of bone fragility: hyperthyroidism, malabsorption/coeliac disease, monoclonal gammapathy, mastocytosis, hypogonadism, subclinical inflammation…

→ perform a densitometry

PLO: suspect a genetic etiology

PLO	Total	w/o RV	With RV	w/o vs. with RV
	(*n* = 42)	(n = 21)	(n = 21)	p, χ^2
Age at onset, *years*	34.3 ± 4.9	34.5 ± 4.8	34.1 ± 5.1	0.79
BMI, kg/m^2	23.2 ± 3.6	23.5 ± 2.6	23.0 ± 4.4	0.69
Clinical onset, *n (%)*				
1 Para	34 (81.0)	17 (81.0)	17 (81.0)	1
2 Para	6 (14.3)	3 (14.3)	3 (14.3)	1
3 Para	2 (4.8)	1 (4.8)	1 (4.8)	1
Antepartum	8 (19.0)	4 (19.0)	4 (19.0)	1
Postpartum	34 (81.0)	17 (81.0)	17 (81.0)	1
Lactation, *months*	5.0 ± 5.2	4.4 ± 5.1	5.6 ± 5.4	0.48
Historical height loss, *cm*	−3.2 ± 3.6	−2.0 ± 2.0	−3.9 ± 4.2	0.14
Positive family history, *n (%)*	21 (50%)	9 (42.9)	12 (57.1)	0.35
Fracture history				
VCF, *n*	3.3 ± 3.4	1.8 ± 2.3	4.8 ± 3.7	**0.02**
Peripheral Fx, *n*	0.4 ± 0.8	0.3 ± 0.6	0.4 ± 1.0	0.52
TOH, *n (%)*	10 (23.8)	5 (23.8)	5 (23.8)	1
Basic therapy, *n (%)*	42 (100)	21 (100)	21 (100)	1
Specific therapy, *n (%)*	18 (42.9)	8 (38.0)	10 (47.6)	0.53
Bisphosphonate	2 (4.8)	1 (4.8)	1 (4.8)	1
Denosumab	2 (4.8)	1 (4.8)	1 (4.8)	1
Teriparatide	11 (26.2)	5 (23.8)	6 (28.6)	0.72
Denosumab + teriparatide	3 (7.1)	1 (4.8)	2 (9.5)	0.54
DXA, Z-score				
Femoral neck	−2.0 ± 0.9	−2.1 ± 0.9	−1.8 ± 0.9	0.32
Lumbar spine	−2.7 ± 0.9	−2.8 ± 0.8	−2.7 ± 1.0	0.77
Femoral neck vs. lumbar spine (p)	**0.002**	0.06	**0.02**	



Butscheidt et al. *Bone* **2021**, 147, 115911

Clinical history

Low height:

- most diseases are associated (at least in severe cases) with low height

- exception: Marfan associated syndroms (usually high, not always)

Unusual dental problems:

- dentinogenesis imperfecta: in osteogenesis imperfecta

- early tooth loss of decidous/definitive teeth with the root: hypoPAL

- spontaneous dental abcesses: hypoP rickets-XLH

Musculo-squelettal diffuse pain: look for osteomalacia/hypoPAL

Early osteoarthritis:

- skeletal dysplasias

- chondrocalcinosis in hypoPAL

→ standard biological and radiological examinations

Clinical history

Hyperlaxity: in many skeletal dysplasias, osteogenesis imperfecta, Ehlers-Danlos, Marfanoid syndroms

→ anamnesis on hyperlaxity comorbidities: herniations, recurrent joint dislocations, joint pain, pneumothorax

→ look for comorbidities: dental problems, small height, marfanoid morphotype, blue sclera

→ Beighton score

→ standard biological and radiological examinations

Beighton score

For more information www.dralisongrimaldi.com/blog

Dr. Alison Grimaldi

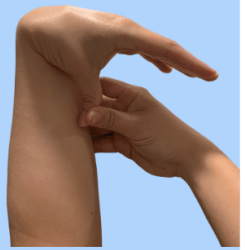
The Beighton Score for Generalised Joint Hypermobility

