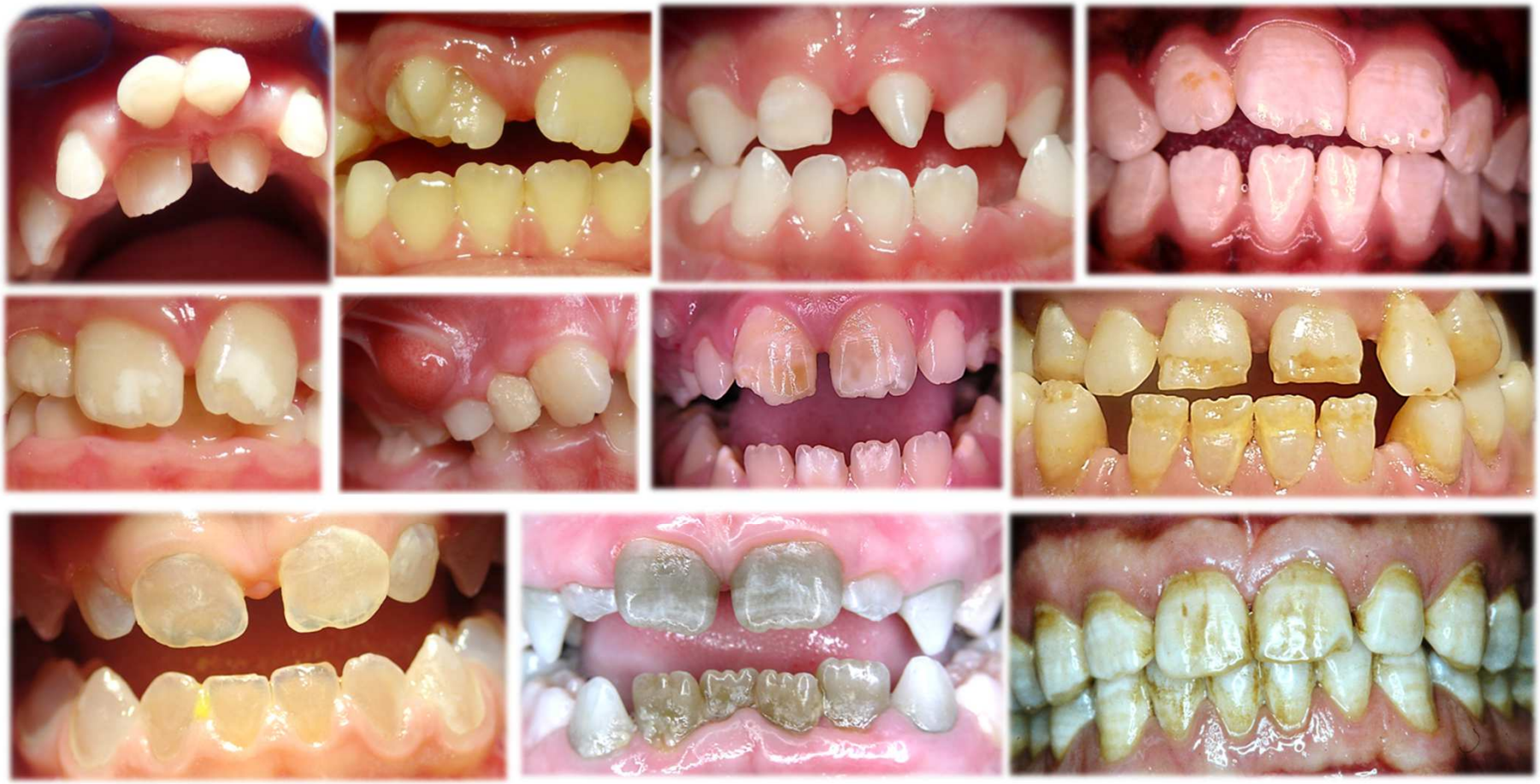
Comprendre les maladies : apport de la recherche odontologique

Pr Catherine Chaussain *et al.*

Comprendre les maladies : Exemple des maladies rares liées au métabolisme minéral



Dr Courson and from Bardet et al. 2016

Endocrine CONNECTIONS | C Nguyen *et al.* | OHRQoL in patients with XLH | 11:1 | e210564

RESEARCH

Oral health-related quality of life in patients with X-linked hypophosphatemia: a qualitative exploration

Caroline Nguyen[1], Elisabeth Celestin[2], Delphine Chambolle[3], Agnès Linglart[2,4,5,6], Martin Biosse Duplan[1,7,8,9], Catherine Chaussain[1,7,8,10] and Lisa Friedlander[1,11,12,13]

Abstract

Introduction: X-linked hypophosphatemia (XLH) is a rare, hereditary, and lifelong phosphate-wasting disorder characterized by rickets in childhood and impaired teeth mineralization. In the oral cavity, spontaneous abscesses can often occur without any clinical signs of alteration of the causal tooth. The objective of our study was to evaluate the oral care pathway and the oral health-related quality of life (OHRQoL) of patients following in an expert oral medicine department located within a Parisian hospital and working in close collaboration with an endocrinology department expert in this pathology.

Methods: This study employed a qualitative descriptive design including semi-structured interviews using guiding themes.

Results: Twenty-one patients were included in the study. The topics brought up exceeded the initial objectives as the patients mostly addressed the alteration of their oral health-related and general quality of life; a very chaotic oral health care pathway with oral health professionals not aware of their pathology; consequences on their social, professional, and school integration. Patients declared the importance of having a multidisciplinary team around them, including medical and dental professionals.

Conclusions: The variety of manifestations in patients with XLH necessitates high coordination of multidisciplinary patient care to optimize quality of life and reduce disease burden. Oral health care pathways are very chaotic for patients who have difficulty in finding professionals with sufficient knowledge of the disease. OHRQoL is therefore diminished. This situation improves when patients enter a coordinated care network.

Key Words

- X-linked hypophosphatemia
- rare disease
- oral health-related quality of life
- care pathways

Découvrir de nouveaux liens entre les dents et une maladie rare

Exclure: Fluorose ,MIH, intoxication médicamenteuse ou environnementale

Email

Amélogenèse imparfaite et anomalies de l'émail
(Toutes les dents des deux dentures atteintes)

Non syndromique
AMELX, ENAM, AMBN, Col17A1 DLX 3, ITGβ6, LAM β3, LAMA3, WDR72, MMP20, SLC24A4, KLK4, C4ORF26, FAM83H, CNNM4

Associée à un trouble rénal
(néphrocalcinose, IR)

- Sans anomalie du métabolisme minéral mais avec calcification ectopiques gencive + pulpe : Enamel-Renal syndrome **FAM20A**
- Avec anomalie métabolisme minéral: Hypomagnésémie et hypercalciurie FHNNC: **CLDN16 et 19** HELIX: **CLDN10**

Associée à un trouble hépatique et cutané
(ichtyose et cholangite sclérosante) **CLDN1**

Associée à une hypocalcémie

- Rachitisme pseudocarentiel **CYP27B1**,**VDR**
- Hypoparathyroidie/ pseudohypopara **CasR** (GOF), **PTH**, **GNAS1**

Dentine

Dentinogénèse imparfaite et Anomalie de structure dentinaire

Non syndromique
DSPP, SMOC2, VPS4B, TRIP10,

Associée à une pathologie osseuse constitutionnelle
OI, Ostéopétrose, dysplasie fibreuse, **COL1A1, COL1A2, FKBP10**

Avec anomalie métabolisme minéral

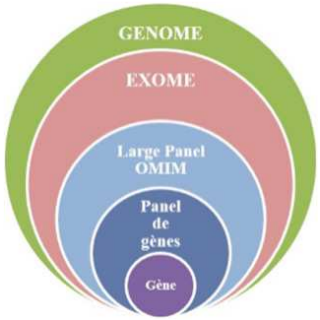
Rachitismes Hypophosphatémiques
Dentine hypominéralisée avec persistance de calcosphérites
Pulpes dentaires larges
Susceptibilité accrue à la maladie parodontale
PHEX, **FGF23** (GOF**)**, **ENPP1**, **DMP1**, **FAM20C**, **CICN5**, **SLC34A3**

Exclure: Papillon lefevre…..

Cément

Calcinose tumorale (avec hyperphosphatémie)
Pulpes dentaires oblitérés
Calcifications ectopiques gingivales
Susceptibilité accrue à la maladie parodontale dès adulte jeune
FGF23 (LOF), **GALNT3**

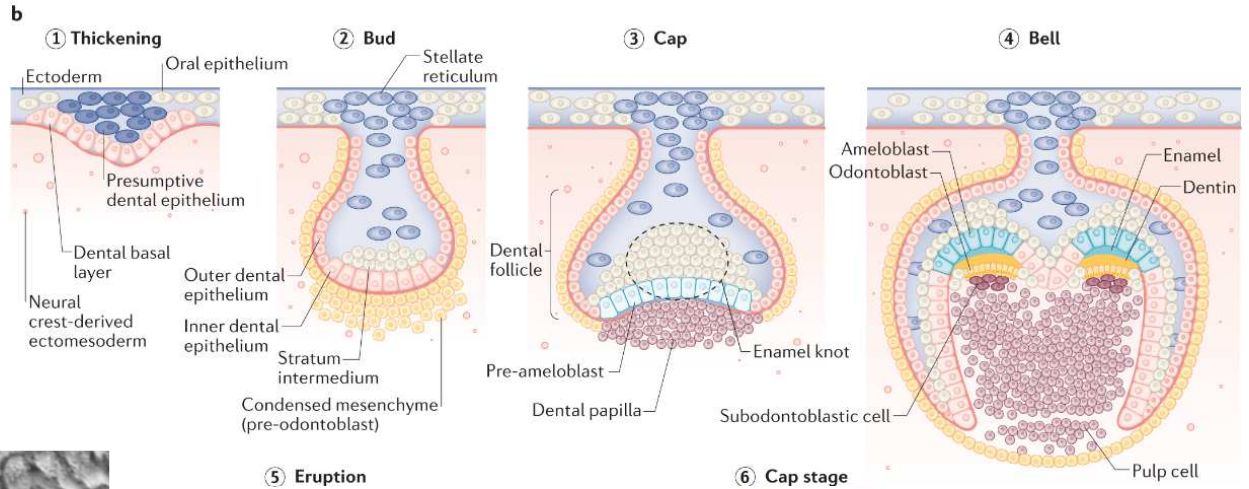
Hypophosphatasie
Perte prématurée d'une ou plusieurs dents de lait avec racine intacte avant 5 ans
Perte prématurée des dents permanentes
Hypoplasie amélaire
ALPL

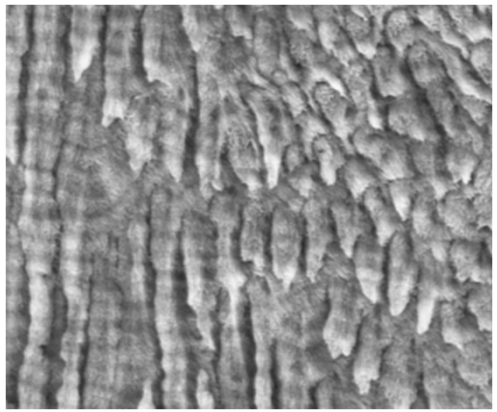


FILIÈRE SANTÉ MALADIES RARES TeteCou
MALFORMATIONS RARES TÊTE COU DENTS

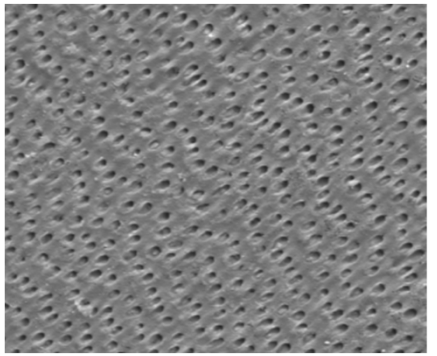
OSCAR FILIÈRE SANTÉ MALADIES RARES

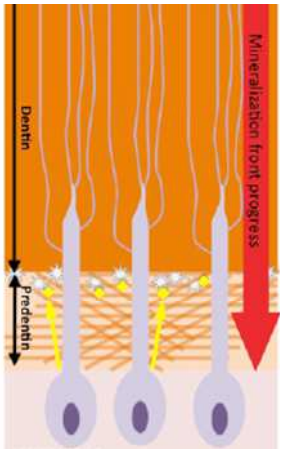
Le développement dentaire : un processus complexe fondé sur un dialogue épithélio-mésenchymateux.





