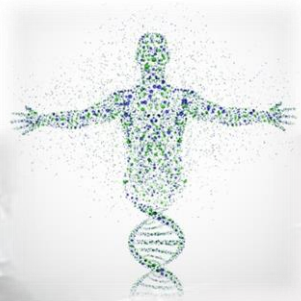
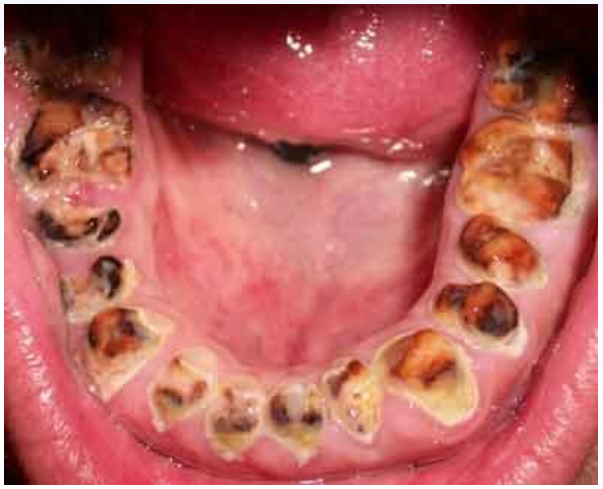
Developmental Disturbances in Tooth Formaton: Special Needs

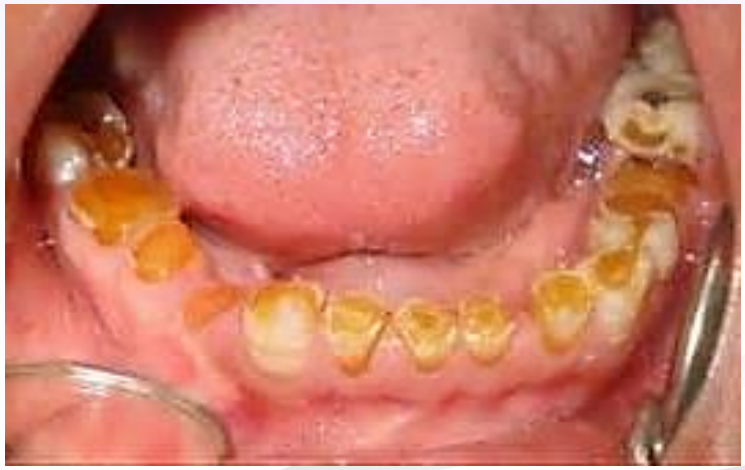
John J. Sauk DDS, MS Dean & **Professor**
University of Louisville

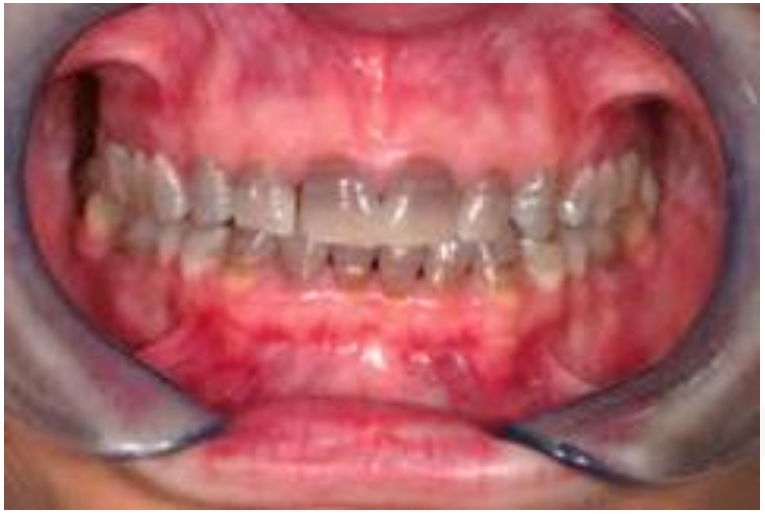
Interprofessional Collaboration &Care

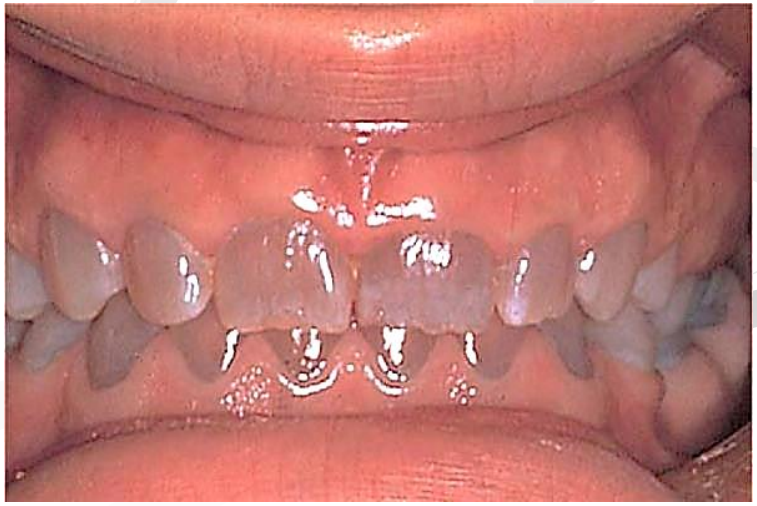


First Look!

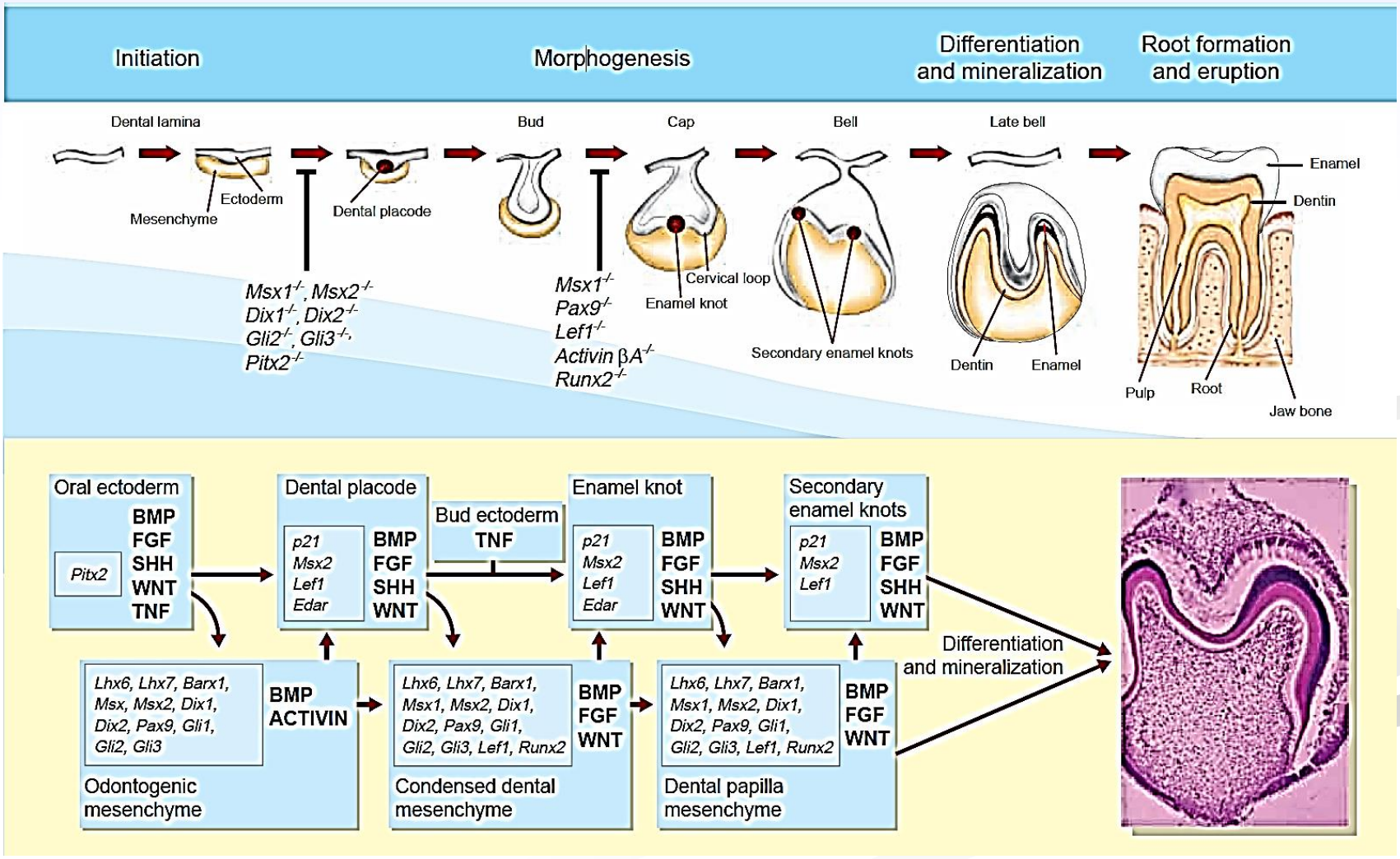




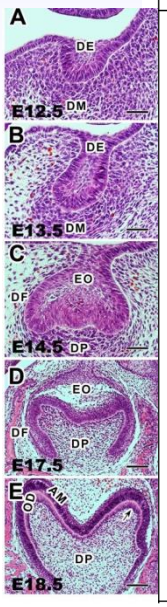




Signaling in Tooth Development



Stages of Tooth Development



Stage of tooth development	Protein factors involved in signaling from epithelium	Protein factors involved in signaling from mesenchyme
Initiation Stage	Fgfs, Bmps, Shh, Pitx2 and Wnts	Pax9, Ptc, Msx1, Msx2, Bmp4, Lhx6, Lhx7, Lef1, Dlx1, Dlx2,Gli1,Gli2, Gli3 and Barx1
Bud Stage	Bmp, Fgf, Wnts, Shh, Pdgf, p21, Msx2, Lef1 and Tgf-β	Pax9, Bmp, Dlx1, Dlx2, Lhx6, Lhx7, Msx1, Lef1, Gli1,Gli2, Gli3, Barx1 and Fgfs
Cap Stage	Bmp, Fgf, Wnts, Shh, Pdgf, p21, Msx2, Lef1 and Tgf-β	Pax9, Bmp, Dlx1, Dlx2, Lhx6, Lhx7, Msx1, Lef1, Gli1,Gli2, Gli3, Barx1, Bmp4, Msx2 and Fgfs
Bell Stage		

Developmental Disturbances in Tooth Formaton

- Some genes affecting early tooth development (MSX1, AXIN2,PAX9, LTBP3,EDA) are associated with tooth agenesis and systemic features (cleft palate, colorectal cancer).
- By contrast, genes involved in enamel (AMELX, ENAM, MMP20, and KLK4) and dentin (DSPP) structures are highly specific for tooth formation.



Genes Associated with Tooth Agenesis

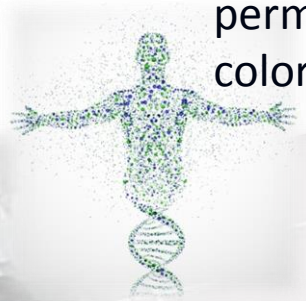
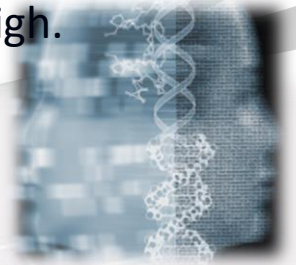
Gene involved	Mutations of Genes associated with agenesis	Defect	Mode of transmission
MSX1	M61K, S105X, Q187X, R196P & S202X	Hypodontia Hypodontia Oligodontia	Autosomal dominant Autosomal recessive Autosomal dominant
PAX9	K114X, L21P, R26W, R28P, G51S, K91E, G73fsX316, V265fsX316 & R59fsX177	Molar hypodontia Oligodontia Peg shaped laterals	Autosomal dominant Autosomal dominant Autosomal dominant
AXIN2	Arg656Stop, 1994-1995insG	Incisor agenesis	Uncertain
LTBP3	Y774X	Oligodontia	Autosomal recessive
EDA	Thr338Met	Hypodontia	X linked recessive



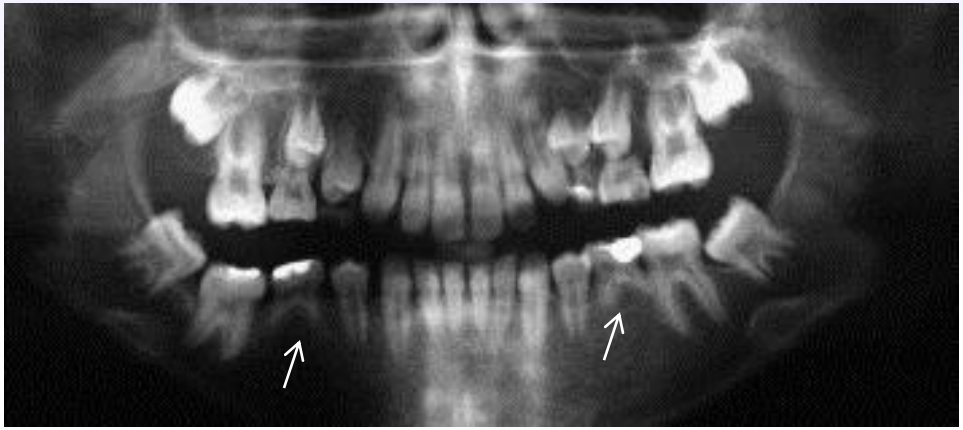
Non-syndromic oligodontia

- Oligodontia with mutations in *MSX1* (4p16.1)
- Oligodontia with mutations in *PAX 9* (14q12–q13)
- Oligodontia with mutations in *AXIN 2* (17q23–24)
- Oligodontia with locus mapped to chromosome 10q11.2

- Mutations in the homeobox gene *MSX1* lead to specific hypo/oligodontia. Second premolars and third molars are the most commonly affected teeth
- Mutations in the transcription factor gene, *PAX9*, lead to absence of most permanent molars with or without hypodontia in primary teeth.
- Mutations in *AXIN2* cause tooth agenesis and colorectal cancer (OMIM 608615). The patients who carry the mutation lack 8–27 permanent teeth. Penetrance of colorectal cancer is very high.