A 9 point scoring system

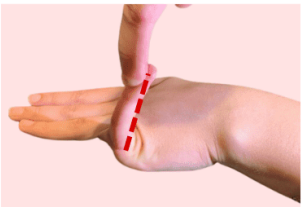
Palms flat on the floor
= 1 point

Knee hyper-extension ≥ 10°
= 1 point each

Elbow hyper-extension ≥ 10°
= 1 point each



Thumb to forearm
= 1 point each



5th MCP joint extension > 90°
= 1 point each side

Using a Beighton score cut-off of ≥4 for generalised joint hypermobility has a 60% false positive rate

Use age & sex specific cutoffs, appropriate for your population

Singh H, McKay M, Baldwin J, Nicholson L, Chan C, Burns J, Hiller CE. Beighton scores and cut-offs across the lifespan: cross-sectional study of an Australian population. Rheumatology (Oxford). 2017 Nov 1;56(11):1857-1864. doi: 10.1093/rheumatology/kex043.

Standard biology (fasting)

Fasting albumin corrected **calcium**

Fasting **phosphate**

25-OH **vitamin D**:

- if <50 nmol/l, replete and do the tests again

Creatinine

ALP (+gGT to exclude hepatic origin):

- if low ALP send for investigations

Exclusion of secondary osteoporosis:

- TSH

- proteins immunosustraction

- tryptase

- coeliac disease antibodies

- fasting total testosterone (men)

- VS

- if hypophosphatemia, hypo/hypercalcemia: determine phosphate/calcium loss, PTH

Standard radiology

AP and lateral dorso-lumbar spine:

- vertebral fractures/deformations
- enthesopathies

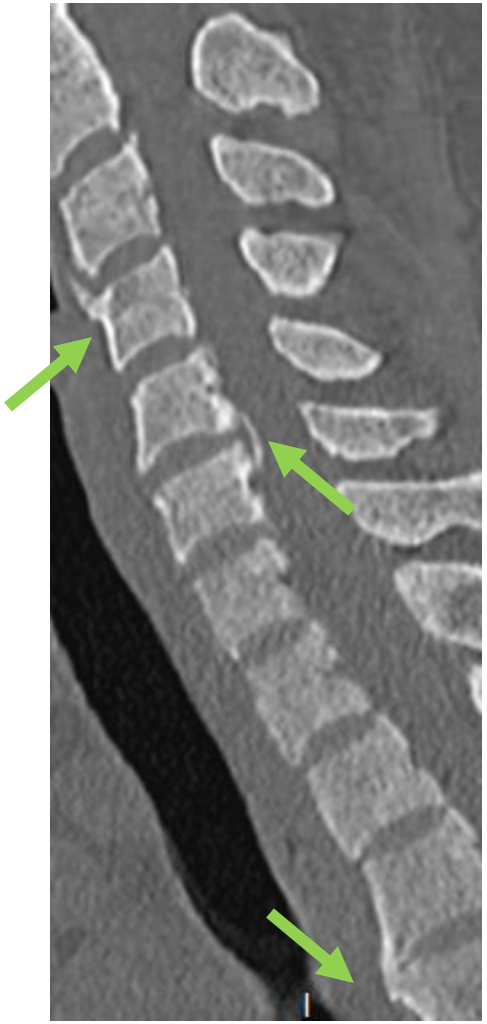
AP pelvis:

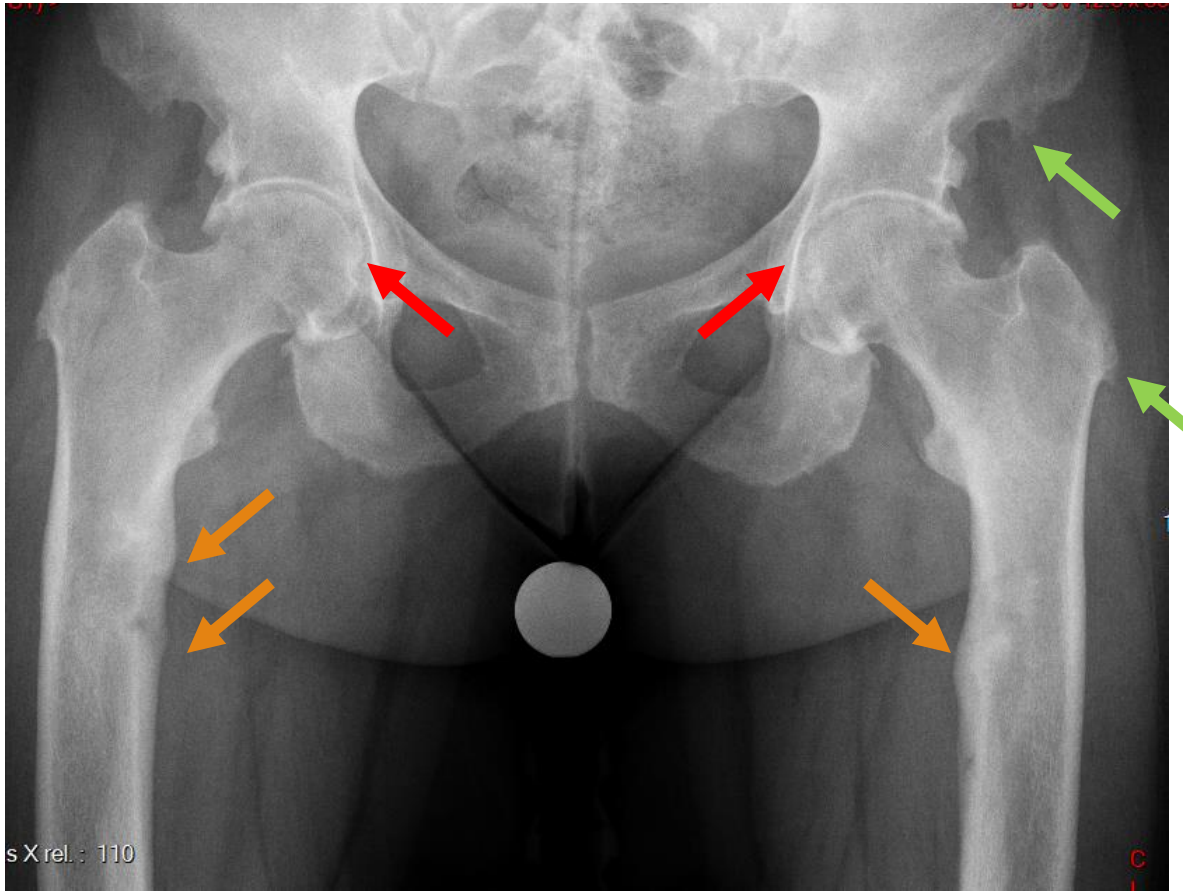
- femoral dysplasia
- enthesopathies
- atypical/osteomalacic fractures

Hand, knee:

- dysplasias
- metacarpal abnormalities (brachydactily)
- exostosis/membrane calcifications
- intraarticular calcium deposits
- early osteoarthritis