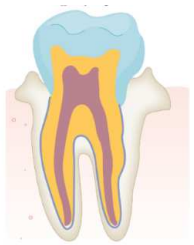
96 % d'hydroxyapatite
- de 1 % de protéines

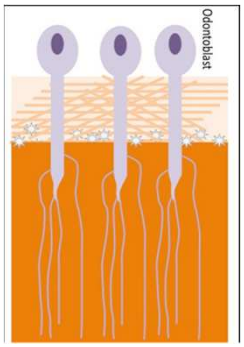


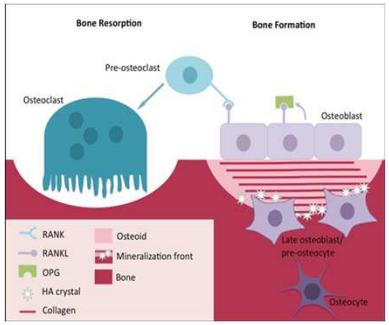


Kovacs, C. S. et al. The role of biomineralization in disorders of skeletal development and tooth formation. *Nat. Rev. Endocrinol.* https://doi.org/10.1038/s41574-021-00488-z (2021).

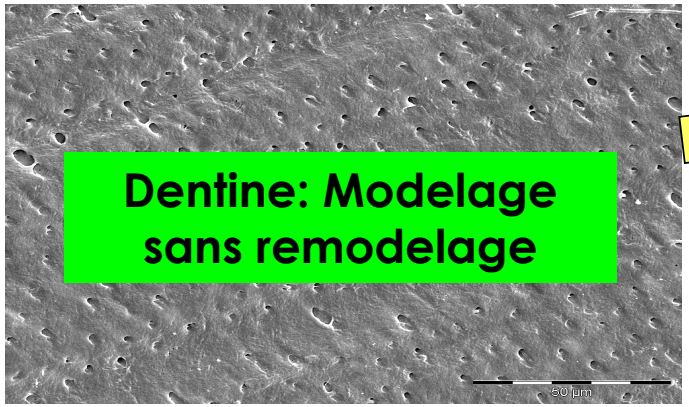
La matrice extracellulaire de la dentine (ou cément): un processus très similaire à celui de l'os … mais sans remodelage

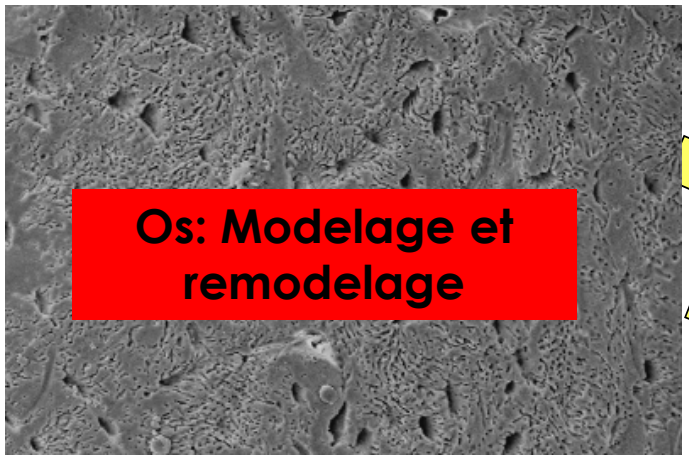






70% minéral





30% matrice organique

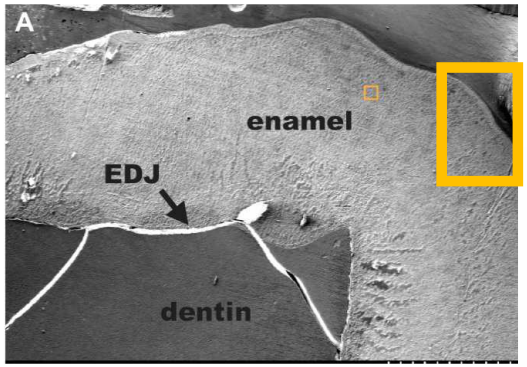
- Collagènes type 190%
- Protéines phosphorylées (SIBLINGs/ DSP dentin specific)
- Osteocalcine, Osteonectine…
- GAG, PGs
- MMPs
- Lipids

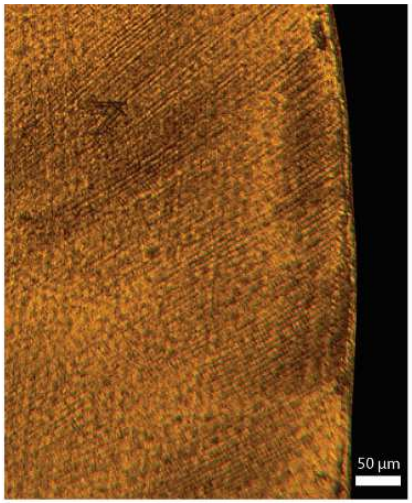
Opsahl Vital *et al. Bone* 2012;50:989

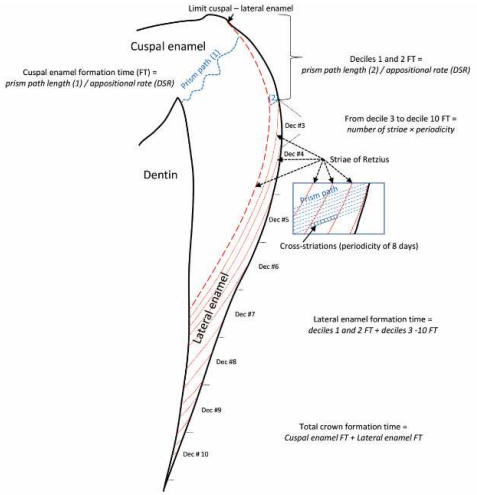
Chirurgien-dentiste et maladies rares liées au métabolisme minérale

- ✓ Découvrir de **nouveaux liens directs** *vs* indirects entre la dent et une maladie rare liée au métabolisme minéral
- ✓ Comprendre la physiopathologie des maladies rares par l'étude des dents de modèles murins ou de modèles de cellulaire ou de dents humaines
- ✓ Évaluer l'impact des nouveaux traitements
- ✓ Développer des **soins dentaires adaptés**

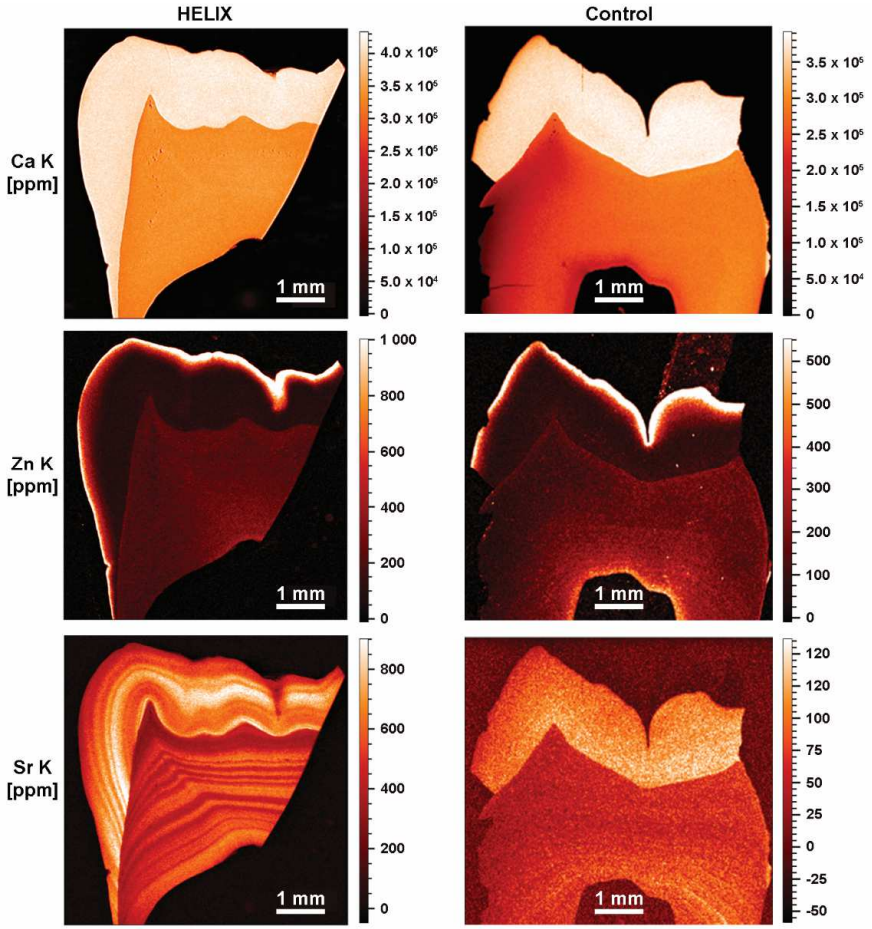
Modèles pour étudier la dent dans le cadre des maladies osseuses rares : la dent