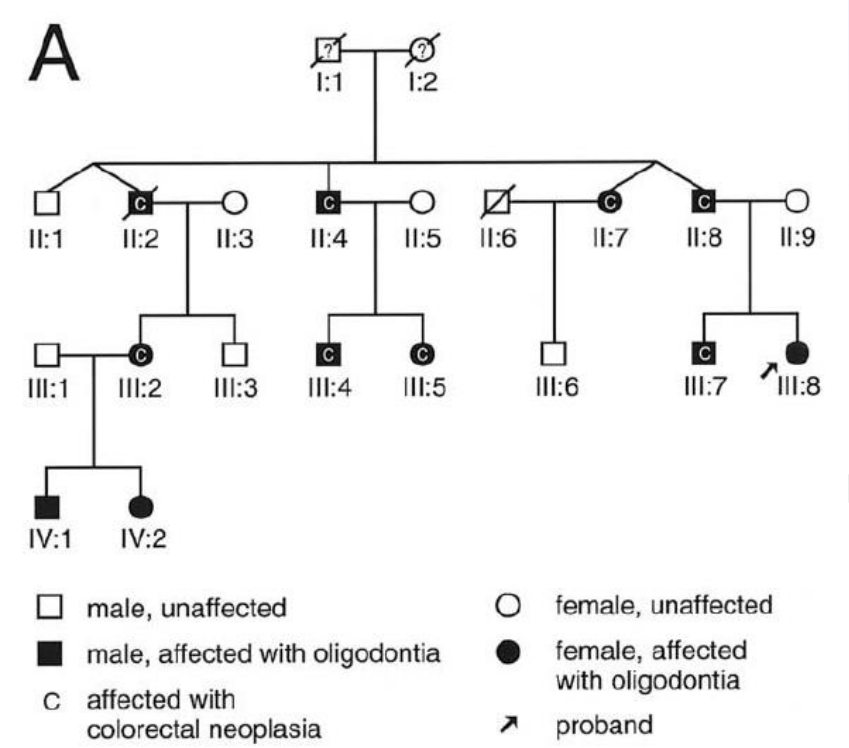
MSX1 (4p16.1)

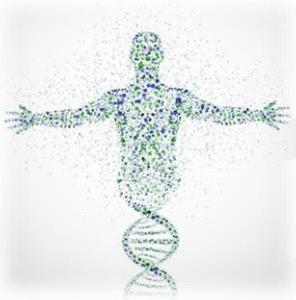


Congenital agenesis of second premolars at the lower jaw orthopantomogram.

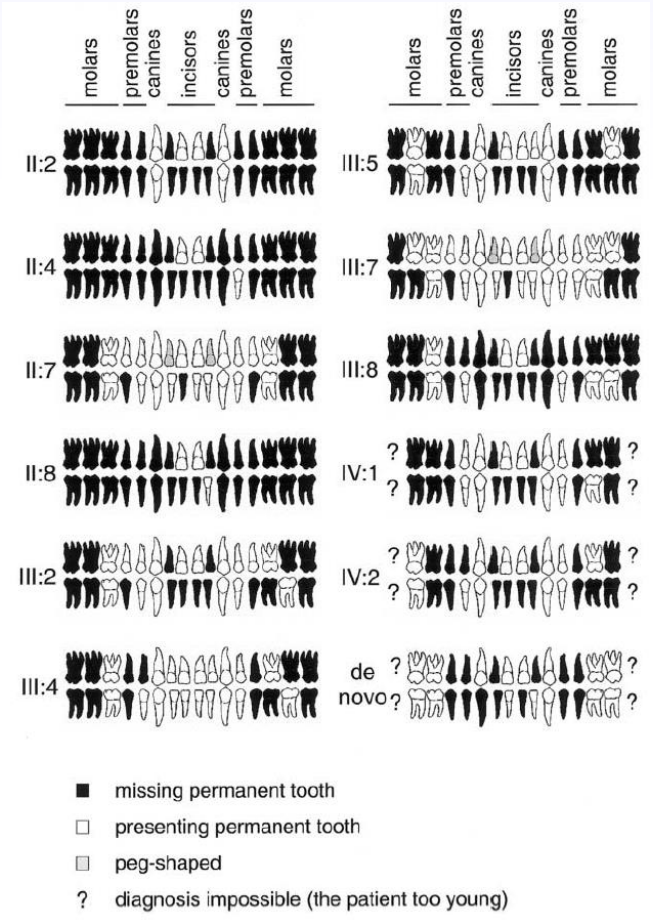
Mutations in AXIN2 cause familial tooth agenesis and predispose to colorectal cancer

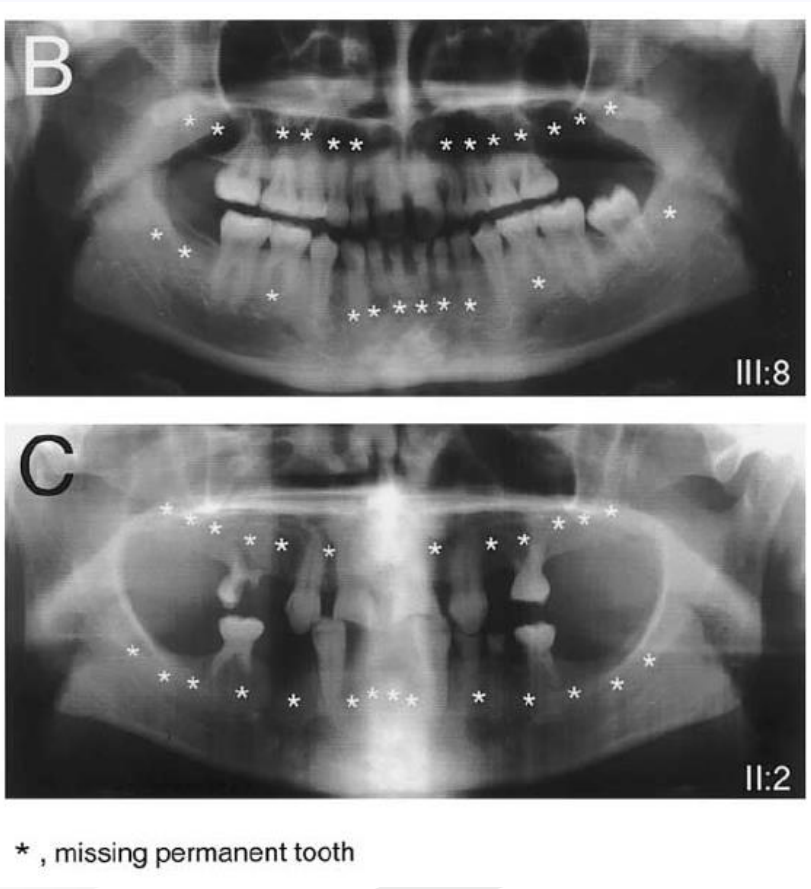
- Severe permanent tooth agenesis (oligodontia)
- Colorectal neoplasia
- Dominant inheritance
- Nonsense mutation Arg656Stop, in the Wnt-signaling regulator *AXIN2*





Mutations in AXIN2 cause familial tooth agenesis and predispose to colorectal cancer





Lammi L et al. Am. J. Human Genet. 74 (2004) pp. 1043-1050.

Hypodontia as a risk marker for epithelial ovarian cancer
Leigh A. Chalothorn, et al. JADA, 2008.

Genetic analysis of the genes of interest is necessary to explore similarities between hypodontia and EOC further. An association could allow hypodontia to serve as a potential risk marker for EOC.

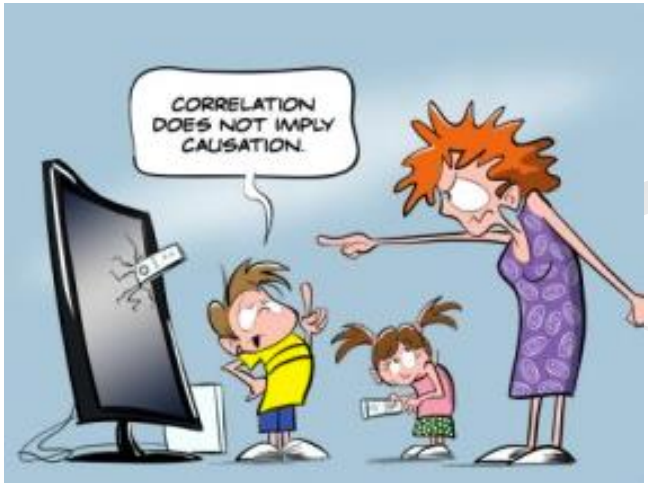
Is there a link between ovarian cancer and tooth agenesis?
John Bonds et al. Eur. Jol of Medical Genetics, 2014

This study…*revealed evidence that one half of the dually affected patients had an independent causation of the two conditions, thus reducing the previously estimated ovarian cancer risk for women with congenital tooth agenesis quite significantly.*

…we know that the investigated genes represent only a minority of all the possible candidates that may be involved in hypodontia and it would certainly be worthwhile to investigate additional genes which are commonly associated with ovarian cancer such as BRCA2, BRCA-interacting protein, ErbB2 and p53, for example, which are also quite strongly expressed in the tooth bud of developing mouse embryos [Diez-Roux et al., 2011].

Kutcher EC et al. J Dent Res. 2013 Feb;92(2):149-55
In conclusion, tooth agenesis was associated with positive self-reported family history of cancer and with variants in *AXIN2, FGF3, FGF10*, and *FGFR2*.

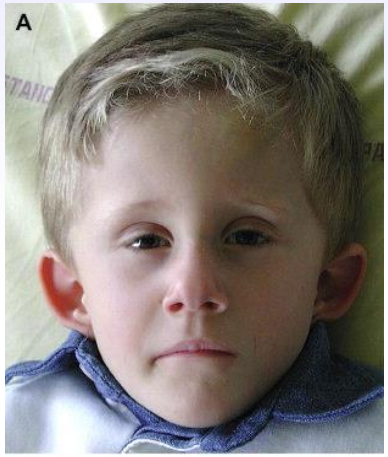
Correlation does not imply causation

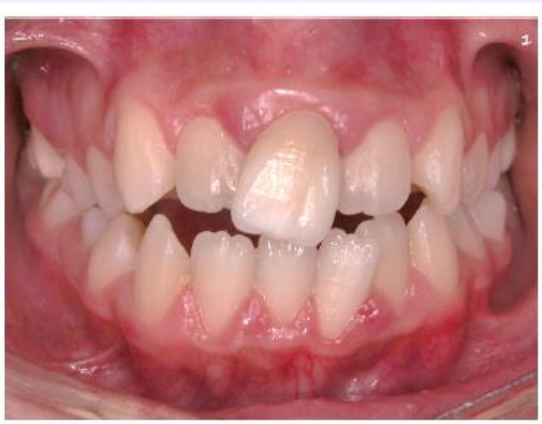


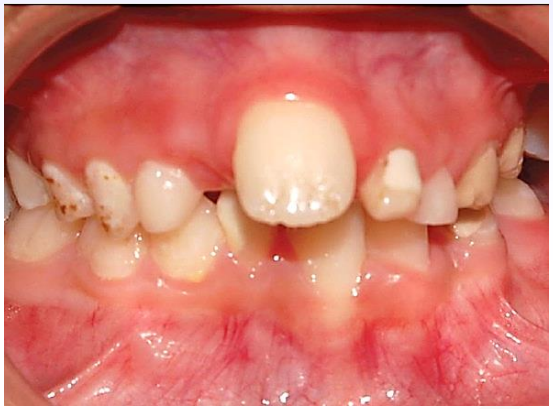
Syndromes with congenital absence of teeth

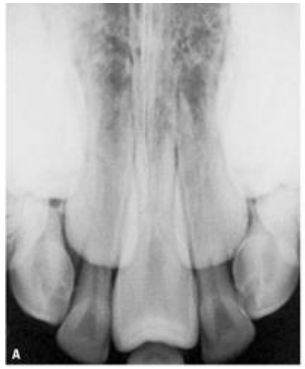
- Down syndrome
- Wolf-Hirschhorn syndrome
- Holoprosencephaly
- Kallmann syndrome
- Ectodermal dysplasias
  - Hypohidrotic ectodermal dysplasia
  - Incontinentia pigmenti, hypohydrotic ectodermal dysplasia, and immune deficiency (HED-ID)
  - P63 mutation related syndromes
- Lacrimo-auricular-dento-digital syndrome (LADD,OMIM 149730)
- Axenfeld-Rieger malformation and Rieger syndrome
- Johansson-Blizzard syndrome
- Wilkie oculo-facio-cardio-dental syndrome

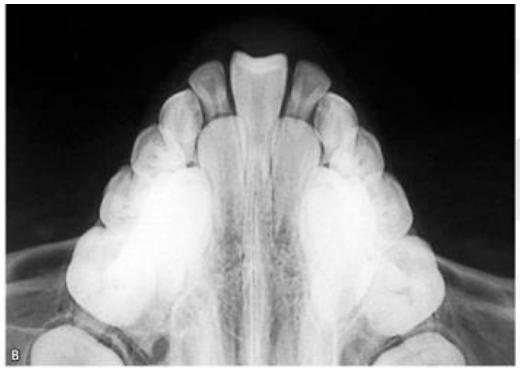
Holoprosencephaly











Holoprosencephaly: paucisymptomatic expression with solitary median maxillary central incisor. (A) Face and (B) Oral view of solitary maxillary central incisor.

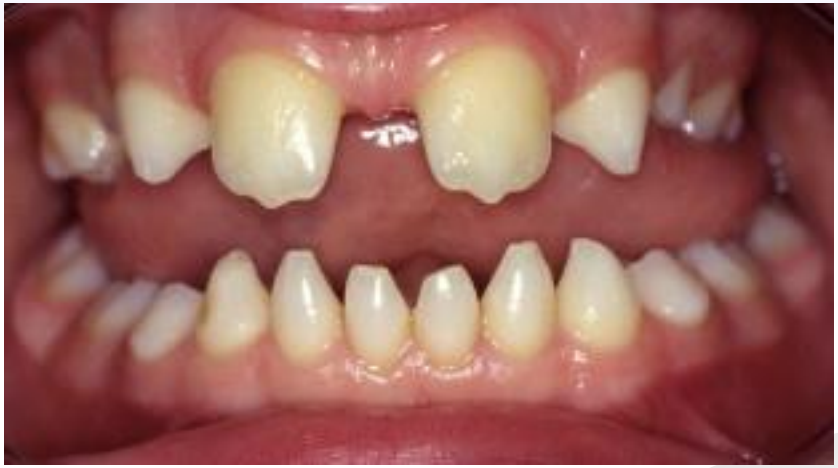
Isabelle Bailleul-Forestier , Ariane Berdal , Frans Vinckier , Thomy de Ravel , Jean Pierre Fryns , Alain Verloes
European Journal of Medical Genetics, Volume 51, Issue 5, 2008, 383 - 408
http://dx.doi.org/10.1016/j.ejmg.2008.05.003

“Ollie Syndrome”

Ectodermal dysplasias

- Ectodermal dysplasias form a large and complex group of disorders characterized by various combinations of defects in hair, nails, teeth and sweat glands, either isolated or associated with malformations.
- Of the approximatively 170 clinical types of ectodermal dysplasias described so far, a gene is identified in less than 30.