Women, 38 yo: hypophosphatemic rickets



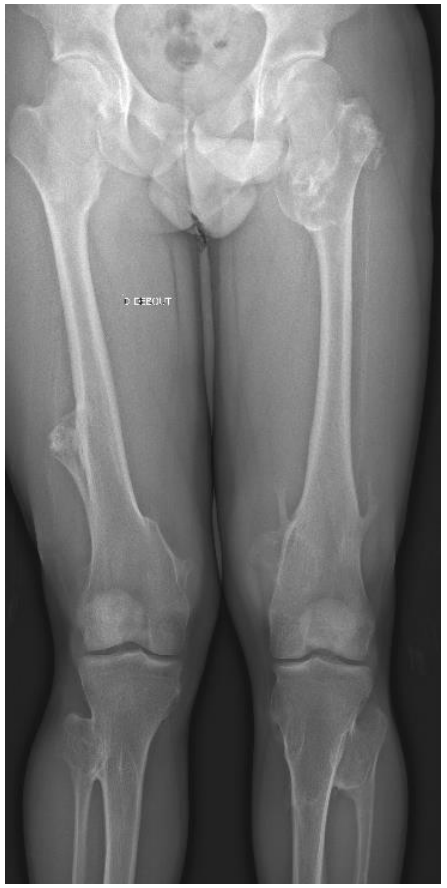


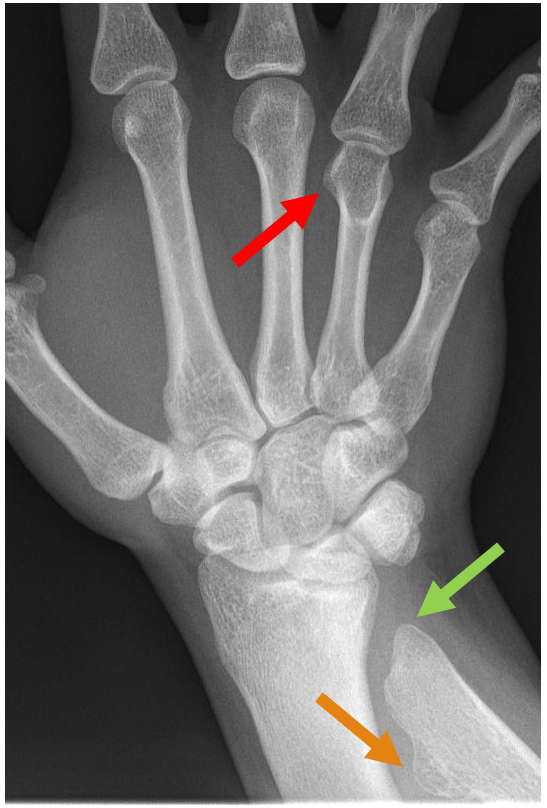
Osteomalacic fractures

Enthesopathies

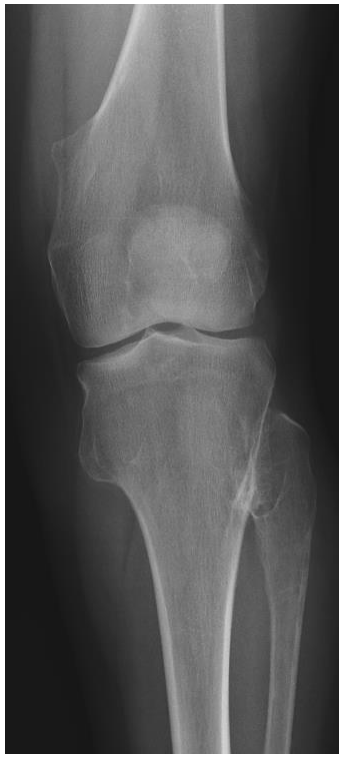
Early osteoarthritis

Man, 20 yo: exostosis multiplex





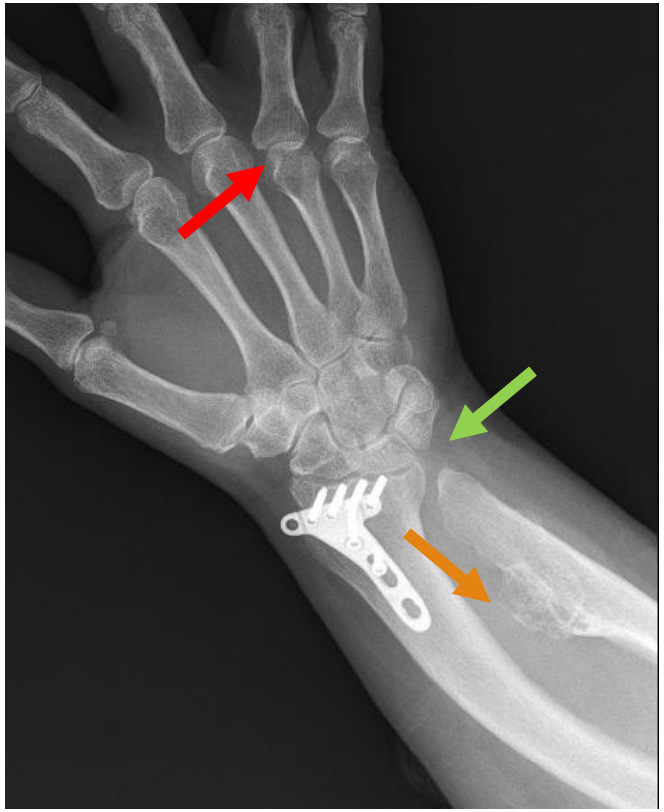
Woman, 60 yo (mother)