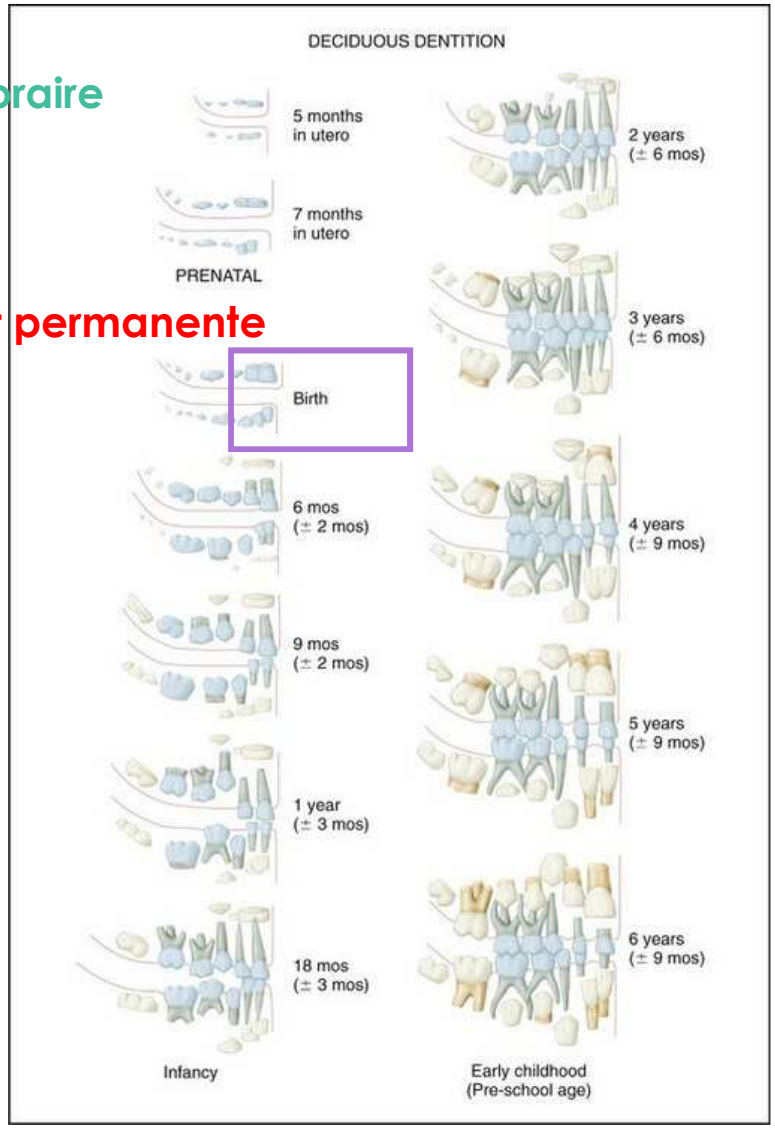


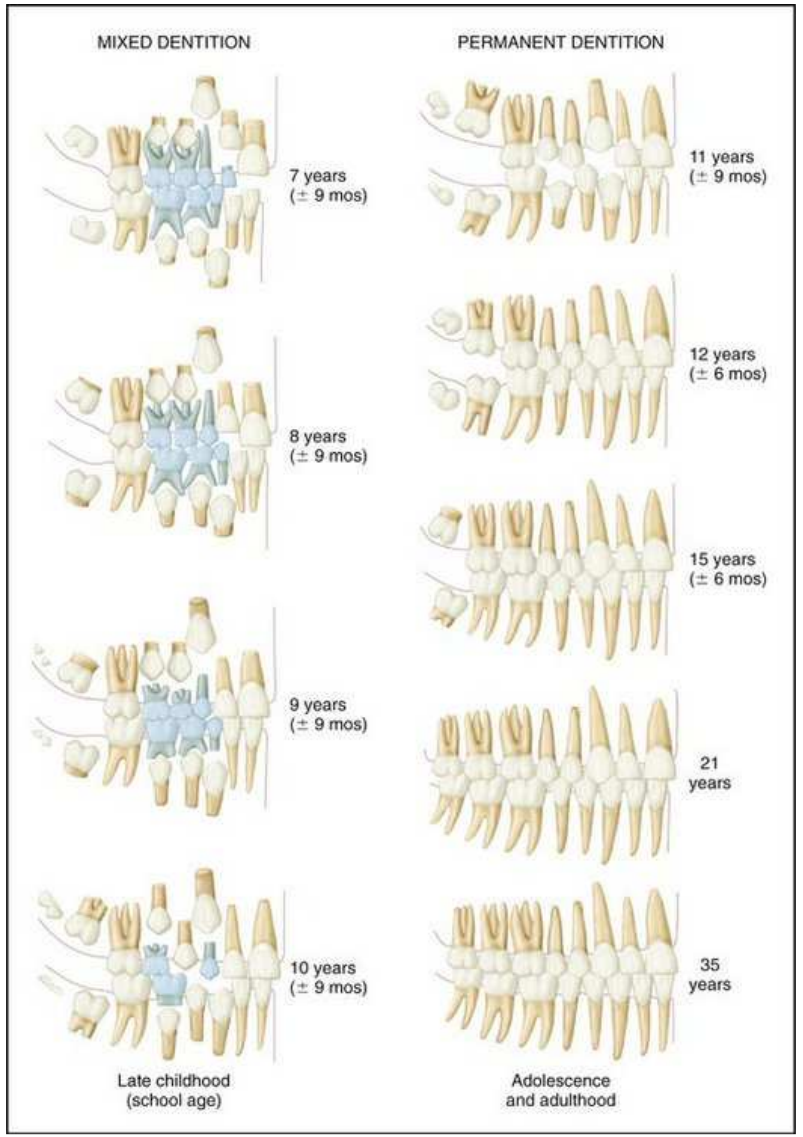
Supplementary Fig. S1: Schematic of the methodology for the quantification of the HELIX crown formation time



Dent temporaire

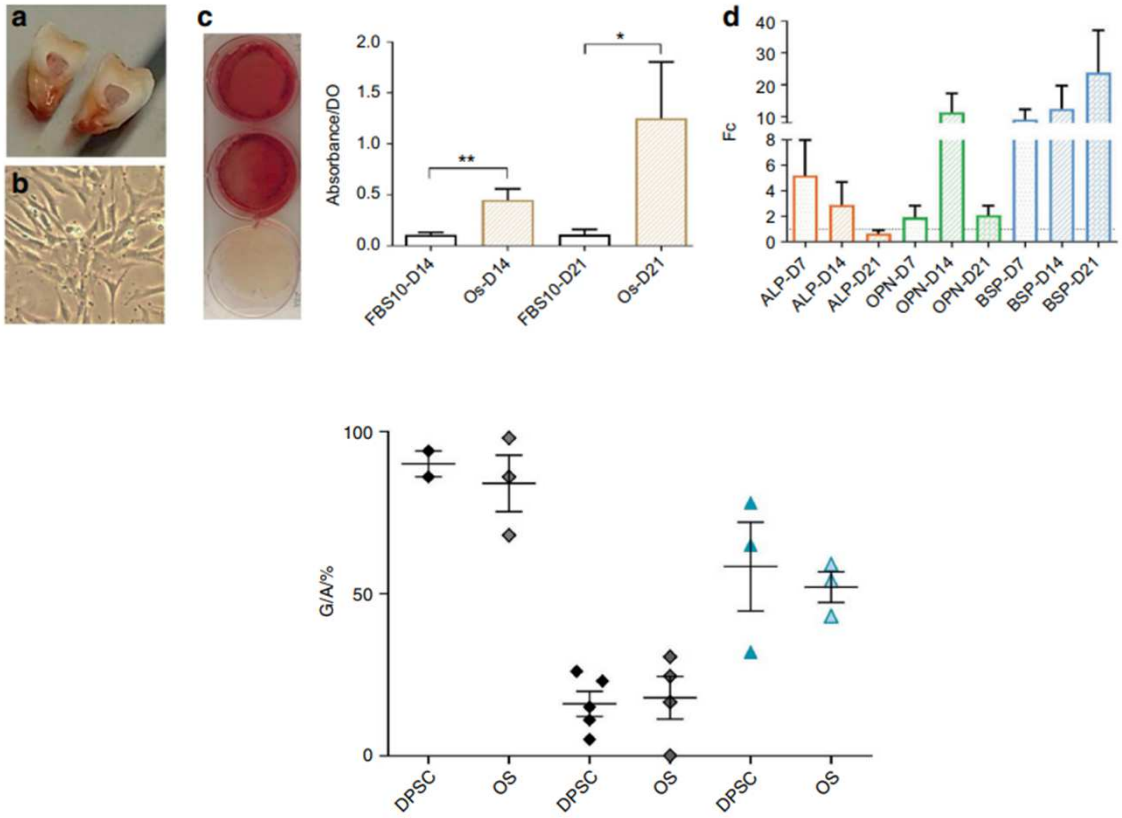
Dent permanente



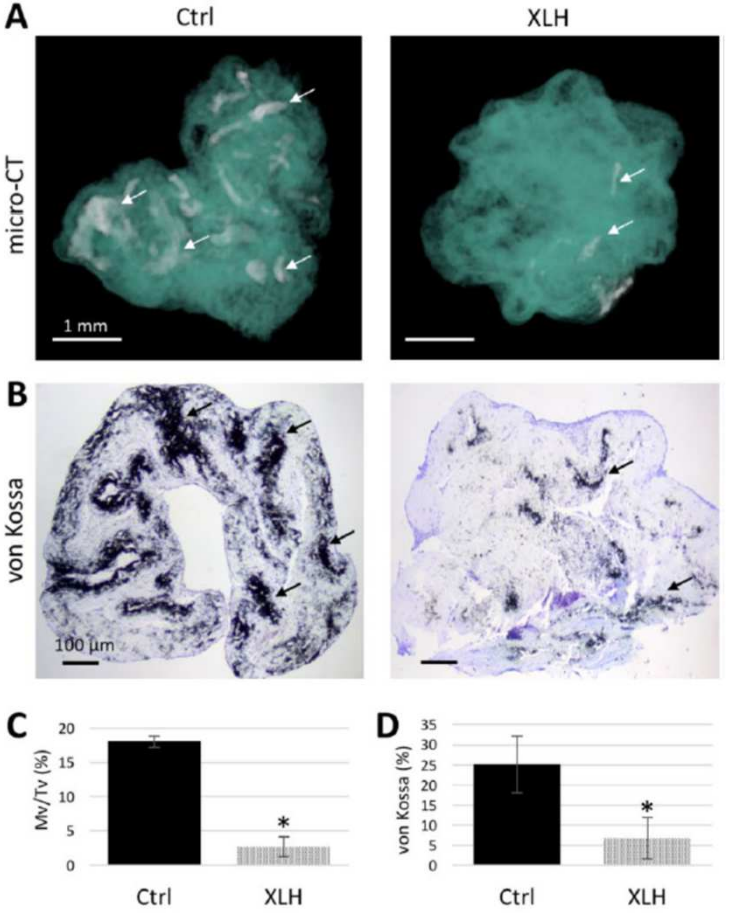


Adapté de Schour L, Massler M: The development of the human dentition, J Am Dent Assoc 28:1153, 1941

Modèles pour étudier la dent dans le cadre des maladies osseuses rares: Cultures de cellules orales (pulpaires ou gingivales)