Ectodermal Dysplasias



Ectodermal dysplasia with abnormal-shaped, conical incisor and missing teeth.

Isabelle Bailleul-Forestier et al.

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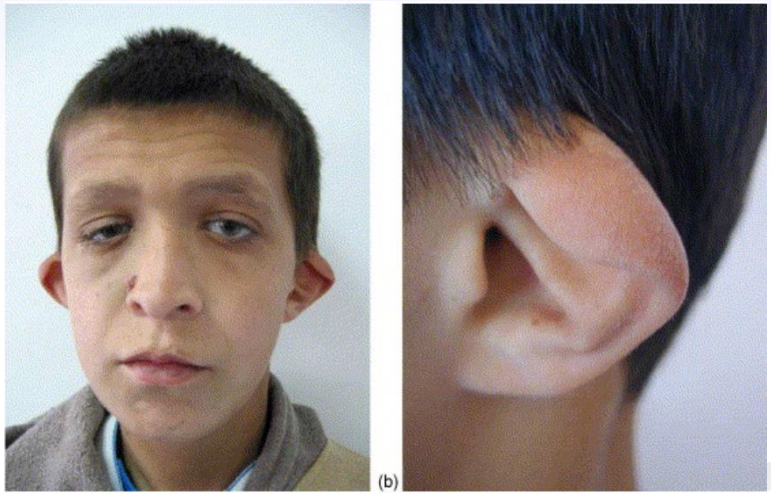
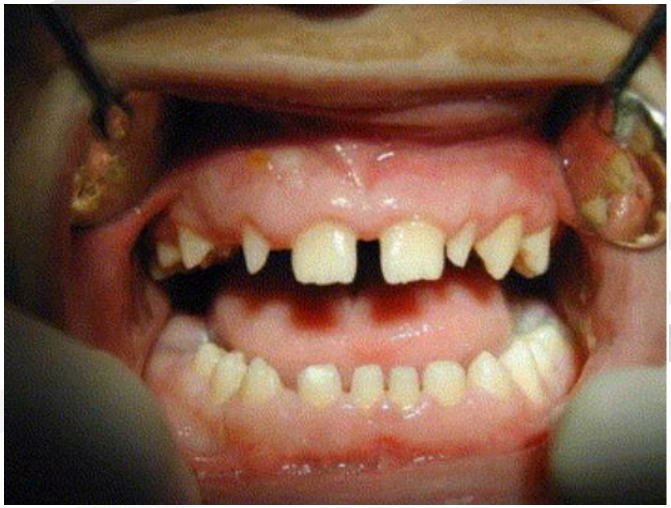
Lacrimo-auricular-dento-digital syndrome (LADD)

- LADD syndrome is characterized by defects in the tear-producing lacrimal system (lacrimo-), ear problems (auriculo-), dental abnormalities (dento-), and deformities of the fingers (digital).
- Ears that are low-set and described as cup-shaped
- **H**earing loss, are a common feature of LADD syndrome (sensorineural deafness), changes in the middle ear (conductive hearing loss), or both (mixed hearing loss).
- **U**nderdeveloped or absent salivary glands, which impairs saliva production. A decrease in saliva leads to dry mouth (xerostomia) and a greater susceptibility to caries.

Lacrimo-auriculo-dento-digital syndrome

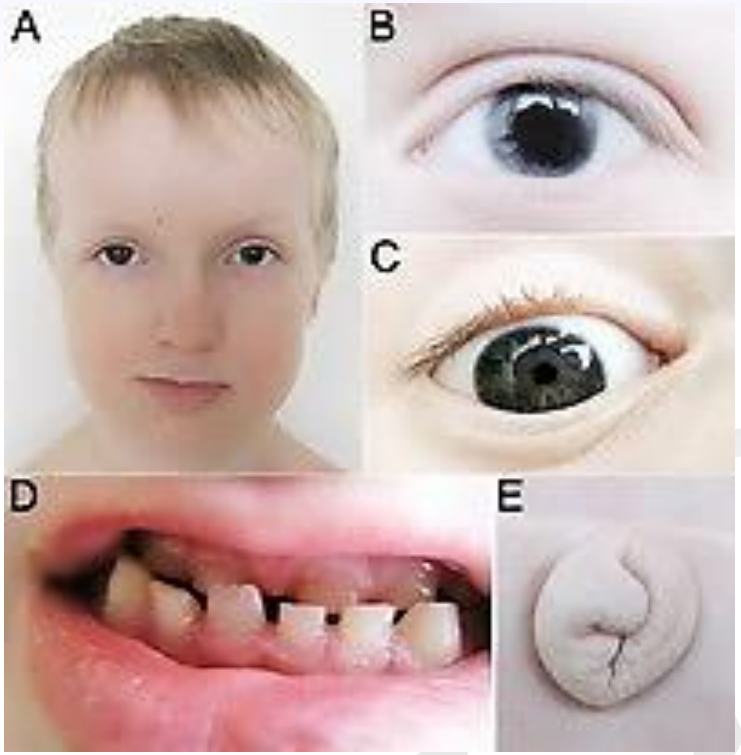
- Mutations in the FGFR2, FGFR3, or FGF10 genes.
- **N**ephrosclerosis and hydronephrosis.
- **C**left palate with or without cleft lip.
- **S**mall, underdeveloped teeth with thin enamel and peg-shaped front teeth (incisors).



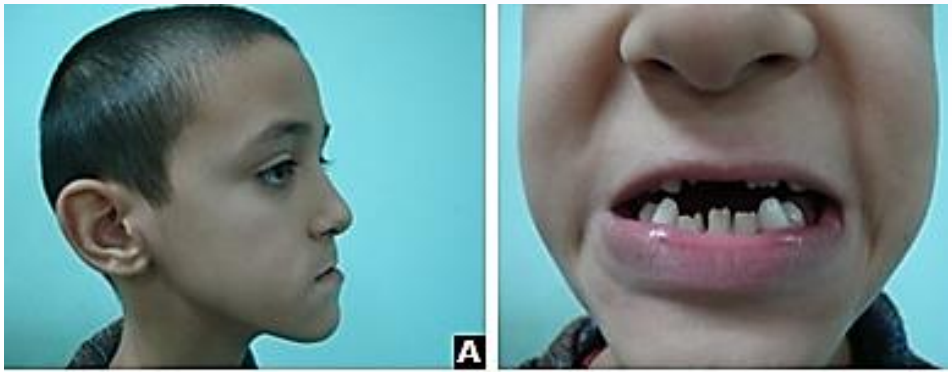


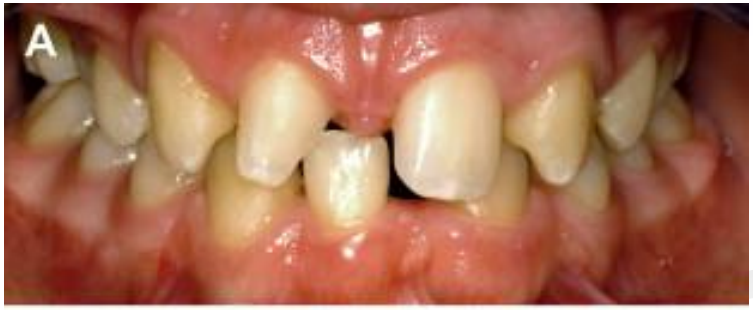
Axenfeld-Rieger malformation and Rieger syndrome

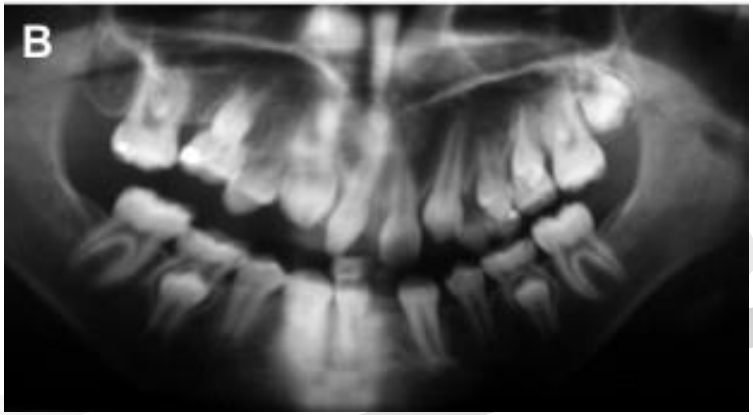
- The Axenfeld-Rieger malformation (ARM) consists of various anomalies of the anterior chamber of the eye.
- Fifty percent of affected individuals have a propensity to develop glaucoma.
- Rieger syndrome is - association of Axenfeld malformation with dental, craniofacial, and somatic anomalies, such as redundancy of periumbilical skin.

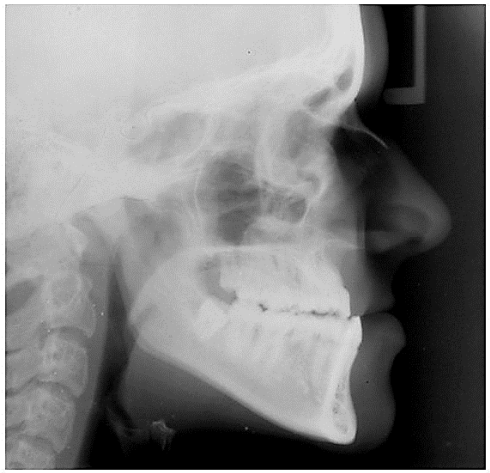


Axenfeld-Rieger malformation and Rieger syndrome



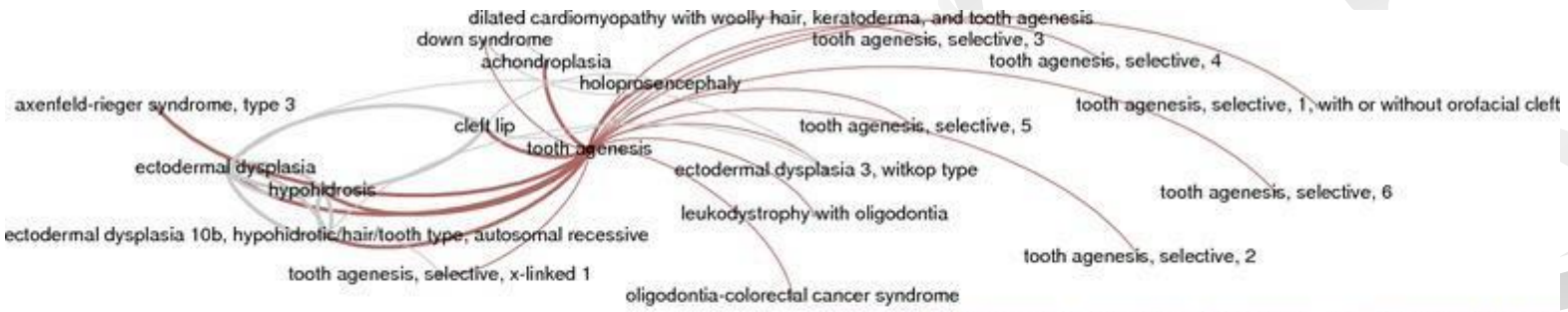






Syndromic Conditions Associated with Dental Agenesis (147)

id	Related Disease	Score	Top Affiliating Genes
1	ectodermal dysplasia	30.7	EDA, EDAR
2	ectodermal dysplasia 10b, hypohidrotic/hair/tooth type, autosomal recessive	30.4	EDAR, EDA, EDARADD
3	achondroplasia	30.3	FGF3
4	axenfeld-rieger syndrome, type 3	30.3	TGFA, PITX2
5	hypohidrosis	30.0	EDARADD, EDA, EDAR
6	cleft lip	29.9	BMP4, MSX1, IRF6, PAX9, TGFA, FGFR1
7	holoprosencephaly	29.5	BMP4, MNX1
8	tooth agenesis, selective, 1, with or without orofacial cleft	10.6	
9	tooth agenesis, selective, x-linked 1	10.4	
10	tooth agenesis, selective, 4	10.4	

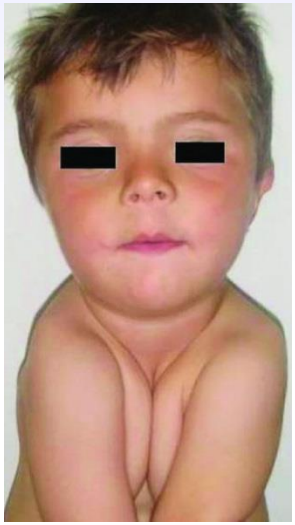


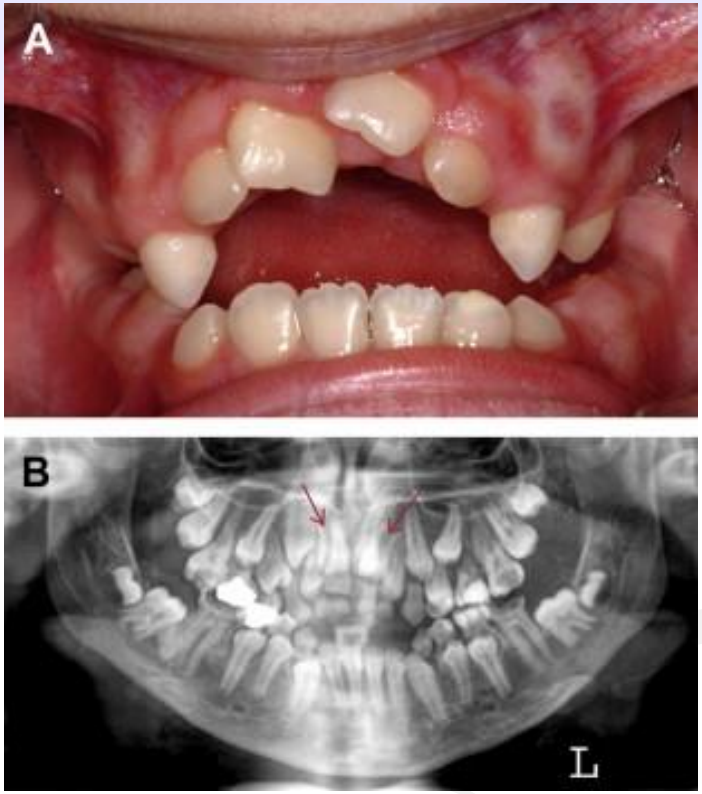
Syndromes Associated Supernumerary teeth (Hyperdontia)

- Apert
- Angio-osteohypertrophy
- Cleidocranial dysplasia
- Craniometaphyseal dysplasia
- Crouzon
- Curtis
- Down
- Ehlers-Danlos
- Ellis-van Creveld Syndrome
- Rubinstein-Taybi Syndrome
- Fabry-Anderson
- Fucosidosis
- Gardner
- Hallermann-Streiff
- Klippel-Trrenaunay-Weber
- Laband
- Oral-facial-digital, type I, and III
- Nance-Horan
- Sturge-Weber
- Tricho-rhino-pharyngeal

Syndromes with supernumerary teeth (hyperdontia)

- Cleidocranial dysplasia is an AD disorder affecting bone and teeth development and is caused by mutations in RUNX2, a gene encoding an osteoblast-specific transcription factor which maps to 6p21 (OMIM 119600).
- The symptoms include hypoplastic calvarial bones and clavicles.
- Dental abnormalities include supernumerary teeth (sometimes leading to a ‘‘third dentition’’), delayed eruption, failure of exfoliation of the primary dentition, and malocclusion





Cleidocranial dysplasia. (A) Oral view after treatment, with open bite (B) orthopantomogram before treatment showing unerupted supernumerary teeth (arrows) (C) brachycephaly, hypertelorism, and small upper jaw.