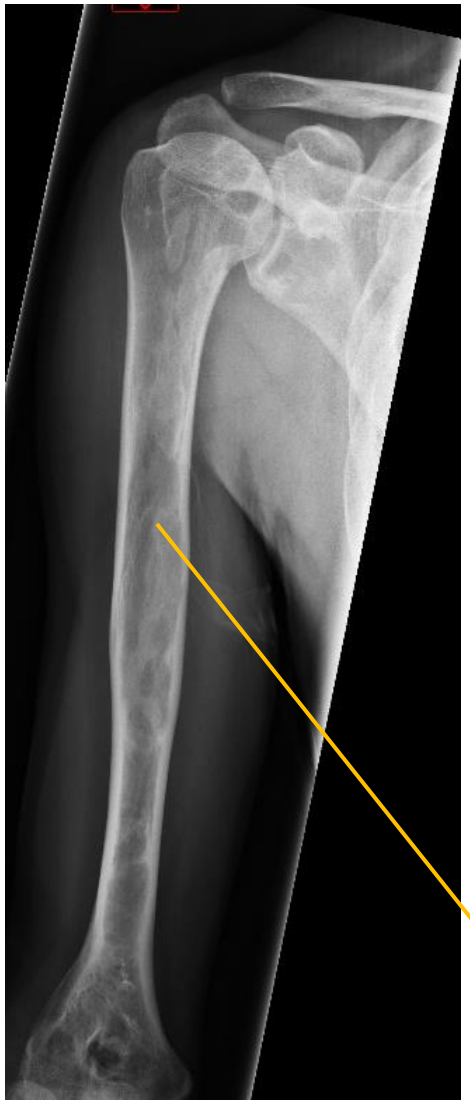
Exostosis

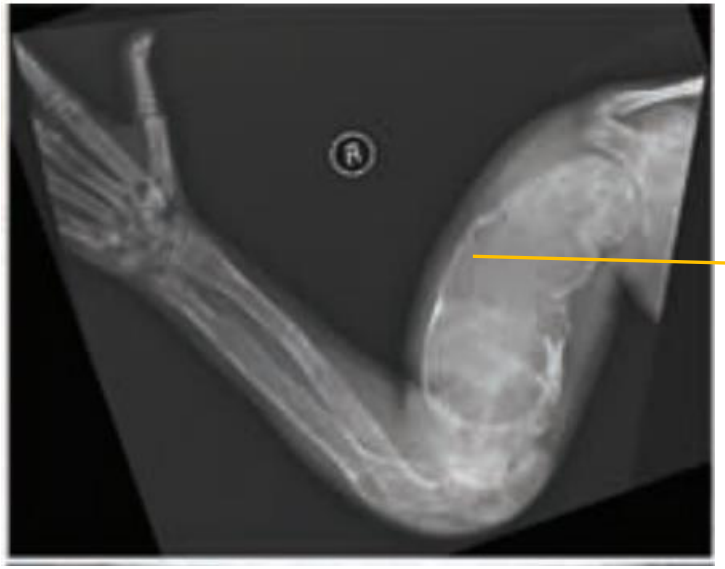
Madelund deformity

Brachydactily



Fibrous dysplasia

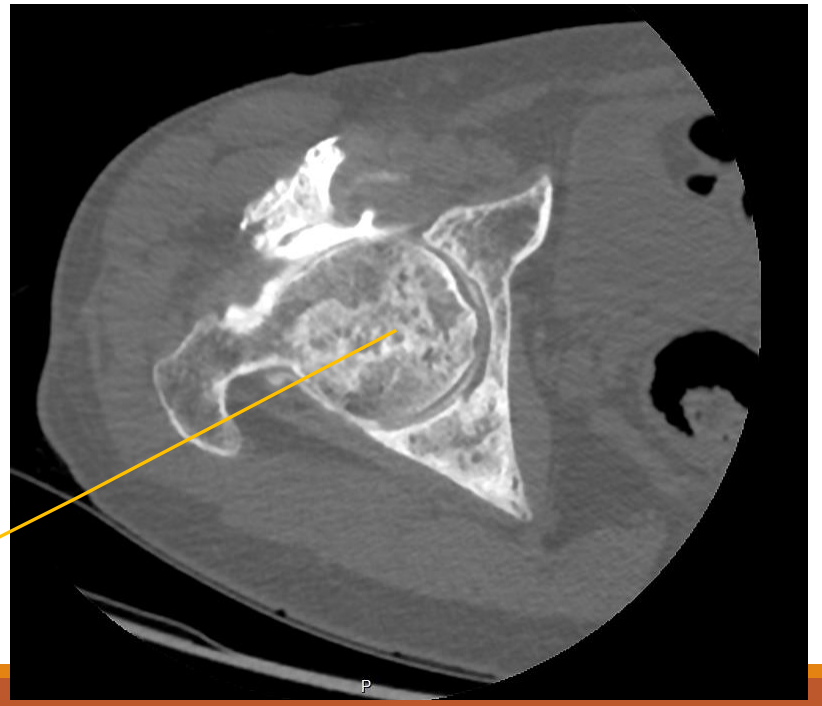




Kystic aspect

- Bone deformation
- Thin cortical

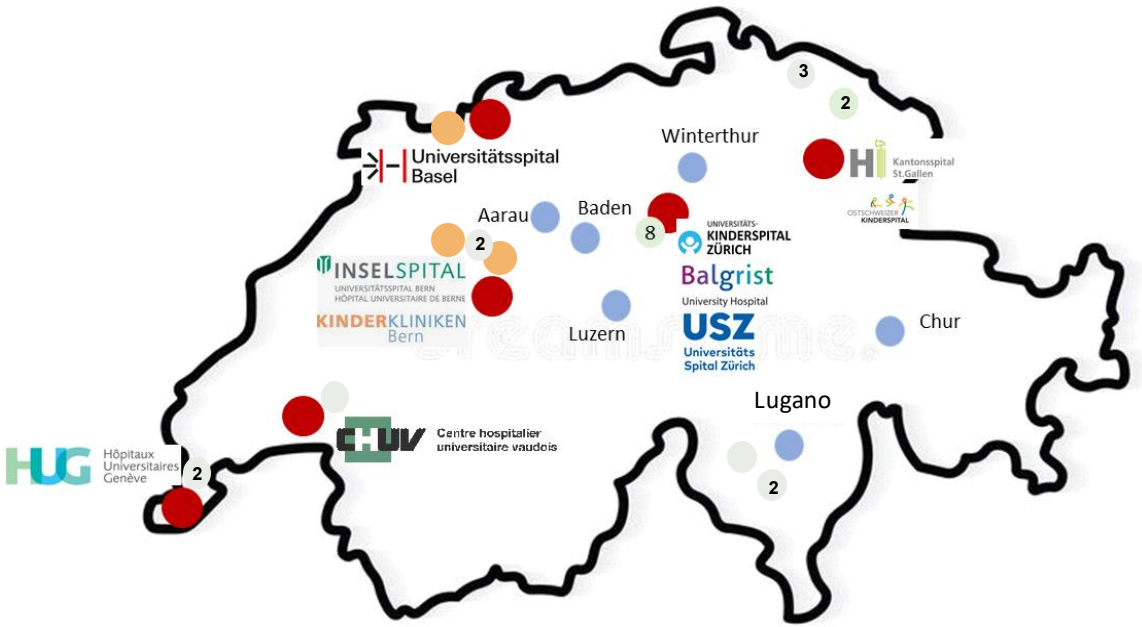
Frosted glass appearance



SG BOND

Swiss Groupment for rare BONe Diseases

Working group at the ASCO/SVGO (Schweizerische Vereinigung gegen Osteoporose) and the SGIEM (Swiss Group for Inborn Errors of Metabolism)



Reference centers:

- Multidisciplinary management for children and adult patients
- Joint follow-up of patients with associated centers/care facilities
- Educational conferences and meetings
- Patient days and relationship with patient organizations
- Patients registries and research projects
- Project: clinical pathwaysfor most frequent diseases

Conclusions

Think of a rare bone disease in case of:

- Inusual fractures (site, number, mechanism) or inusual patients (young, family history)
- Small height, multiple hyperlaxity comorbidities, dental/hearing problems…
- Radiological lesions: lytic/exophytic, trunc or member déformations, early osteoarthritis

If you suspect a rare bone disease:

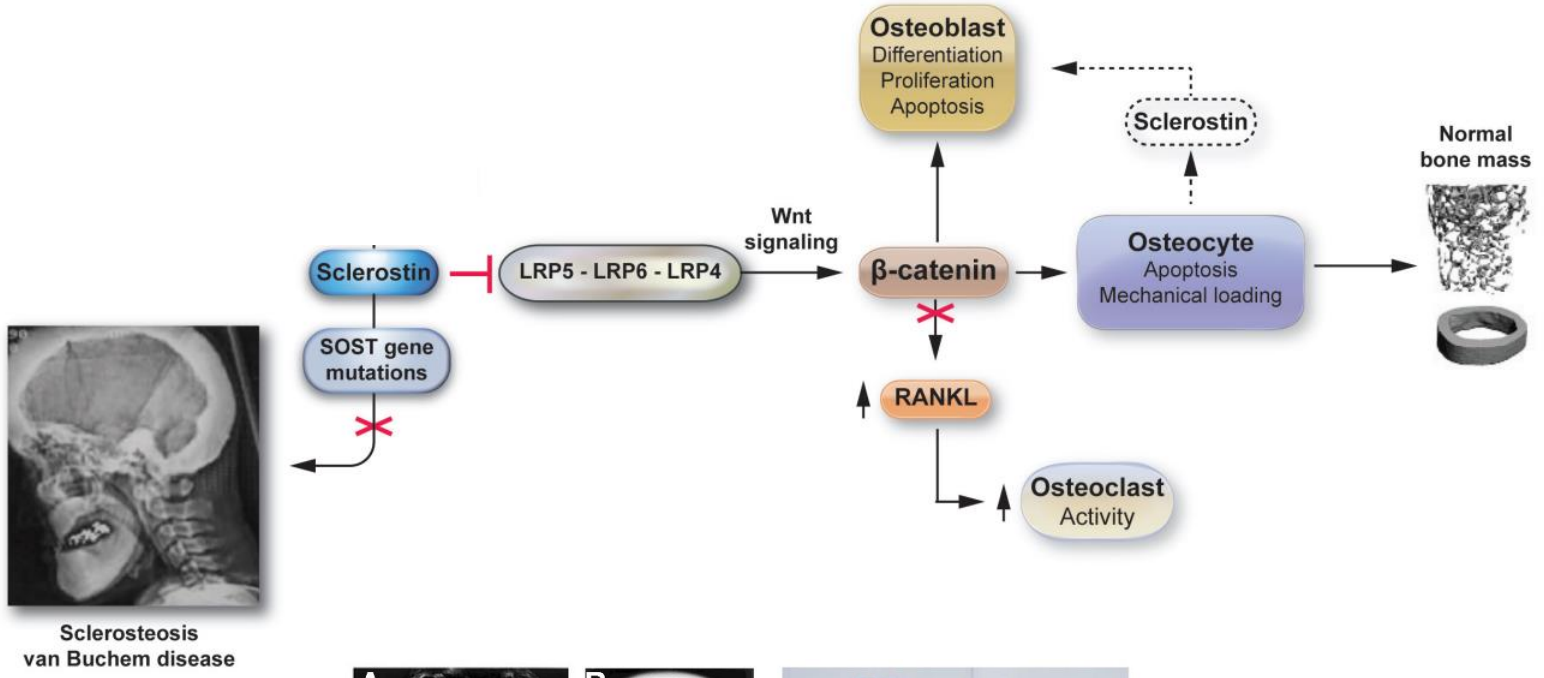
- Do not forget to measure phosphate, alkaline phosphatase, tryptase
- In case of fragility: perform a densitometry, do not give bisphosphonates before excluding osteomalacia
- Do not forget the other conjunctive tissues