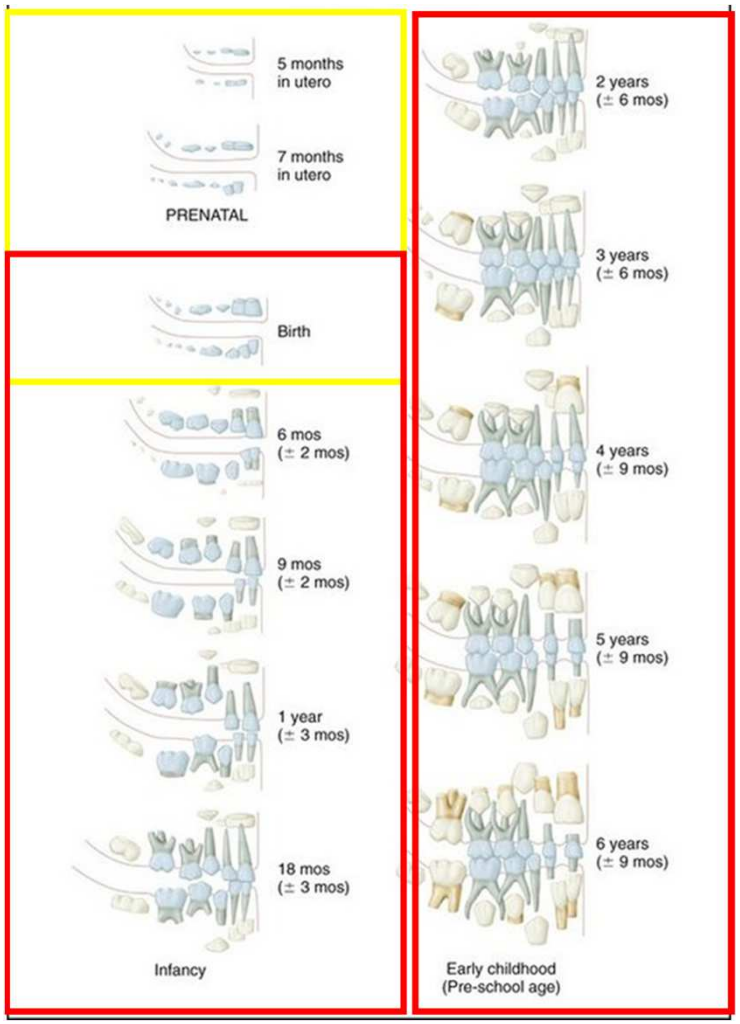


Dental pulp stem cells as a promising model to study imprinting diseases.Giabicani *et al.* International Journal of Oral Science **2022**

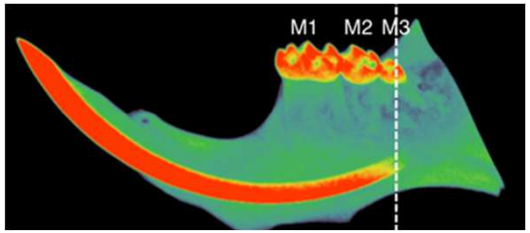


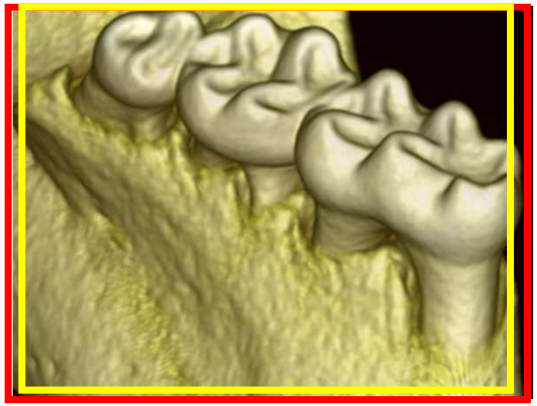
Coyac *et al. JDR* 2017

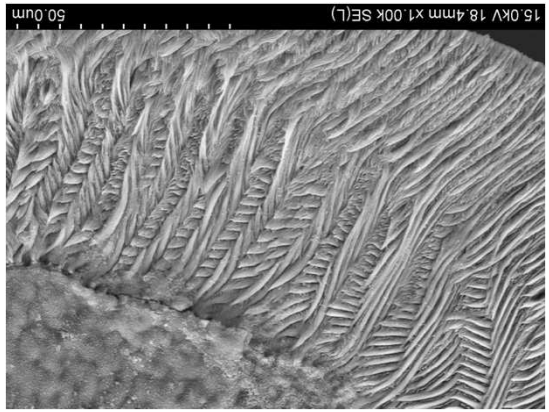
Modèles pour étudier la dent dans le cadre des maladies osseuses rares : modèles murins

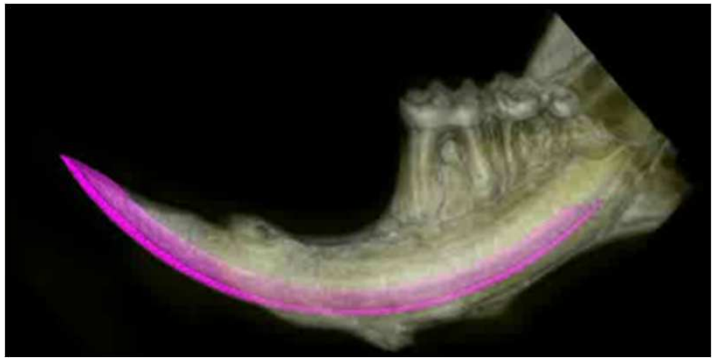


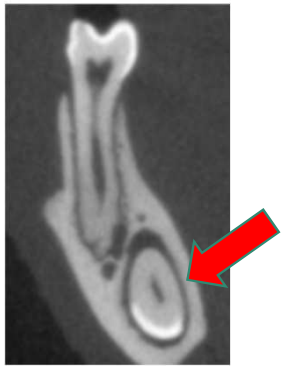
Adapted from Schour L, Massler M: The development of the human dentition, J Am Dent Assoc 28:1153, 1941







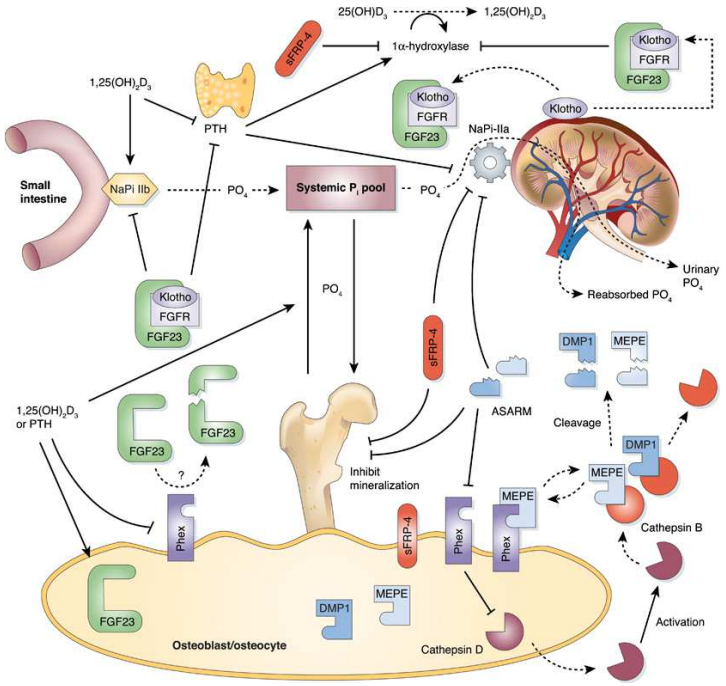


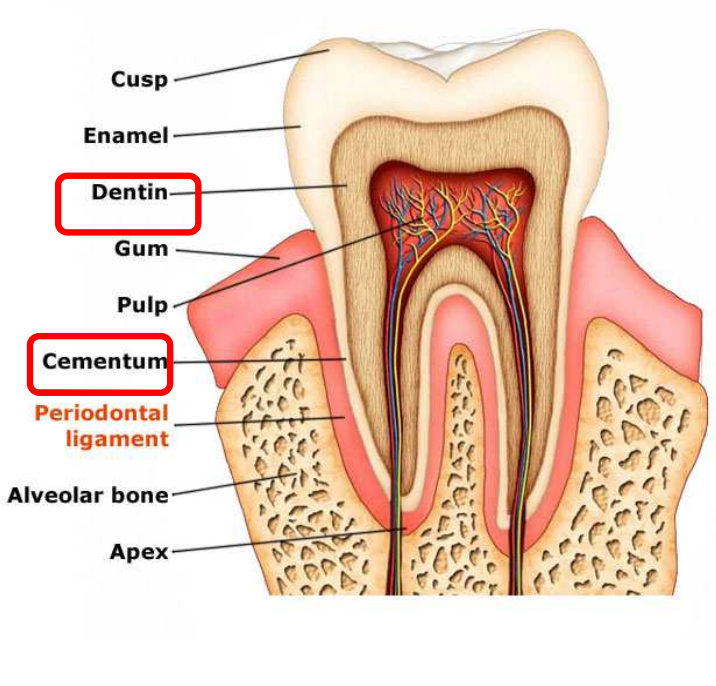


Comprendre la physiopathologie des maladies osseuses rares :

Maladies liées à l'homéostasie minérale

AXE PHOSPHATE



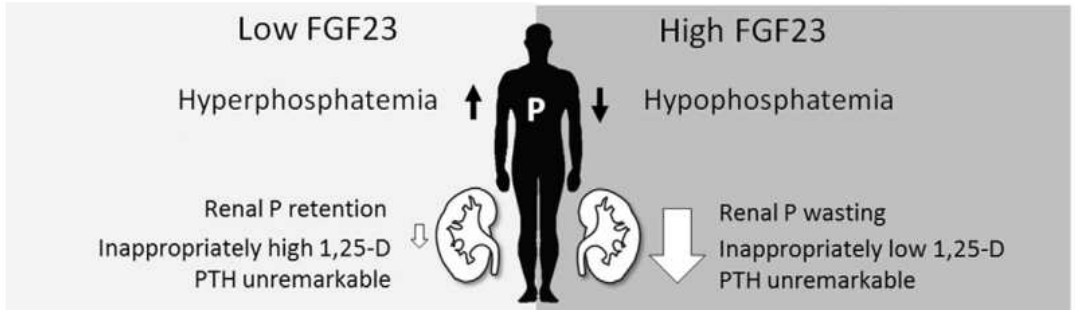


Les maladies osseuses rares avec hyper/hypophosphatémie affectent la minéralisation dentaire

Kiela and Gishan. *Lab Invest* 2009;89:7; Opsahl Vital *et al. Bone* 2012;50:989;
Biosse Duplan *et al. J Dent Res* 2017;96:388; Coyac *et al. Bone* 2017;103:334

Hyper/Hypo Phosphatemie

M. Kuro-o, O.W. Moe / Bone 100 (2017) 4–18



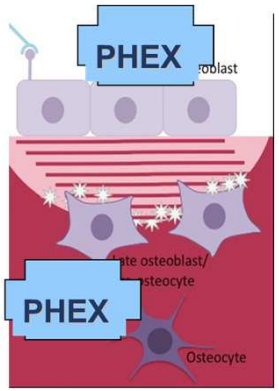
Condition	*Gene*
Familial Tumoral calcinosis	FG[illegible]3
	GALNT3
	αKlotho