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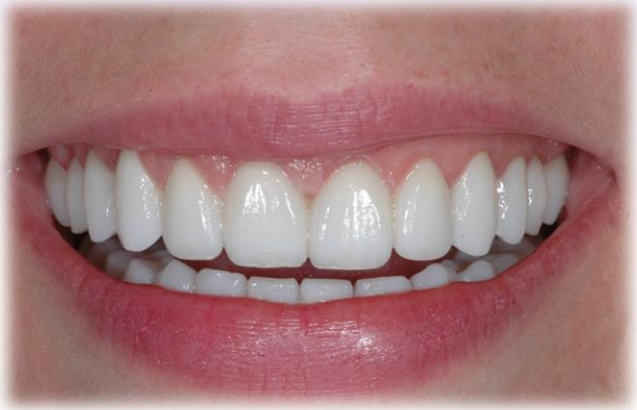
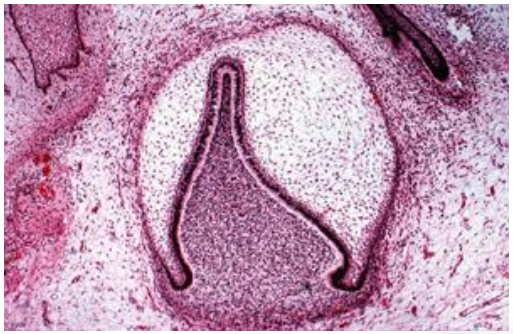
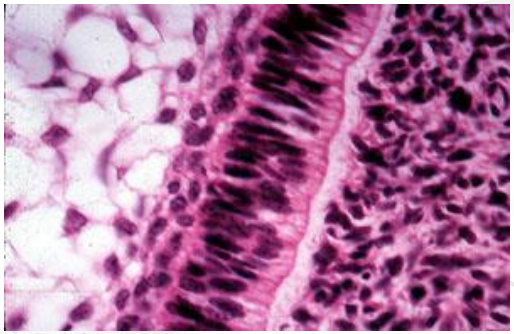
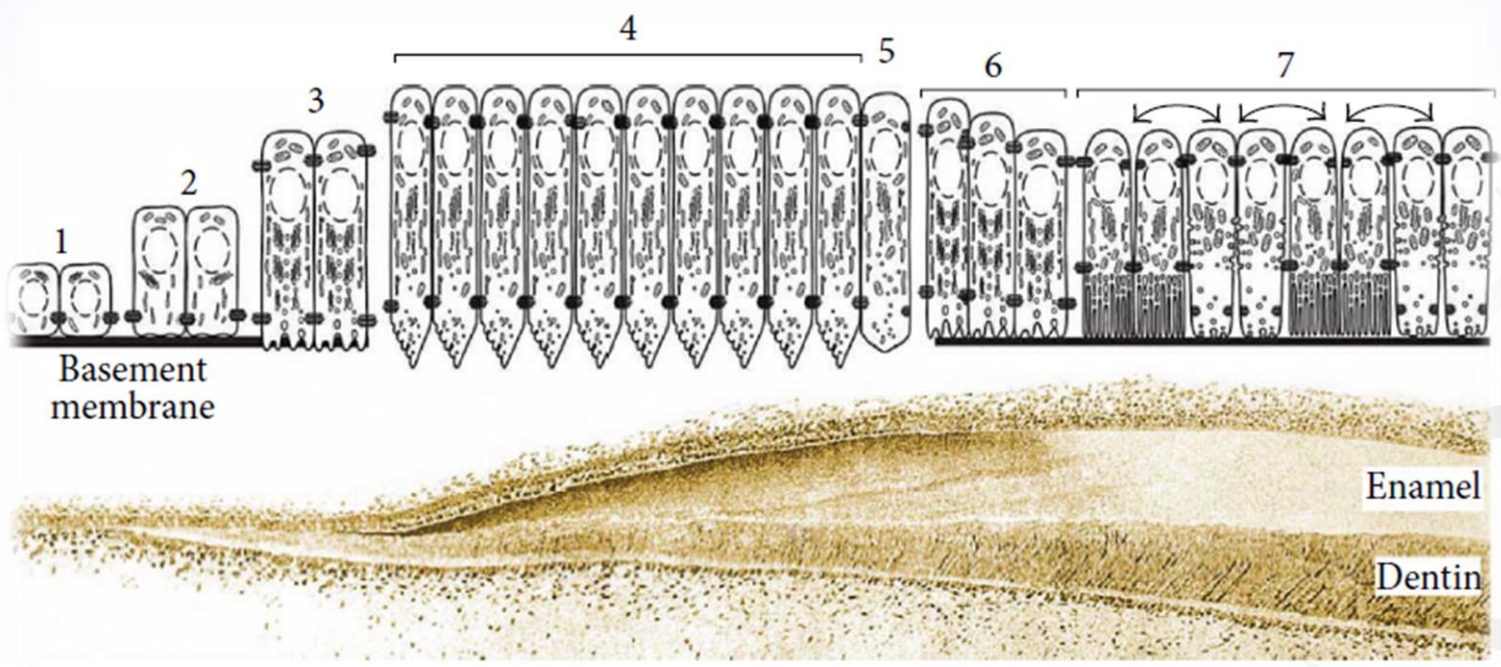
Amelogenesis

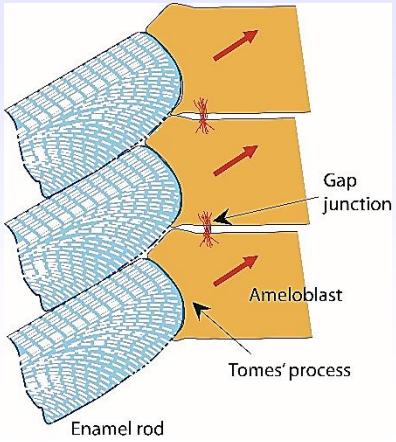


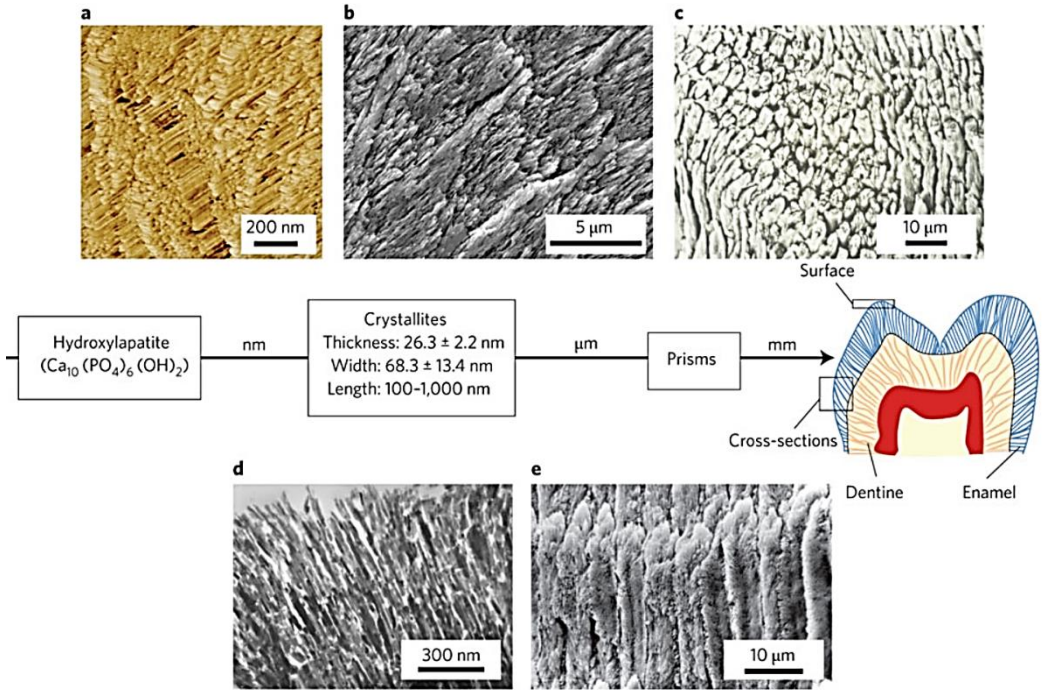




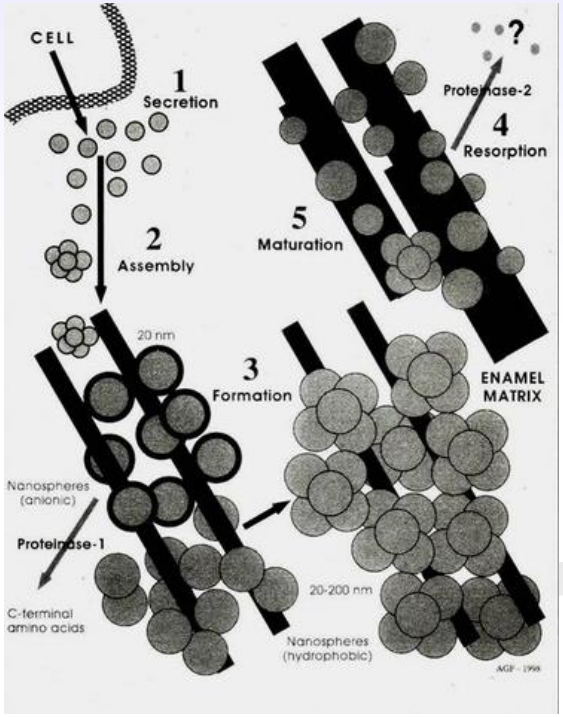
Enamel Formation

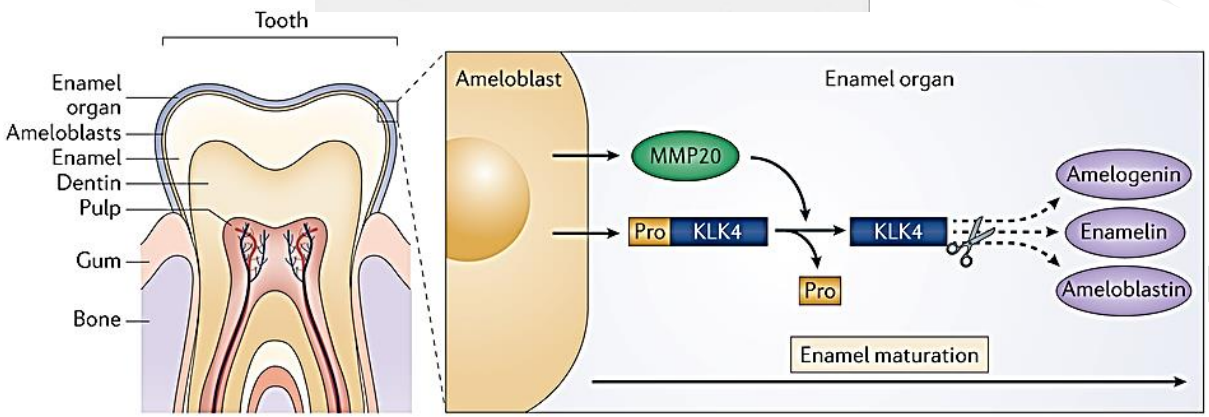



Gap
junction
Ameloblast
Tomes' process
Enamel rod


a
200 nm
b
5 µm
c
10 µm
Hydroxylapatite
(Ca10 (PO4)6 (OH)2)
nm
Crystallites
Thickness: 26.3 ± 2.2 nm
Width: 68.3 ± 13.4 nm
Length: 100–1,000 nm
µm
Prisms
mm
Surface
Cross-sections
Dentine
Enamel
d
300 nm
e
10 µm

Enamel Maturation





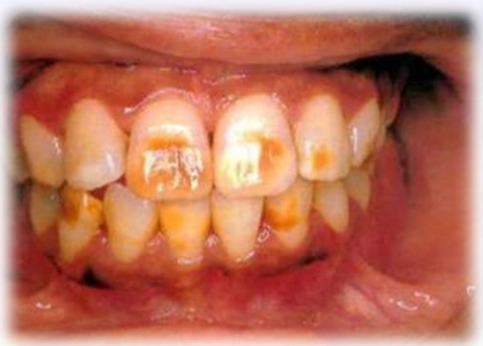
Nature Reviews | Drug Discovery

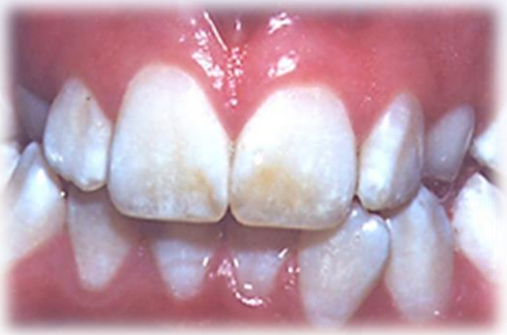
Enamel Alterations

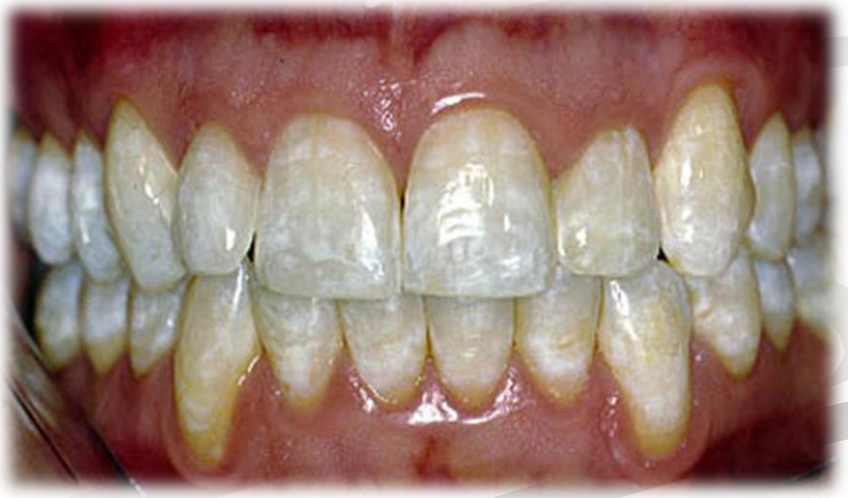
- Nutritional Metabolic Disturbances
- Infectious Disease
- Effects of Pharmaceuticals
- Genetics
- Local Infection and Trauma