COLLABORATE WITH AN EXPERT IN RARE BONE DISEASES!

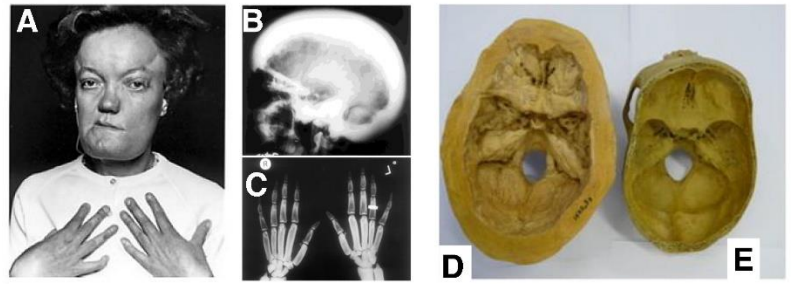
UNIL | Université de Lausanne
Faculté de biologie et de médecine

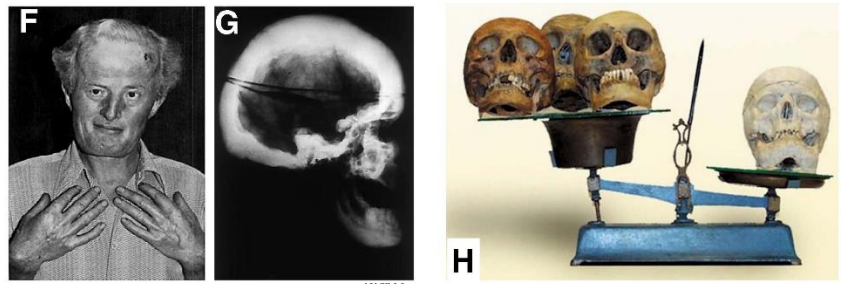
CHUV

Questions?



Sclerosteosis
van Buchem disease





HORMONES 2014, 13(4):476-487