Condition	*Gene*
X-linked hypophosphatemic rickets	PHEX
Autosomal-dominant hypophosphatemic rickets	FGF23
Autosomal-recessive hypophosphatemic rickets 1	DMP1
Autosomal-recessive hypophosphatemic rickets 2	ENPP1
McCune-Albright	GNAS1
Jackson-Weiss, Pfeiffer, Alpert, Kallman's syndromes	FGFR1
Jansens' metaphyseal chondrodysplasia	PTHR1
Raine syndrome	FAM20C
Epidermal melanocytic nevi	R/HRAS

Hypophosphatémie liée à l'X (*PHEX mutation*)

Manifestations

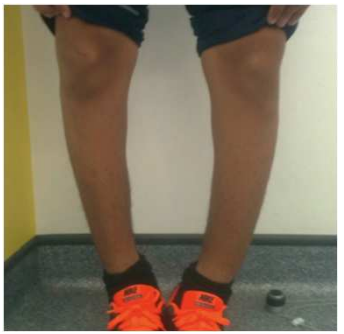
Rachitisme, jambes arquées,
Petite taille
Démarche dandinante

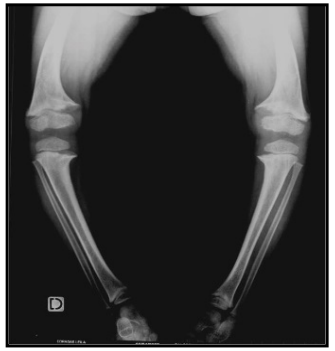


Ostéomalacie et douleurs articulaires (adultes), enthésopathies et fissures osseuses

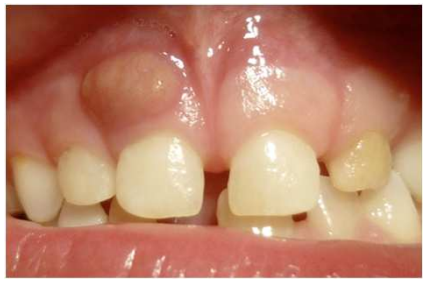
Malformations squelettiques, rachitisme (radiographie), craniosynostose

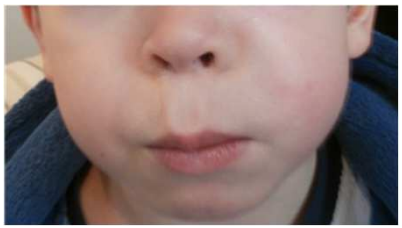
Manifestations orale très sévères





Biochimie :
Hypophosphatémie
Taux de calcium normal ;
taux de PTH normal ou légèrement élevé





Caractéristiques dentaires et XLH

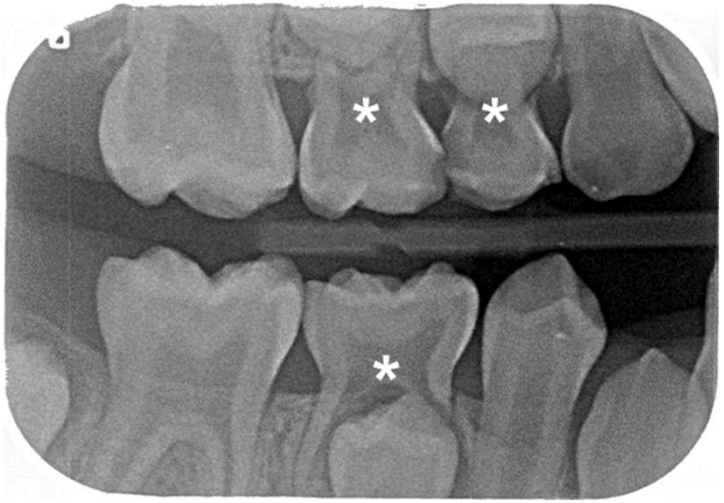
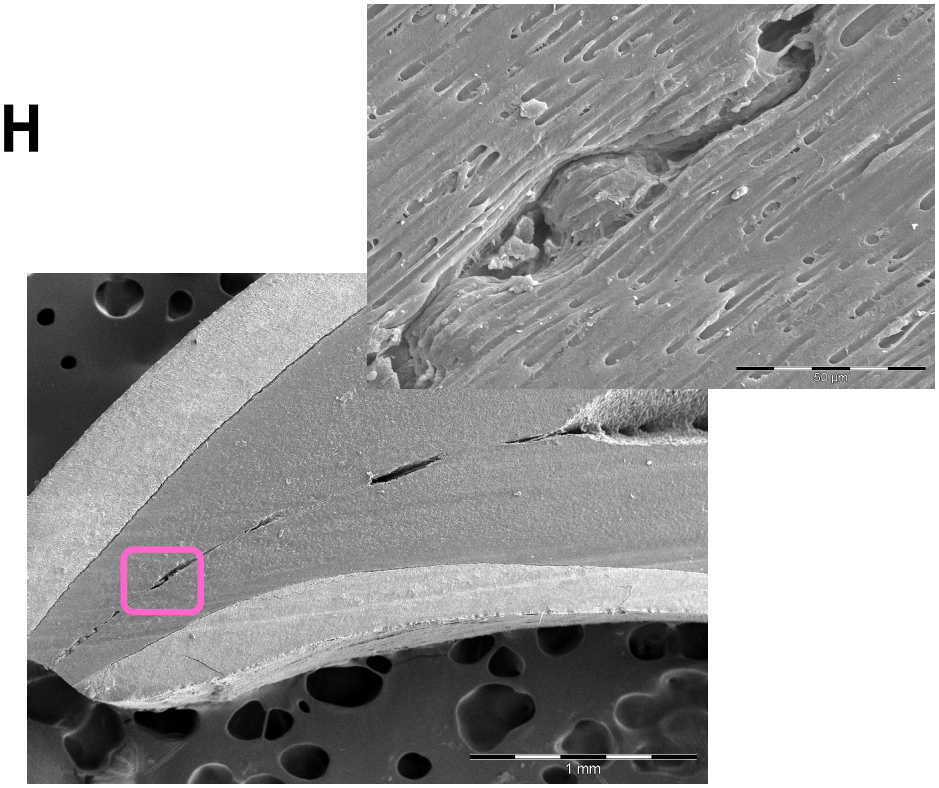
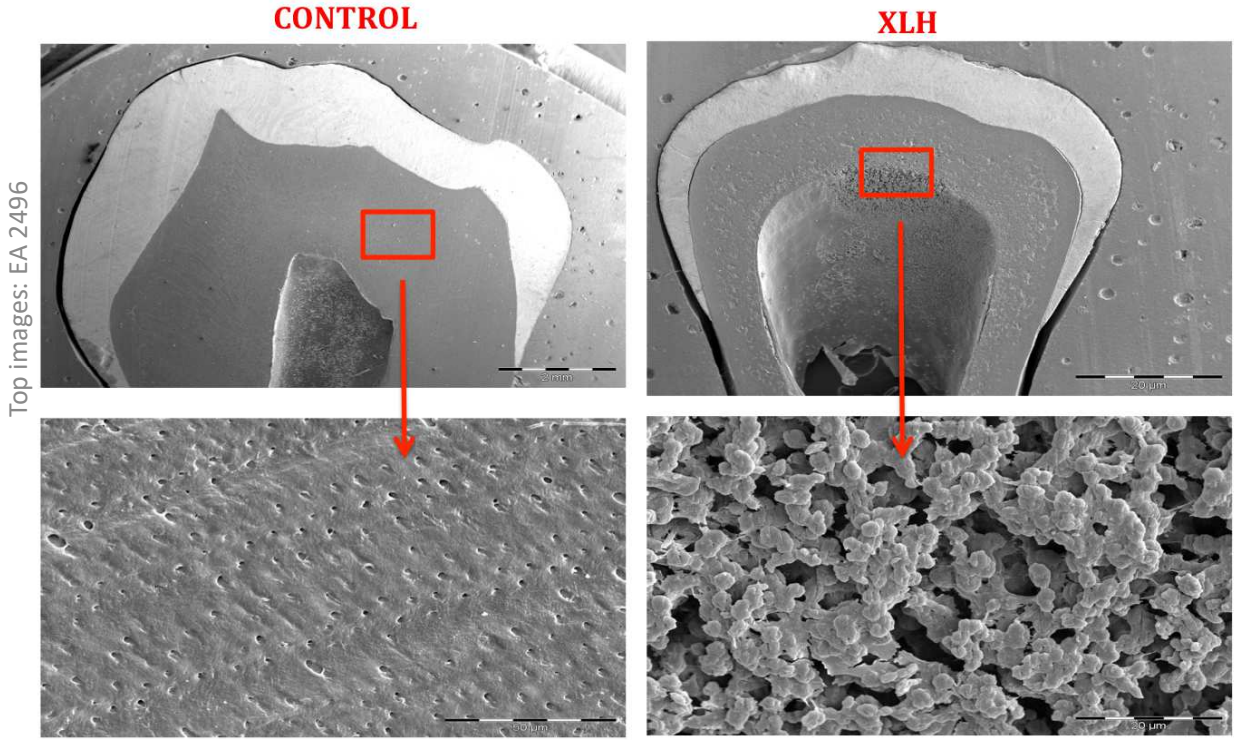


Image: APHP



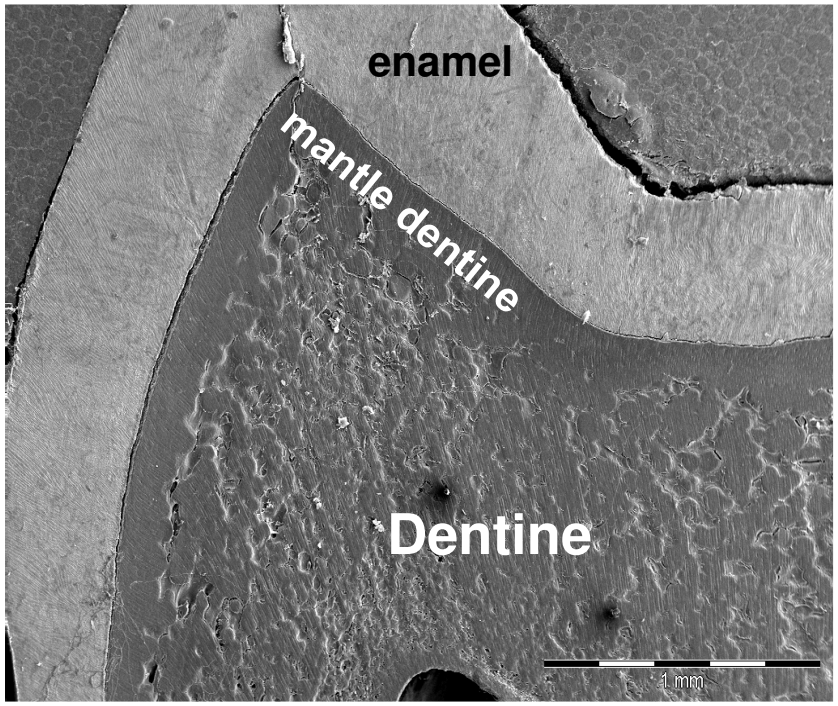
Émail fin : s'use assez rapidement et se fissure
Dentine à faible densité minérale avec des chambres pulpaires élargies
Cornes pulpaires proéminentes s'étendant jusqu'à la jonction émail-dentine