Fluoride incorporation into apatite crystals delays amelogenin hydrolysis

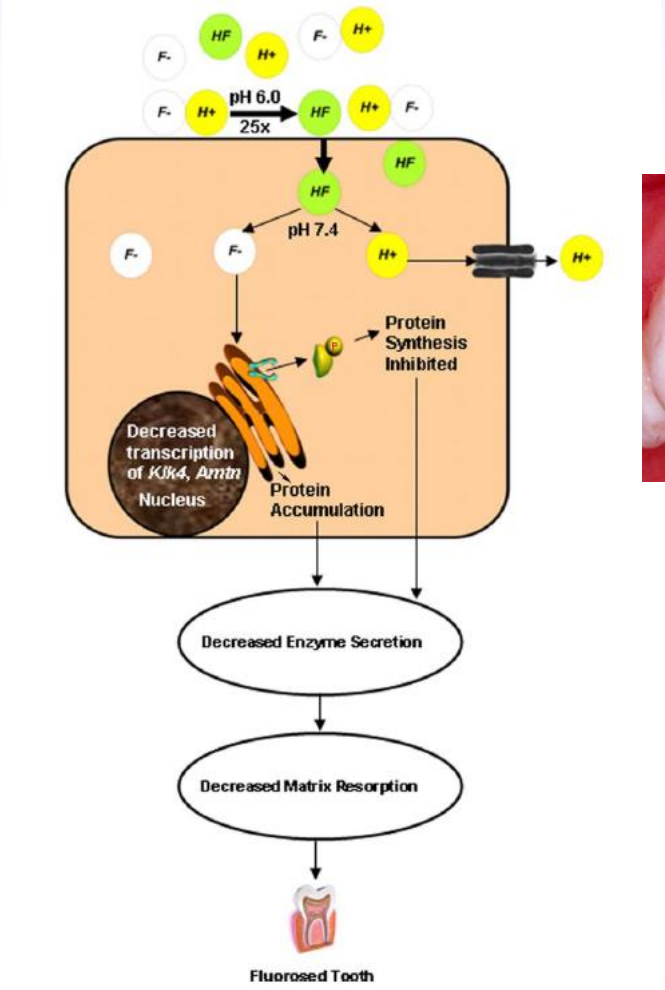
- F(-)-mediates downregulation of TGF-β1 expression contributes to reduced KLK4 protein levels in fluorosed enamel and provides an explanation for why fluorosed enamel has a higher than normal protein content.

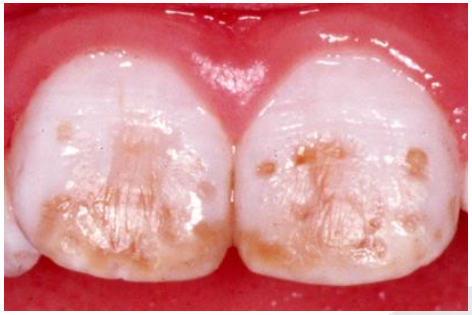


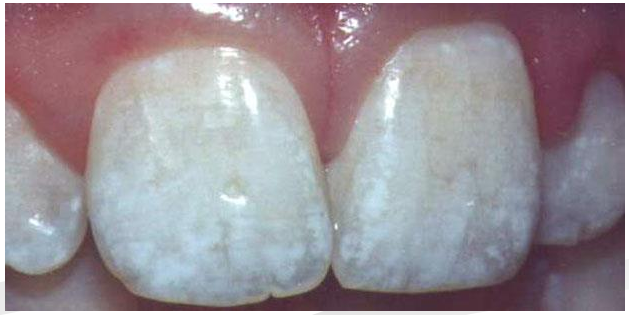


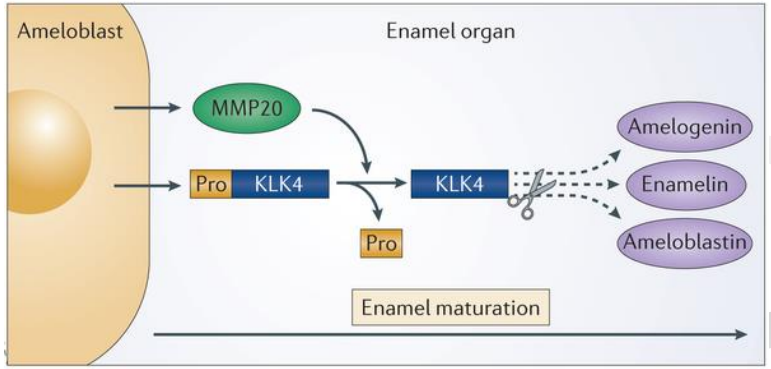


Fluorosis


HF
F-
H+
pH 6.0
25x
pH 7.4
Protein Synthesis Inhibited
Decreased transcription of Klk4, Amtn
Nucleus
Protein Accumulation
Decreased Enzyme Secretion
Decreased Matrix Resorption
Fluorosed Tooth






Ameloblast
Enamel organ
MMP20
Pro
KLK4
KLK4
Pro
Amelogenin
Enamelin
Ameloblastin
Enamel maturation

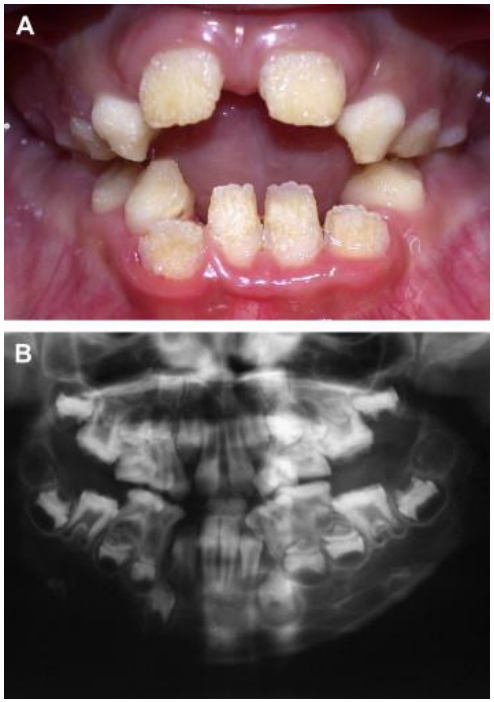
Amelogenesis Imperfecta

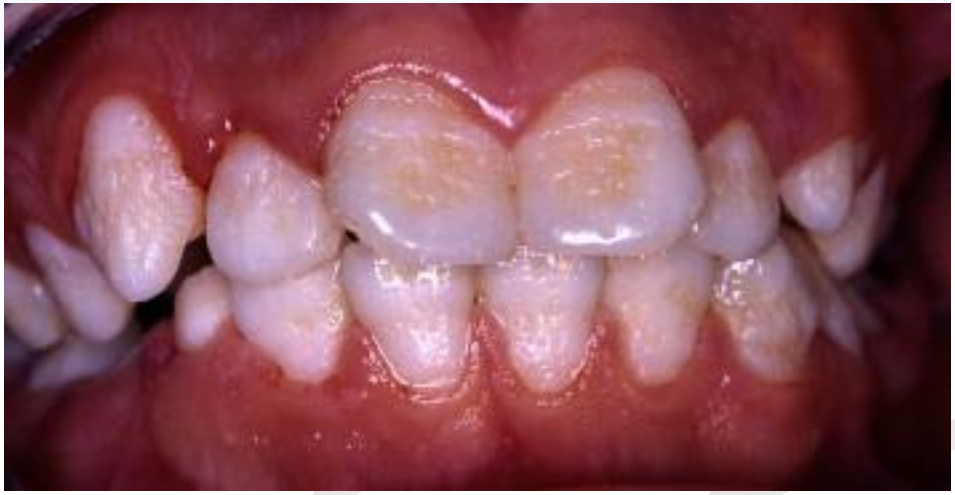
- Amelogenesis imperfecta (AI) represents hereditary conditions affecting the quality and quantity of enamel.
- Ten genes are known to cause Amelogenesis Imperfecta (AI), (AMELX, ENAM, MMP20, KLK4, FAM83H, WDR72, C4orf26, SLC24A4, LAMB3- Laminin beta 3, and COL17a1.
- While there are about 85 hereditary conditions that affect enamel formation found in OMIM 2010 [OMIM, 2010], amelogenesis imperfecta (AI) represents hereditary conditions that predominantly affect the quantity and quality of enamel in the absence of other developmental traits

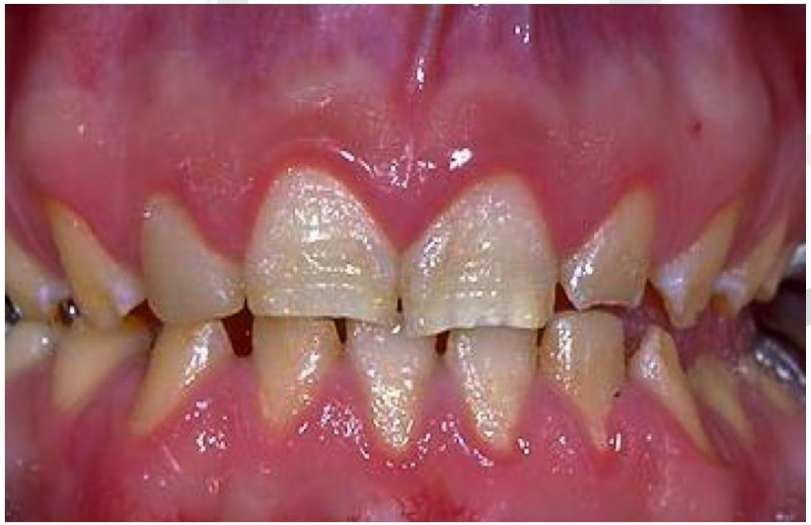
Amelogenesis Imperfecta

- *AMELX- amelogenin, X-linked*
- *ENAM- enamelin, Chromosome 4*
- *FAM83H- family with sequence 83, Chromosome 8*
- *KLK4- Kallilrein-related peptidase 4, Chromosome 19*
- *MMP20- Matrix metallopeptidase 20, Chromosome 9*
- *WDR72- WD repeat domain 72, Chromosome 15*
- *C4orf26- Chromosome 4 open reading frame 26*
- *SLC24A4- Soluble carrier family 24, Chromosome 14*
- *LAMB3- Laminin beta 3, Chromosome 1*
- *COL17a1- Collagen type VII, alpha, Chromosome 10*