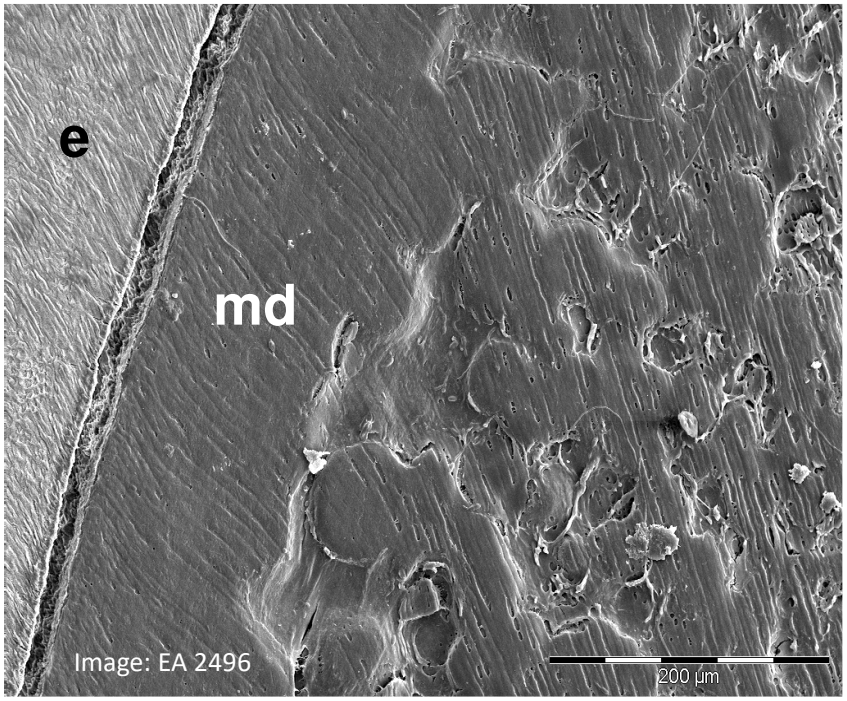
Caractéristiques dentaires et XLH



Dentinomalacie : hypominéralisation de la dentine avec des calcosphérites non fusionnées

Minéralisation dentaire et XLH





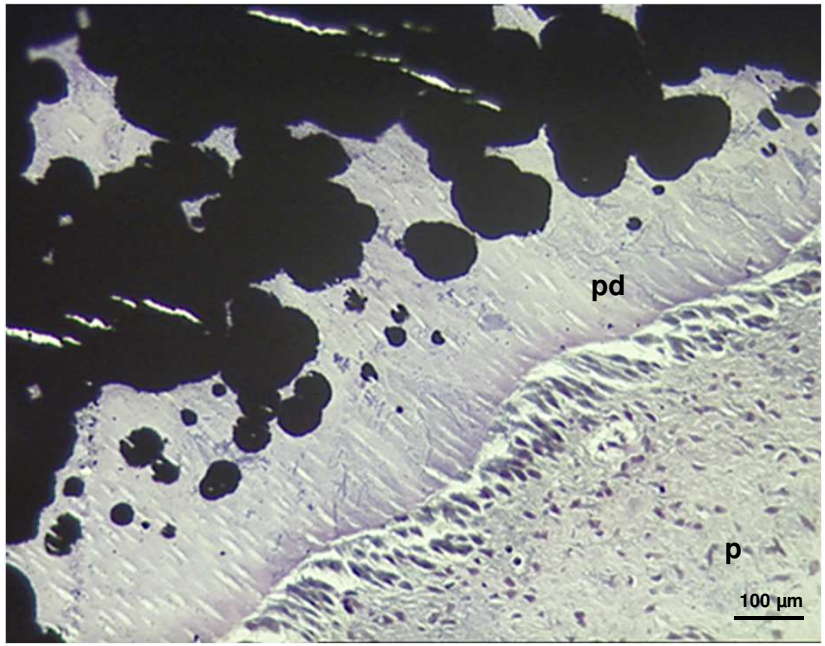
Dentinomalacie : lemanteau dentinaire n'est pas touché

Boukpessi *et al. Calcif Tissue Int* 2006;79:294; Chaussain-Miller *et al. Oral Dis* 2007;13:482

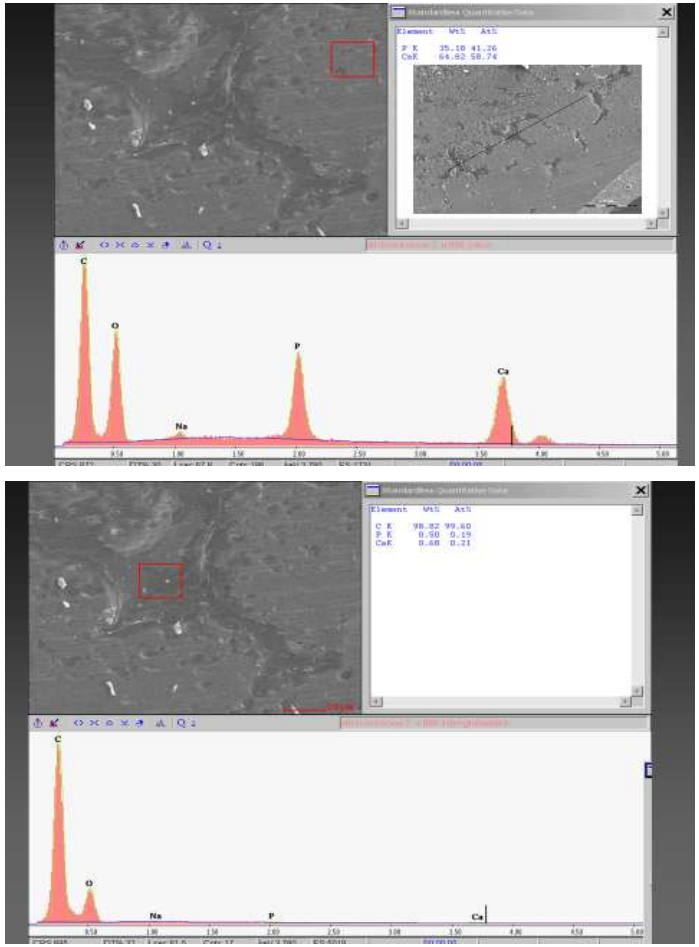
La minéralisation de la dentine est anormale

Coloration Von Kossa

Molaire XLH permanente



Dentinomalacie avec des calcosphérites non fusionnés et de vastes espaces interglobulaires non minéralisés



Identification de peptides MEPE ASARM dans la dentine des patients atteints de XLH

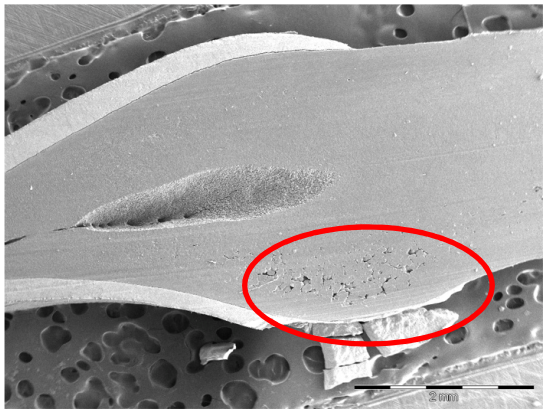
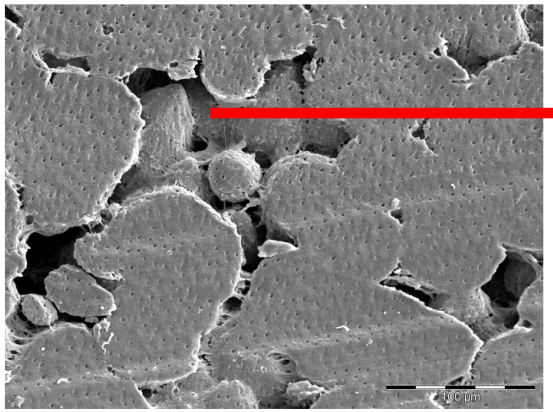


Image: EA 2496



MEPE-ASARM

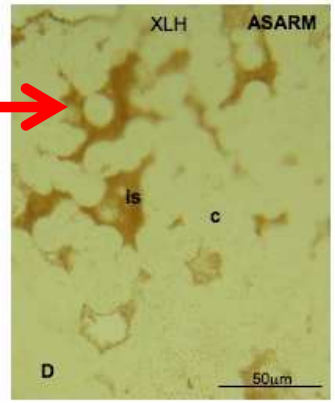


Image: EA 2496

Accumulation de composants dégradés de la matrice extracellulaire, notamment le collagène et les phosphoprotéines SIBLINGs (Small Integrin Binding LIgand N-Glycoproteins) : DSP, DMP1, BSP, OPN, MEPE

MEPE-ASARM est élevé dans le sérum des patients atteints de XLH et dans les reins des souris HYP

Human-MEPE NKGMPQGKGSWGRQPHSNRRFSSRRRDDSSESSDSGSSSESDGD

472 — ASARM-motif

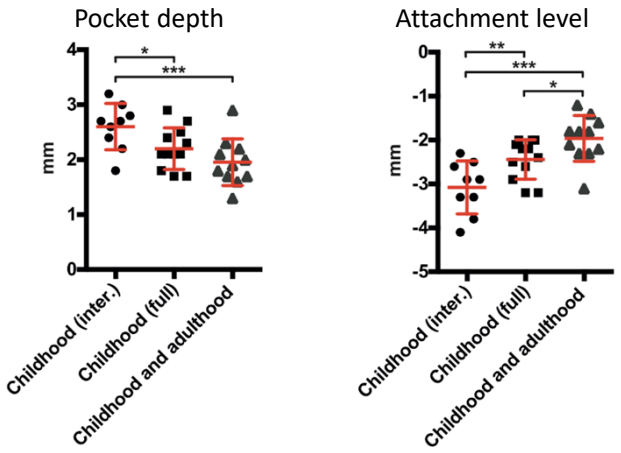
525

Région C terminale

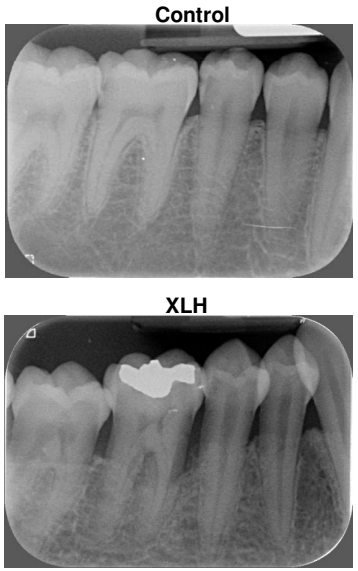
Boukpessi et al, Calcified Tissues Int 2007; Gaucher *et al. Cells Tissues Organs* 2009;189:219;
Boukpessi *et al. Am J Pathol* 2010;177:803; Salmon et al. 2013 Plos One

XLH et parodonte

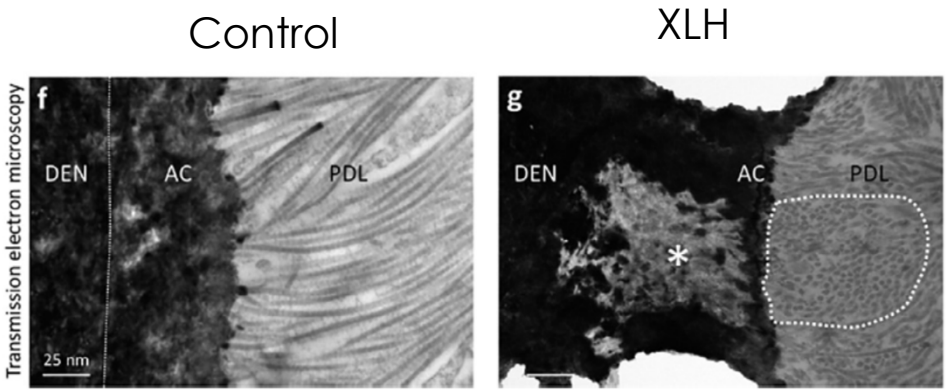
Les patients atteints de XLH sont plus sujets aux maladies parodontales.
Le traitement systémique permet d'améliorer l'état du parodonte.