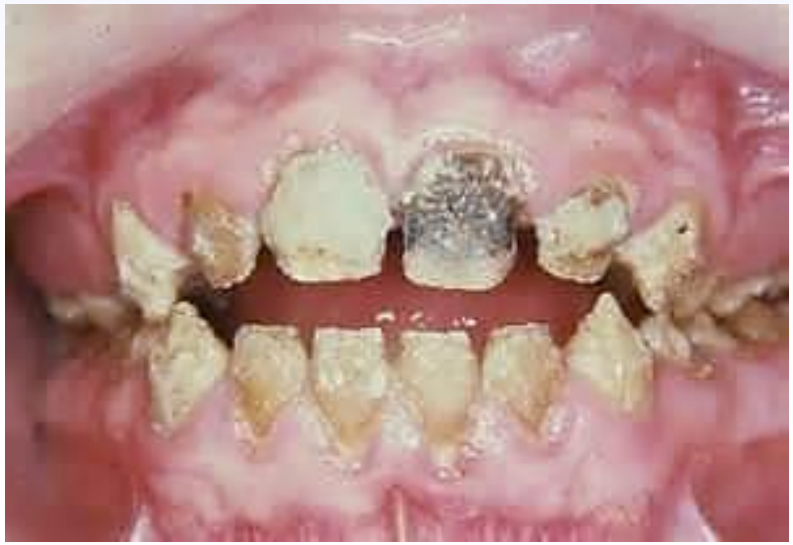
Hypoplastic Amelogenesis Imperfecta

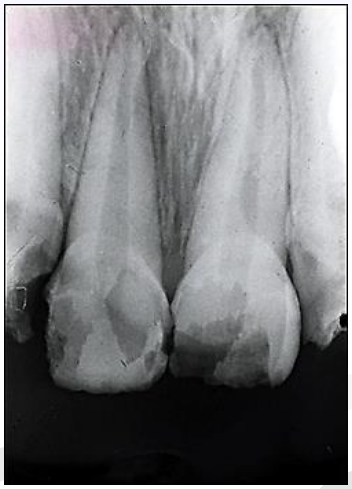


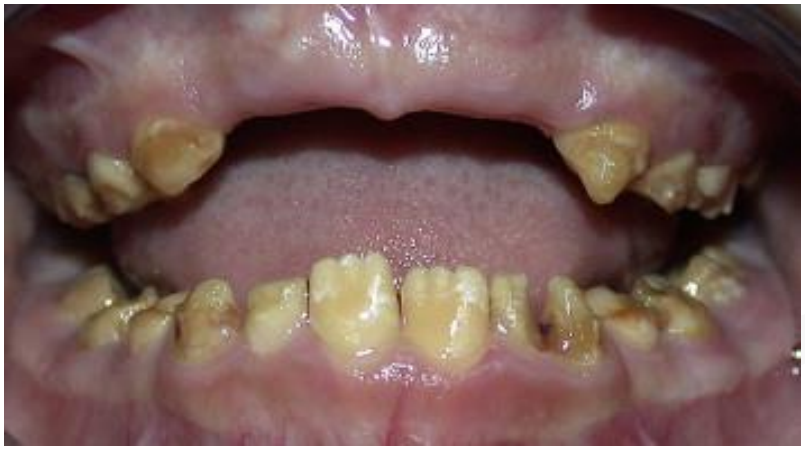




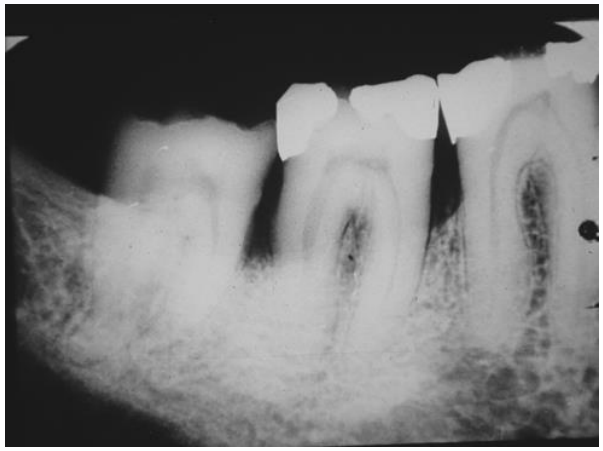
Hypocalcified Amelogenesis Imperfecta

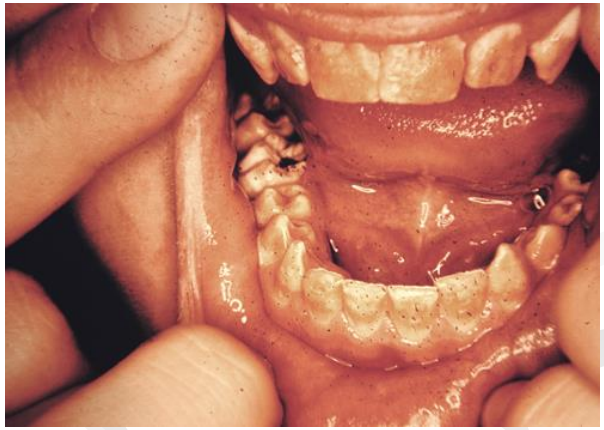


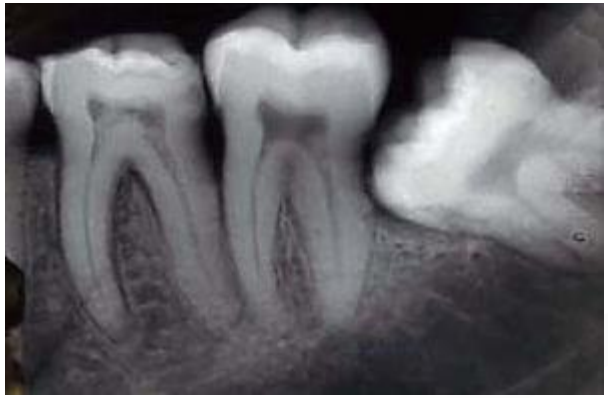




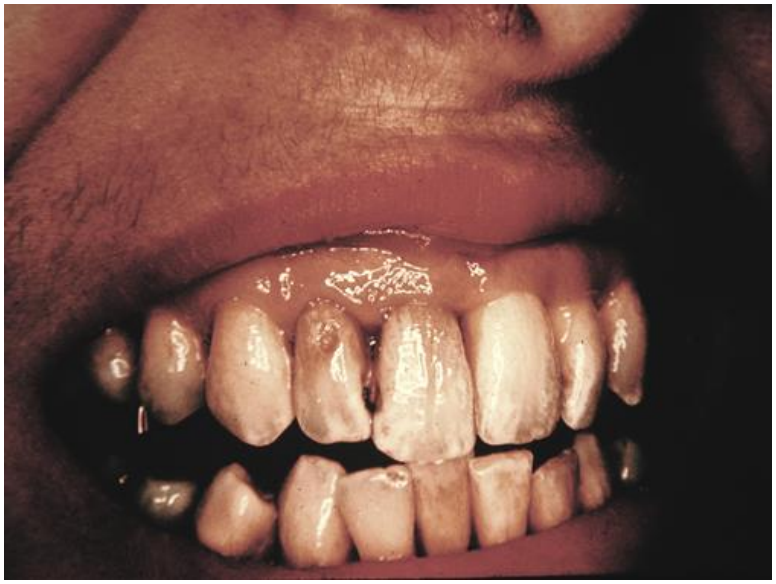
Hypomaturation Amelogenesis Imperfecta

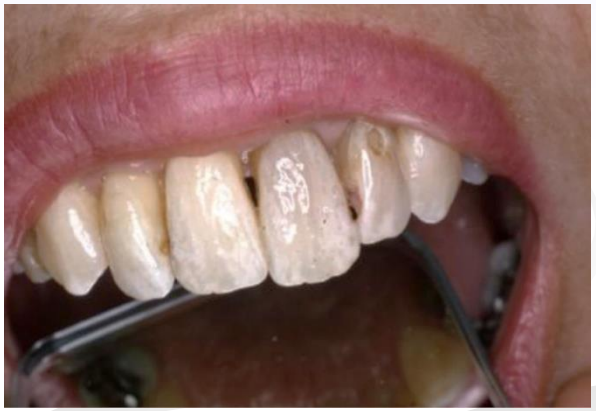


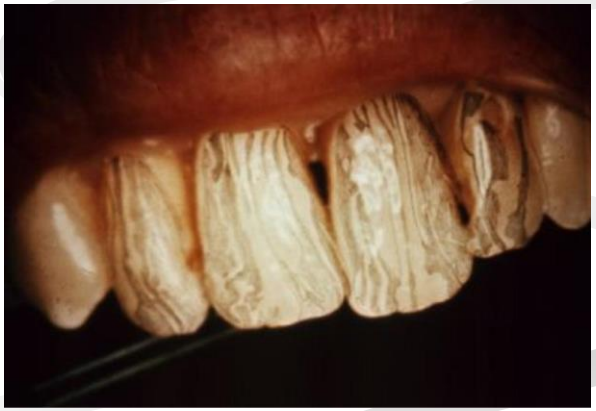




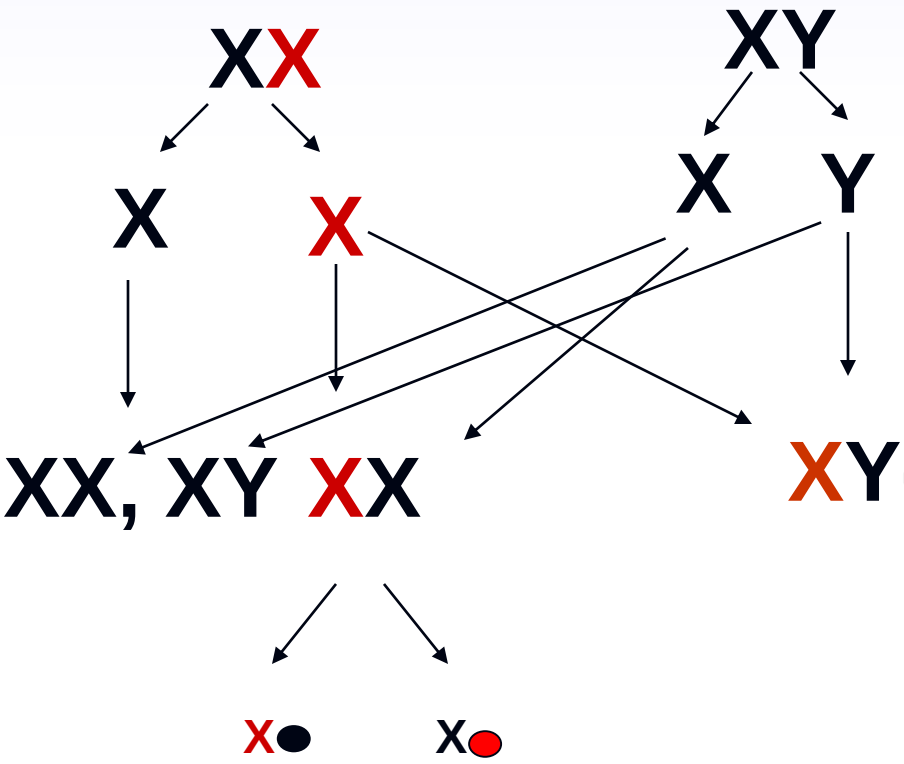
Hypomaturation Amelogenesis Imperfecta



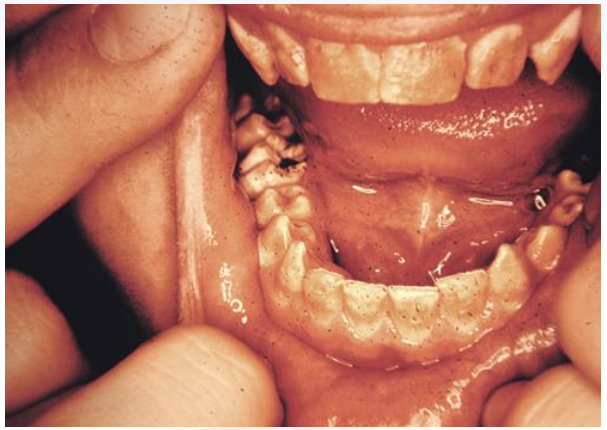




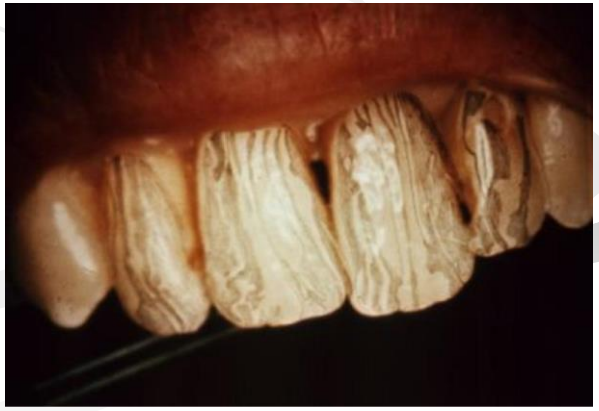
Lyon Hypothesis

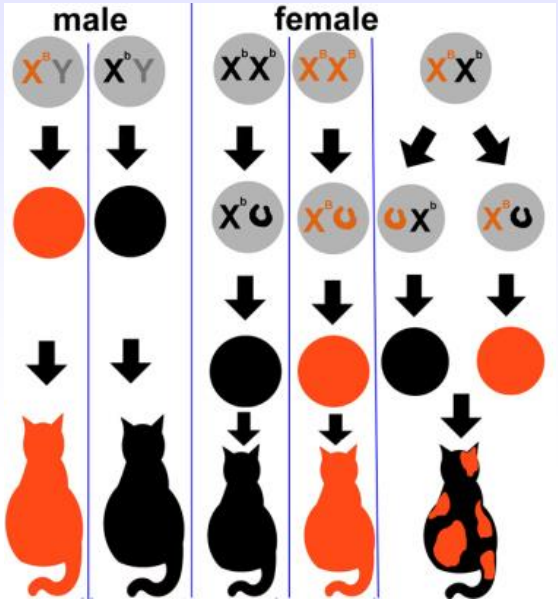


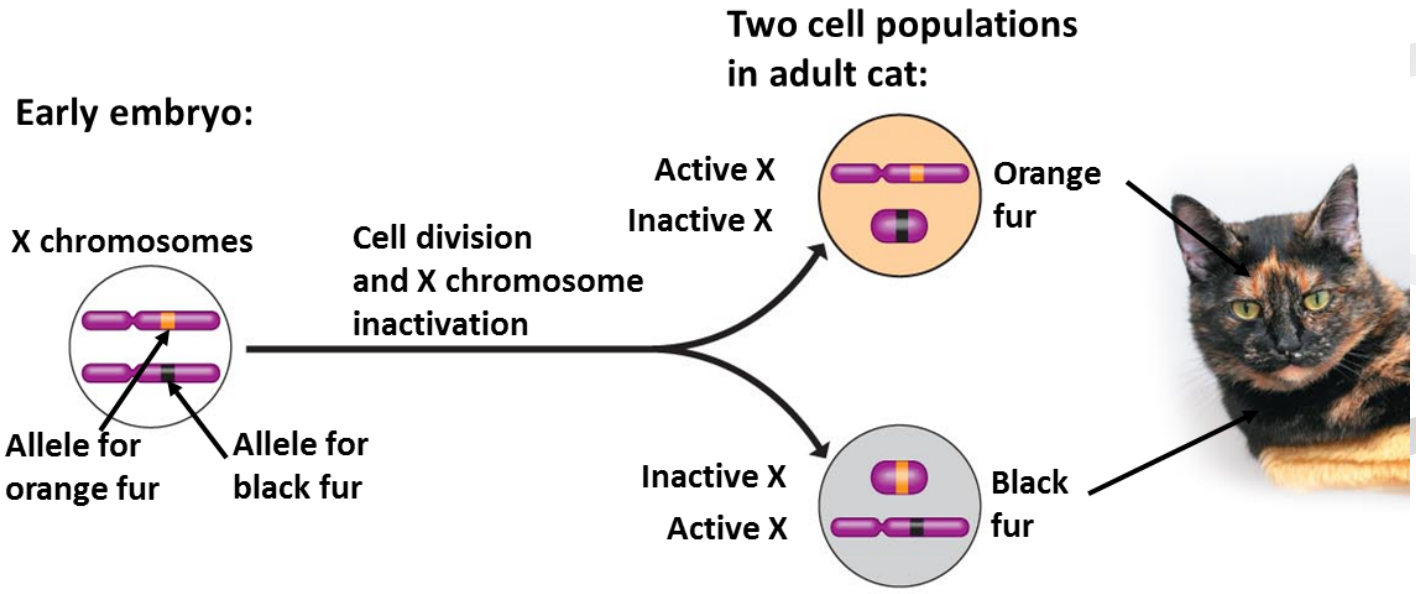
XY



X ● X ●




male
female


Early embryo:
X chromosomes
Allele for orange fur
Allele for black fur
Cell division and X chromosome inactivation
Two cell populations in adult cat:
Active X
Inactive X
Orange fur
Inactive X
Active X
Black fur

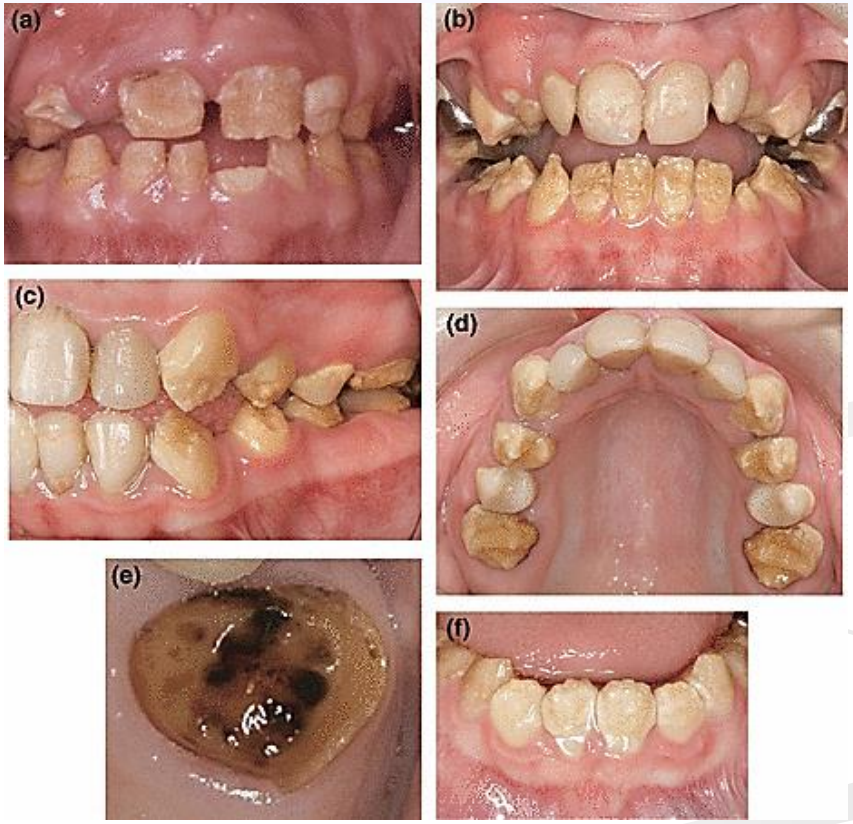
General Patterns

- The majority of families with identifiable mutations are affected, with autosomal dominant hypocalcified AI (*FAM83H* mutations)
- The second most prevalent gene, i.e. *AMELX* .
- The least frequent mutations involved the autosomal recessive hypomaturation associated genes *MMP20* , *KLK4,* and *WDR72* .