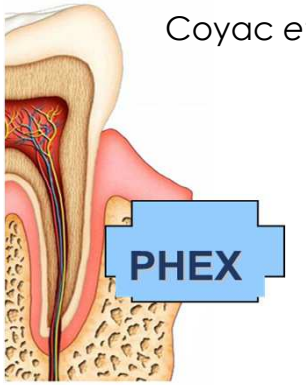
Biosse Duplan *et al. J Dental Res* 2017;96:388



La « cémentomalacie » altère l'ancrage de la dent.

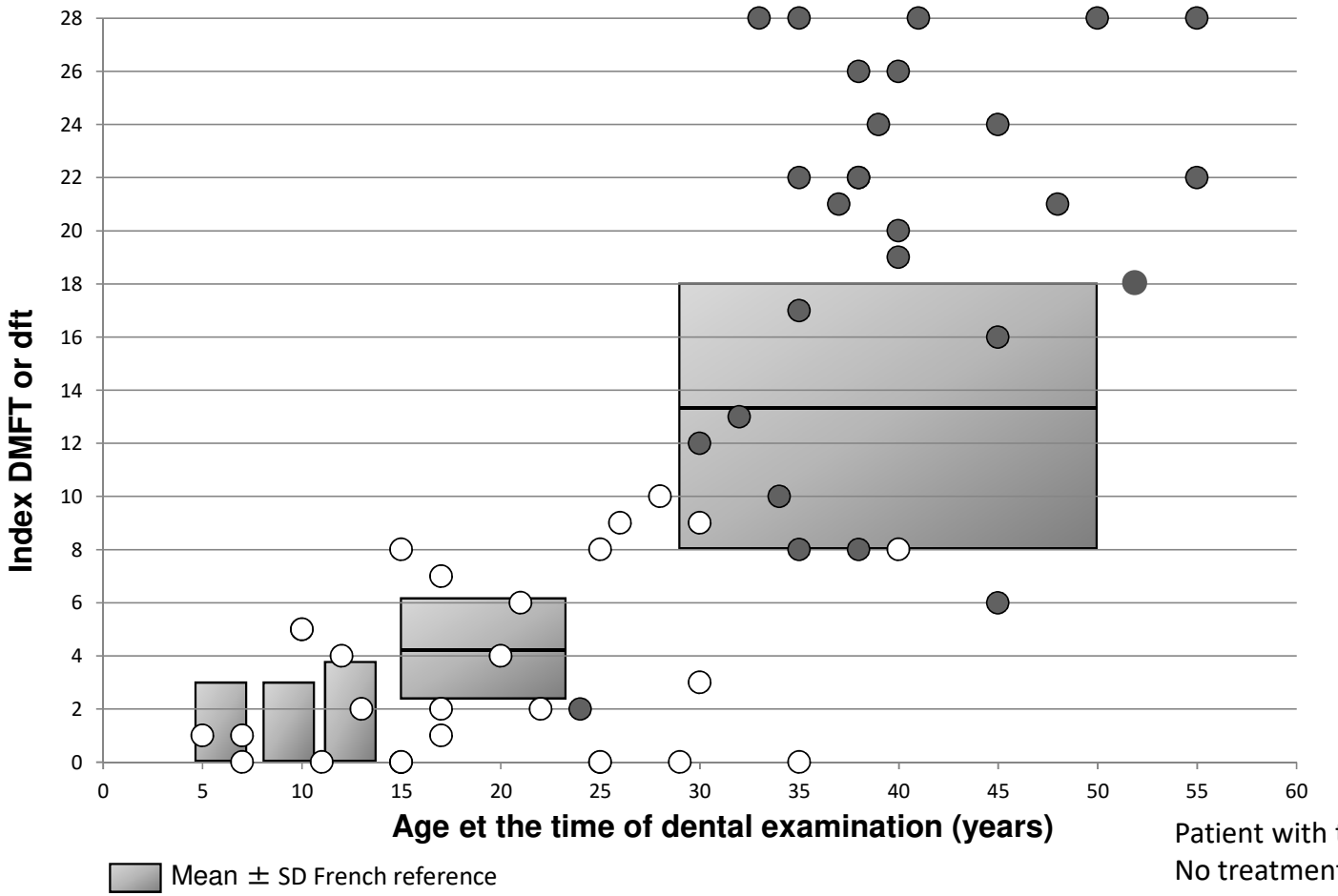


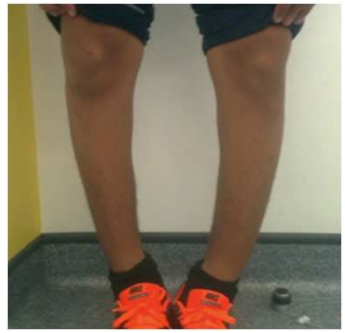
Coyac *et al. Bone* 2017;103:334-346



DENTAL ABNORMALITIES IN PATIENTS WITH FAMILIAL HYPOPHOSPHATEMIC VITAMIN D–RESISTANT RICKETS: PREVENTION BY EARLY TREATMENT WITH 1-HYDROXYVITAMIN D

CATHERINE CHAUSSAIN-MILLER, MD, CHRISTIANE SINDING, MD, MARYSE WOLIKOW, MD, PHD, JEAN-JACQUES LASFARGUES, MD, PHD, GASTON GODEAU, PHD, AND MICHÈLE GARABÉDIAN, MD, PHD



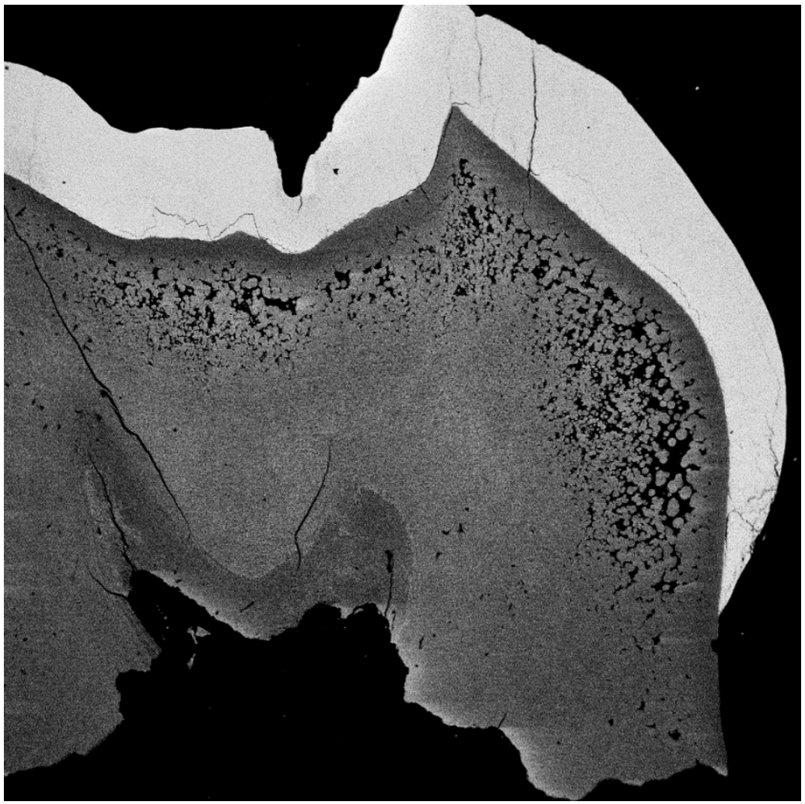


Patient with treatment growth

No treatment during growth

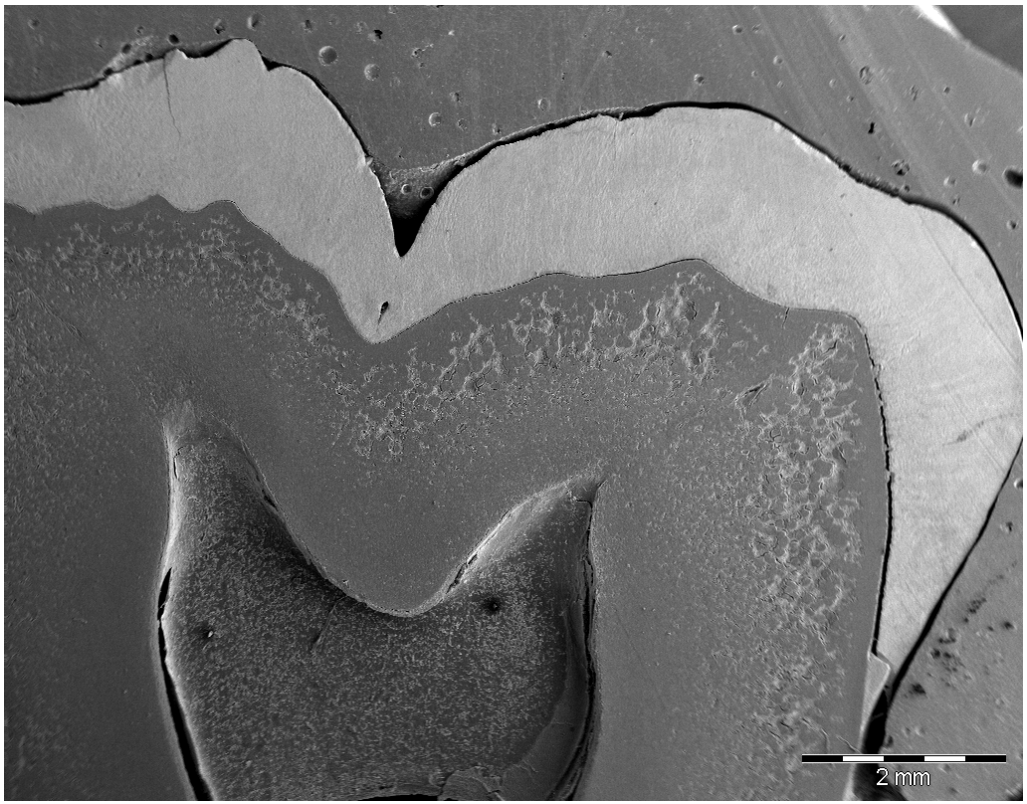
Un traitement conventionnel suivi rigoureusement depuis la petite enfance permet d'améliorer la dentinomalacie