Patterns of Disease

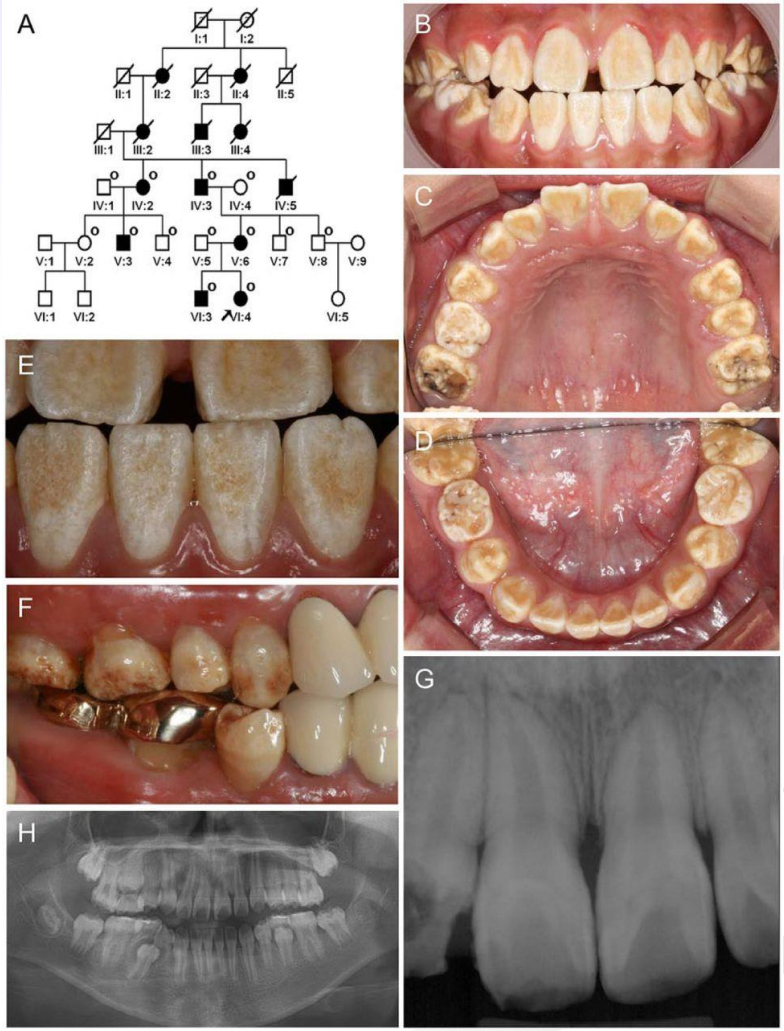
- The clinical phenotypes corresponding to these different mutations are extremely diverse.
- The range of severity in both the hypoplastic and hypomineralized AI subtypes is marked.
- Several of the allelic mutations produced markedly different phenotypes that ranged from localized to generalized as observed with allelic *AMELX, ENAM,* and *FAM83H* mutations.

Autosomal dominant hypocalcified amelogenesis imperfecta (ADHCAI) is a disease with severe dental manifestations (FAM83H)



International Journal of Paediatric Dentistry
Volume 21, Issue 6,pages 407-412, 27 JUN 2011

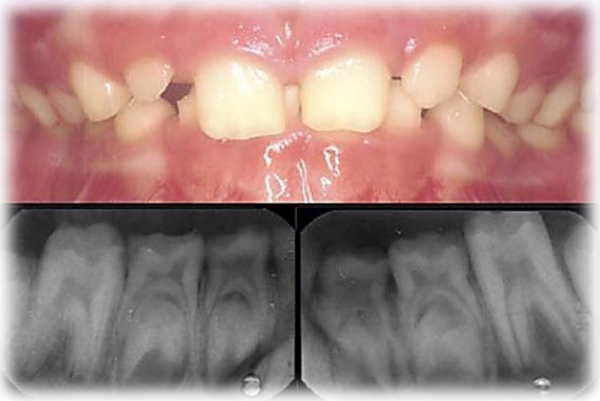
Alteration of Conserved Alternative Splicing in *AMELX* Causes Enamel Defects

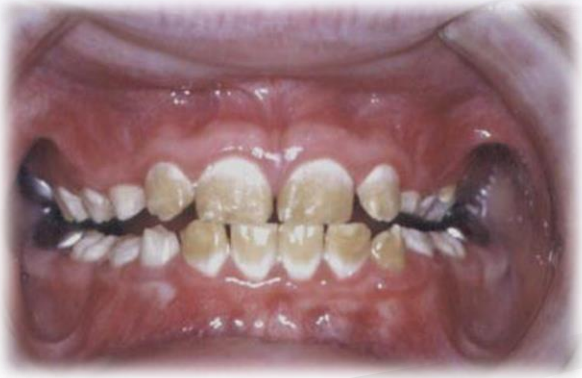


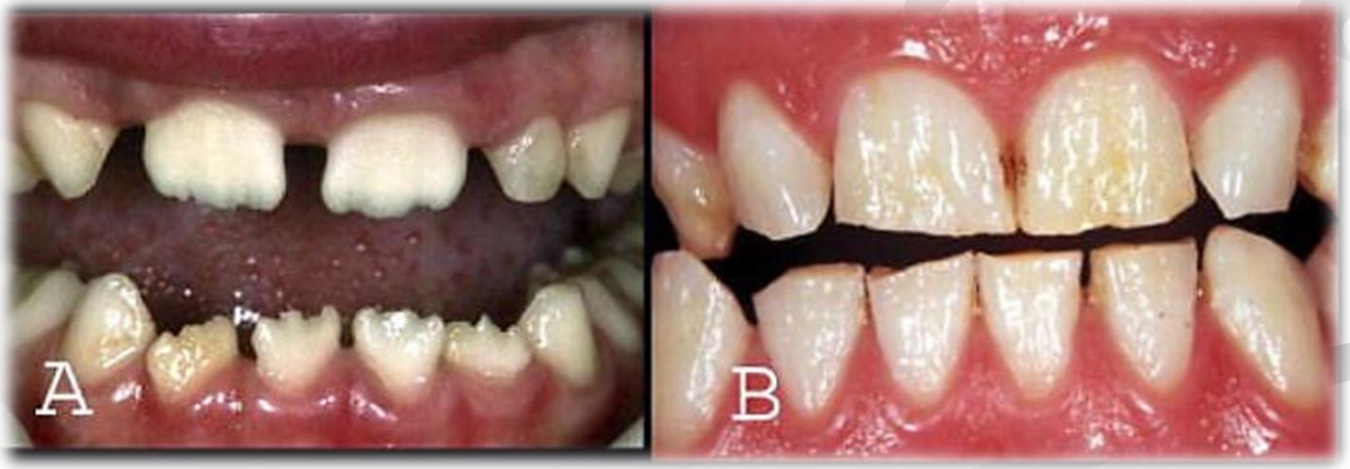
Cho E et al. J DENT RES 2014;93:980-987

JDR JOURNAL OF DENTAL RESEARCH®

AMELX Variations

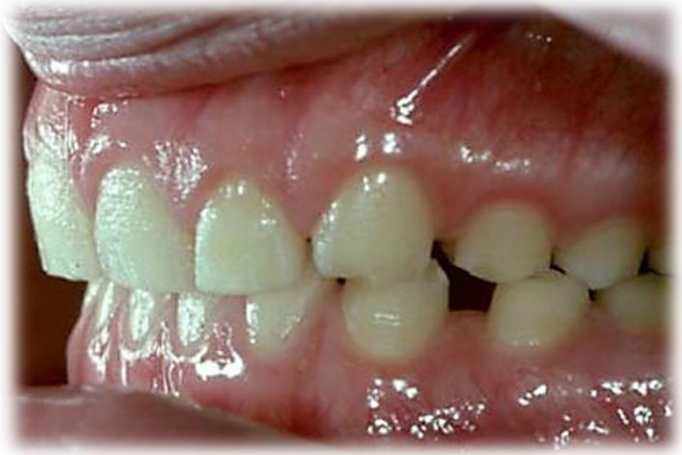


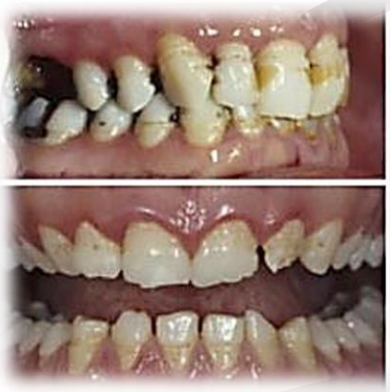


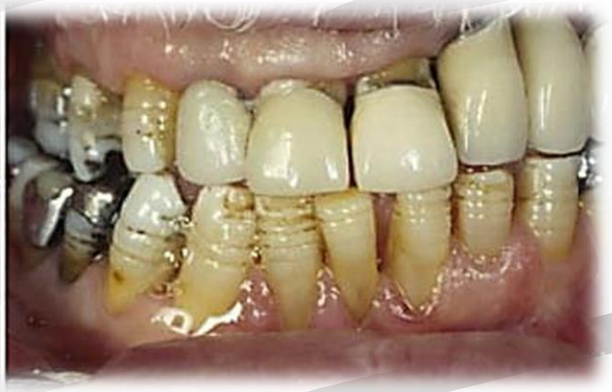


ENAM Mutations

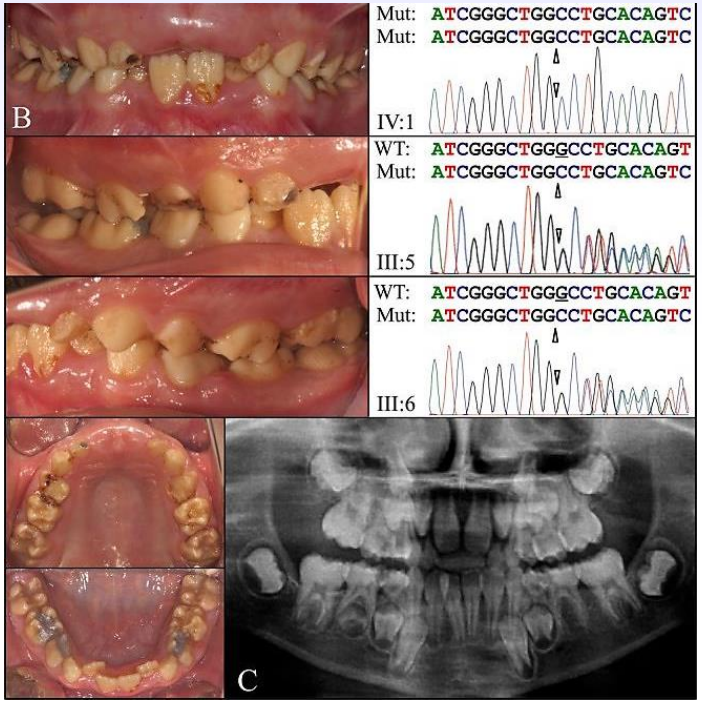
ENAM Mutations (Table 3)				
Genomic DNA^	**cDNA+**	**Protein***	**Phenotype**	**Reference**
g.2382A>T	c.157A>T	p.K53X	Local hypoplastic	Mardh [11]
g.6395G>A	IVS7+1G>A; c.534+1G>A	p.A158_Q178del	Generalized thin hypoplastic	Rajpar [13]
g.8344delG	IVS8+1delG;c.588+1delG	p.N197fsX277	Generalzied thin hypoplastic	Kida 2003 [14] Hart 2003 [15]
g.13185_13186insAG	c/1258_1259insAG	p.P422fsX448	Generalized thin hypoplastic	Hart 2004 [16]