Molaire de lait



84: 13 ans

Troisième molaire définitive



48: 17 ans

Effets du burosumab sur les dents XLH

Burosumab versus conventional therapy in children with X-linked hypophosphataemia: a randomised, active-controlled, open-label, phase 3 trial

Erik A Imel, Francis H Glorieux, Michael P Whyte, Craig F Munns, Leanne M Ward, Ola Nilsson, Jill H Simmons, Raja Padidela, Noriyuki Namba, Hae Il Cheong, Pisit Pitukcheewanont, Etienne Sochett, Wolfgang Högler, Koji Muroya, Hiroyuki Tanaka, Gary S Gottesman, Andrew Biggin, Farzana Perwad, Meng Mao, Chao-Yin Chen, Alison Skrinar, Javier San Martin, Anthony A Portale

	Conventional therapy (n=32)	Burosumab (n=29)
Total adverse events	27 (84%)	29 (100%)
Dental caries	2 (6%)	9 (31%)
Tooth abscess	3 (9%)	8 (28%)

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64 semaines de traitement

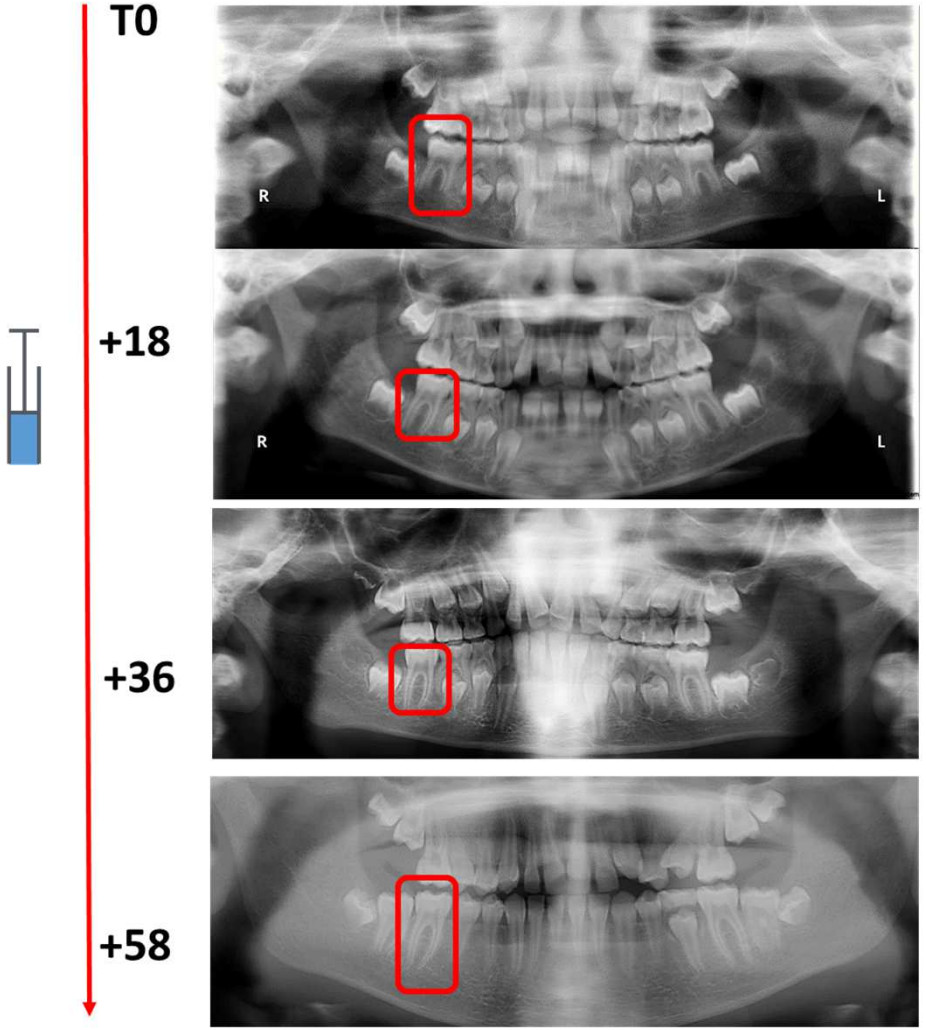
The Journal of Clinical Endocrinology & Metabolism, 2022, **XX**, 1–13
https://doi.org/10.1210/clinem/dgac296
Advance access publication 09 May 2022
Clinical Research Article

Effect of Burosumab Compared With Conventional Therapy on Younger vs Older Children With X-linked Hypophosphatemia

Leanne M. Ward,[1] Francis H. Glorieux,[2] Michael P. Whyte,[3] Craig F. Munns,[4,5] Anthony A. Portale,[6] Wolfgang Högler,[7,8] Jill H. Simmons,[9] Gary S. Gottesman,[3] Raja Padidela, Noriyuki Namba,[11,12] Hae Il Cheong,[13] Ola Nilsson,[14,15] Meng Mao,[16] Angel Chen,[16] Alison Skrinar,[16] Mary Scott Roberts,[16] and Erik A. Imel[17]

Dental abscesses occurred in 3 of 12 (25%) younger children who received Pi/D compared with 0 of 20 (0%) of the younger children who received burosumab, whereas 8 of 15 (53%) older children who received burosumab had dental abscesses compared with 0 of 20 (0%) who received Pi/D. Dental caries, which were reported more frequently with burosumab than Pi/D (9/29 [31%] vs 2/32 [6%]), occurred slightly more often in older than younger children who received Pi/D (2/20 [10%] vs 0/12 [0%]) and slightly more often in younger than older children who received burosumab (5/14 [36%] vs 4/15 [27%]). Other reported AEs, such as constipation, diarrhea,

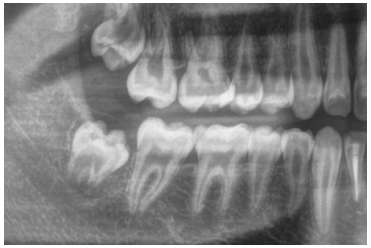
Effet du burosumab sur la minéralisation des dents XLH



Anti-FGF23 antibody

Images: APHP

Patiente XLH ayant débuté à 7 ans le burosumab



RESEARCH ARTICLE

JBMR PLUS Open Access ASBMR

Burosumab and Dental Abscesses in Children With X-Linked Hypophosphatemia

Margaux Gadion,[1,2] Agathe Hervé,[1,2] Julia Herrou,[1,3] Anya Rothenbuhler,[4] Violaine Smail-Faugeron,[1,2] Frédéric Courson,[1,2] Agnès Linglart,[4,5] Catherine Chaussain,[1,2,6] and Martin Biosse Duplan[1,2,7]

71 enfants

Âge moyen ± (écart-type) au début du suivi dentaire : **7,86 ± 3,76 ans**.

53,5 % sous TC, 46,5 % sous burosumab

Tous les enfants traités par burosumab avaient déjà été traités par TC

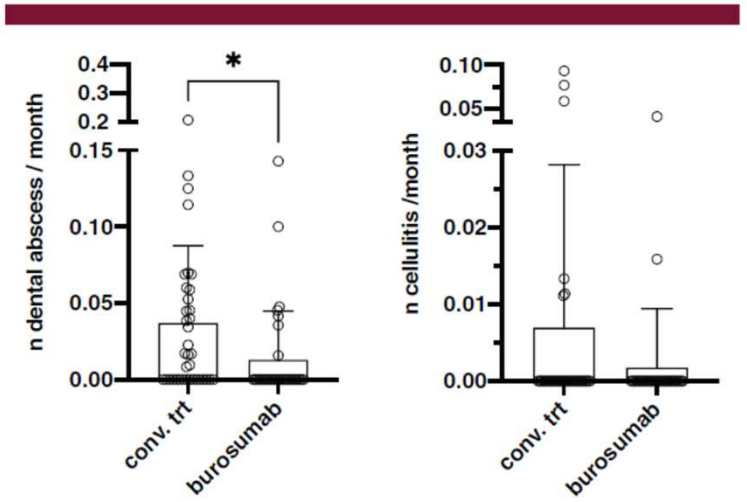


Fig. 1. Comparison of the mean number of abscesses (*A*) and cellulites (*B*) per month of dental follow-up in patients treated with conventional treatment or burosumab. Each point represents a child included in the study. Bars represent SD; *indicates $p < 0.05$.

Durée de traitement : TC 97.9 mois ± 46.9 Bursosumab 38.9 mois ± 29.0

Messages à retenir

- ✓ Le phénotype dentaire doit être étudié dans le cadre d'une maladie rare liée au métabolisme minéral.
- ✓ L'étude de la minéralisation dentaire met en évidence de nouveaux mécanismes de ces maladies.
- ✓ L'étude de la minéralisation dentaire peut aider à évaluer l'impact du traitement général.
- ✓ **Un chirurgien-dentiste doit faire partie de l'équipe multidisciplinaire**.
- ✓ Les patients ont besoin d'un suivi dentaire spécifique et régulier, assorti de soins adaptés, afin de prévenir les infections et la perte précoce des dents, et de réparer les dommages esthétiques et fonctionnels.

- Claire Bardet
- Fernando Ramirez Rozzi
- Thé Nghia Nguyen
- Nicolas Obtel
- Anne-Laure Lakhel
- Tchilalo Boukpessi
- Martin Biosse Duplan
- Frédéric Courson
- Elvire Le Norcy
- Violaine Smail Faugeron
- Olivier Hue
- Céline Gaucher
- Benjamin Salmon
- Philippe François, Matthieu Izart,
- Margot Gadion, Agathe Hervé

- Amina Attia
- Franceska Kovaci
- Lotfi Slimani
- Maya Baroukh
- Asmaa Foda
- Coralie Torrens
- Jerome Ligier
- Baptiste Casel

National Reference Center:

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- Anya Rothenbulher
- Peter Kaminicky
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- JP Bertocchio
- Eric Pasmant
- Karine Briot
- Justine Bacchetta
- Arnaud Molin
- Caroline Bertoye
- Cécile Ghander

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Pr Dominik Muller and Tilman Breiderhoff, La Charité , Berlin
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Dr Adeline Le Cabec, CNRS Bordeaux
Pr M. Deladure, Pr A. Berdal, Dr Lisa Friedlander, FHU DDS-net, Filière Tète et Cou
Pr A. Bloch Zupan, Filière Tète et Cou