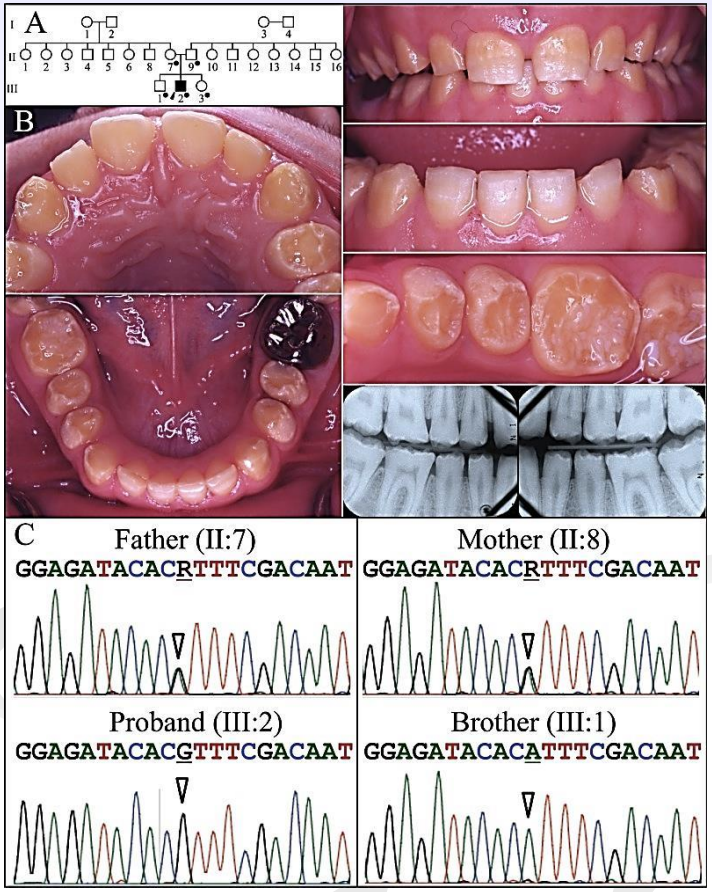






Novel KLK4 and MMP20 mutations



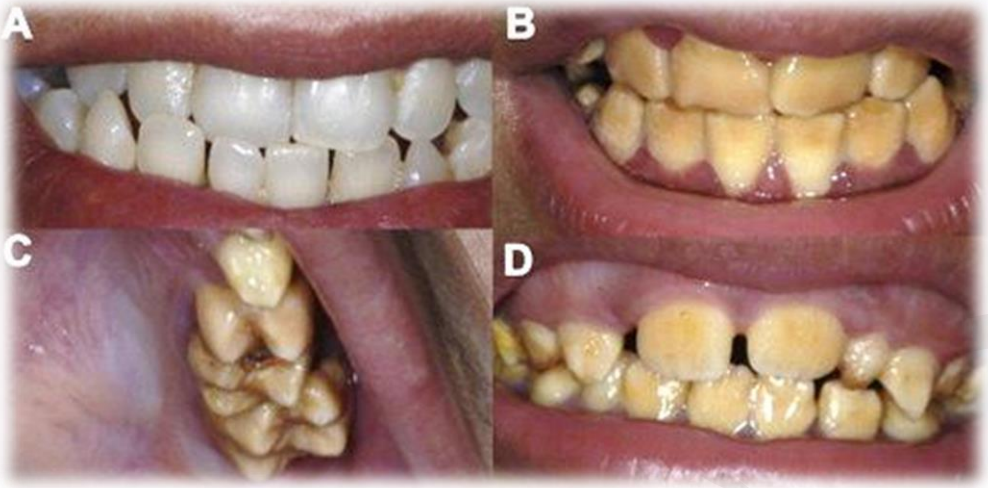


MMP20 and *KLK4* Mutations (Table 4)				
MMP20 Mutations				
Genomic DNA^	cDNA+	Protein*	Phenotype	Reference
g.30561A>T	c.954-2A>T or c.IVS6-2A-T	p.I319Fs338X or p.I319X	Pigmented Hypomaturation Decreased Mineral	Kim et al. 2005
g.16250T>A	c.678T>A	p.H226Q	Hypomaturation	Hart et al. in press
KLK4 Mutations				
g.2142G>A	c.458G>A	p.W153X	Pigmented Hypomaturation Decreased Mineral	Hart et al. 2004

Developmental Defects of the Teeth
Dr. John Timothy Wright DDS,MS

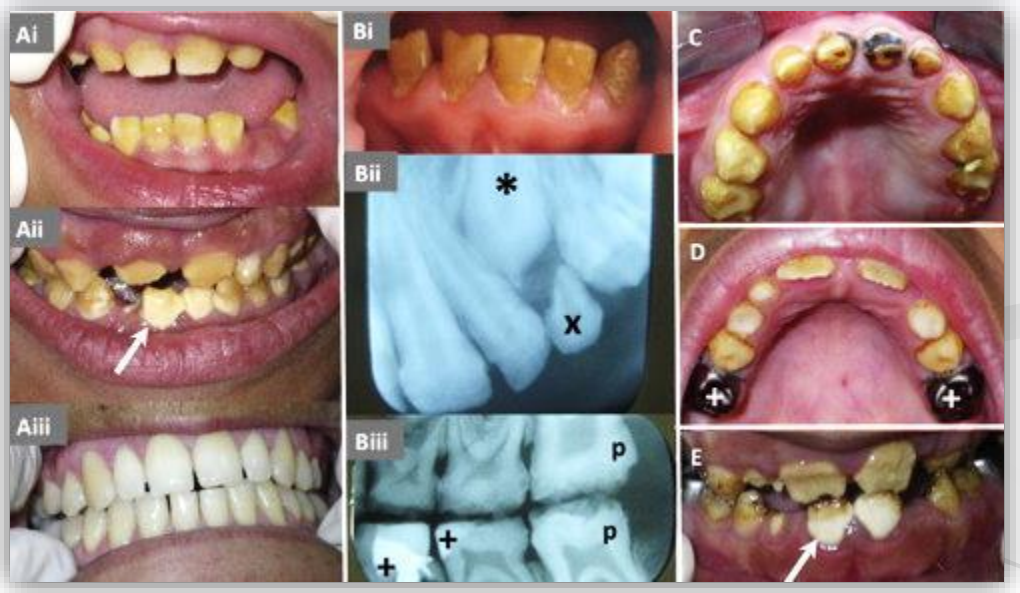
Wang et al. J. Dent Res. 2013

Identification of mutations in SLC24A4, encoding a potassium-dependent sodium/calcium exchanger, as a cause of amelogenesis imperfecta.



Parry DA, et al. Am J Hum Genet. 2013

Mutations in C4orf26, encoding a peptide with in vitro hydroxyapatite crystal nucleation and growth activity, cause amelogenesis imperfecta



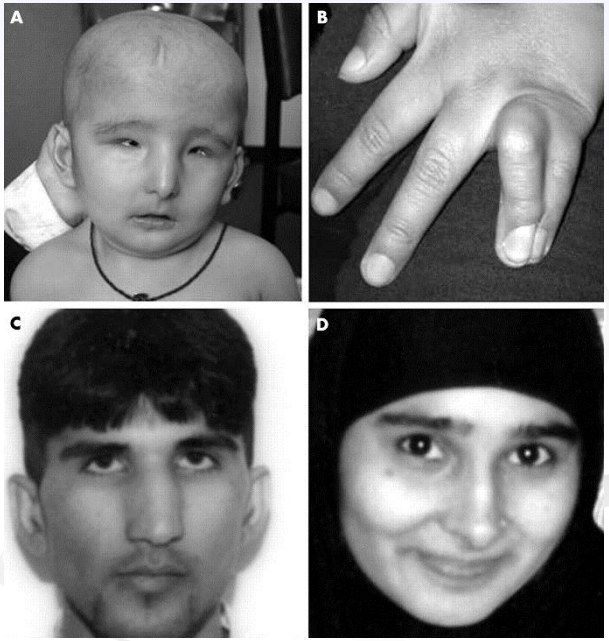
Parry DA et al. Am J. Hum. Genet. 2012

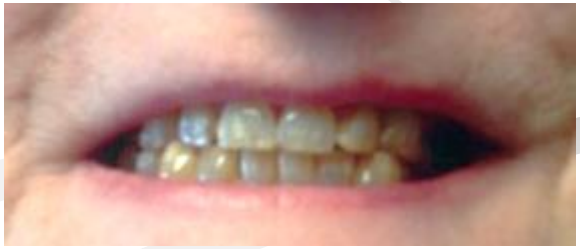
Syndromic -Amelogenesis Imperfecta

- *LAMA3-Laminin, alpha 3, Chromosome 18*
- *LAMB3- Laminin beta 3, Chromosome 1*
- *COL17a1- Collagen type VII, alpha, Chromosome 10*
- *LAMC2- Laminin, alpha 2, Chromosome 1*
- *ITGA6- Integrin, alpha 6, Chromosome 2*
- *ITGB4- Integrin , beta 4, Chromosome 17*
- *GJA1- Gap junction protein, alpha 1, Chromosome 10*
- *CNNM4- Cyclin and CBS metal cation transport 4, Chromosome 4*
- *ORAI1- ORAI calcium release modulator 1, Chromosome 12*
- *FAM20A- family with sequence similarity 20, Chromosome 17*
- *STIM1- Stromal interaction molecule, Chromosome 11*
- *RODGI- Rogdi homolog, Chromosome 16*

Novel Mutations in *GJA1* Cause Oculodentodigital syndrome

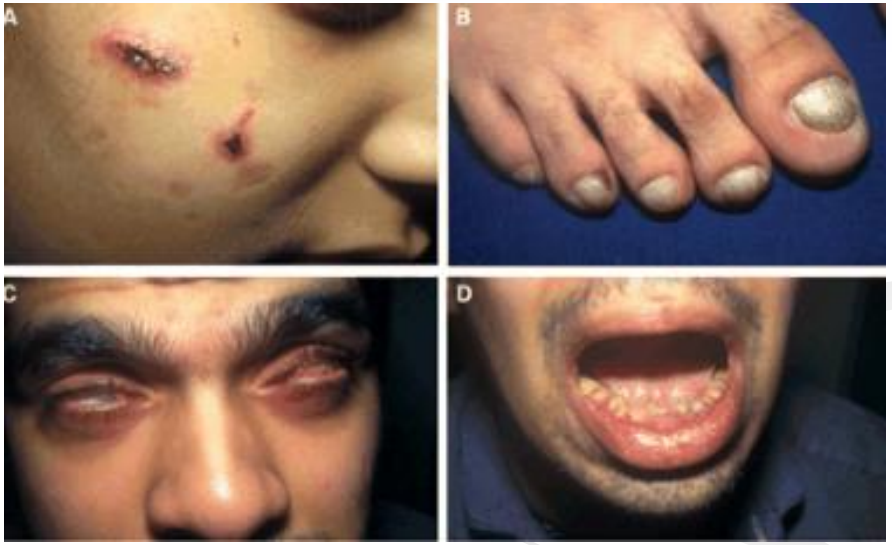
- Oculodentodigital syndrome (ODD) is a rare, usually autosomal-dominant disorder that is characterized by developmental abnormalities of the face, eyes, teeth, and limbs.
- Long, narrow nose, short palpebral fissures, type III syndactyly, and dental abnormalities including generalized microdontia and enamel hypoplasia.
- Recently, it has been shown that mutations in the gene *GJA1*, which encodes the gap junction protein connexin 43, underlie oculodentodigital syndrome.





N-terminal deletion of the laminin α3a isoform leads to the chronic granulation tissue disorder laryngo-onycho-cutaneous syndrome

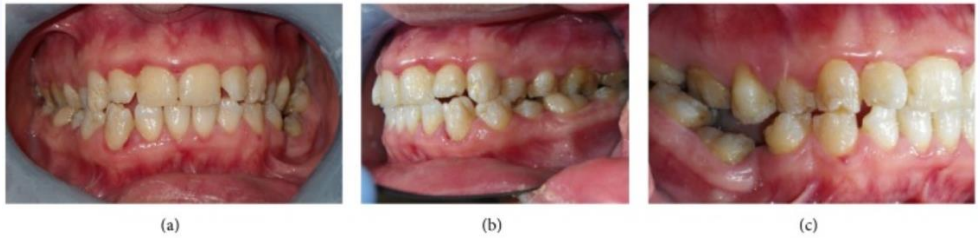
- autosomal recessive
- cutaneous erosions,
- nail dystrophy
- exuberant vascular granulation tissue in conjunctiva, and larynx
- hypoplastic enamel..

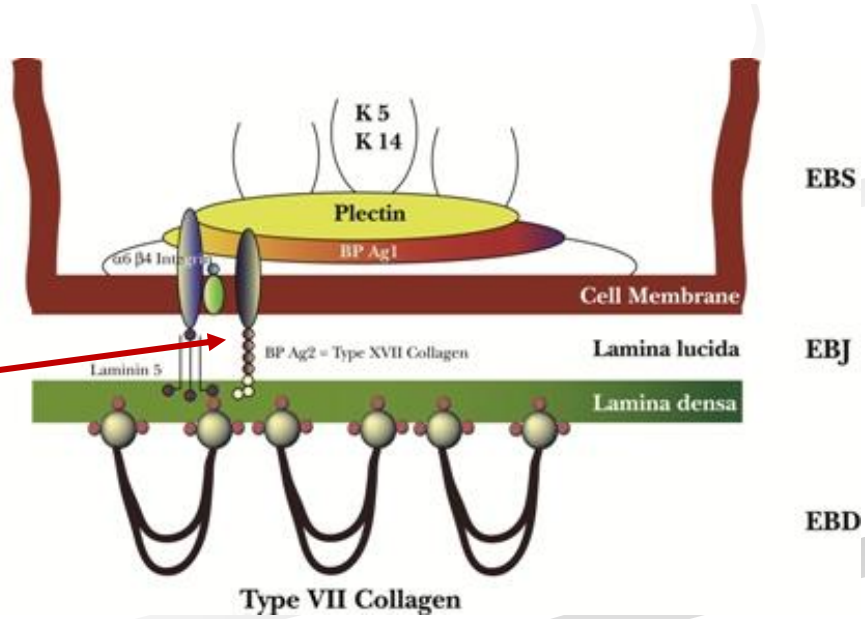


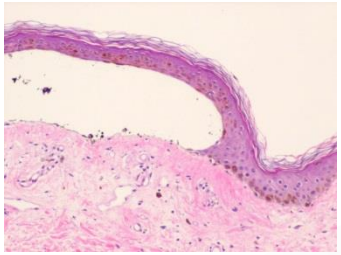
W. H. Irwin McLean et al. Hum. Mol. Genet. 2003;12:2395-2409

Epidermolysis Bullosa Junctional

- Enamel hypoplasia (Pitting and furrowing of thin enamel)
- LAMA3
- LAMB3
- LAMC2
- COL17A1 (BP180)



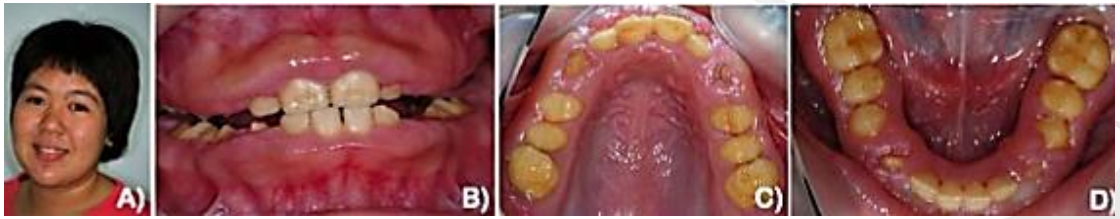




Galeotti A., et al. Case Rep Dent 2014

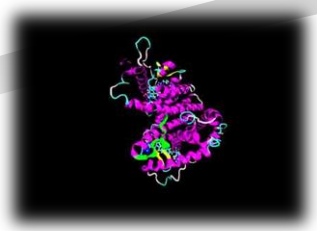
Enamel Renal Syndrome/Amelogenesis Imperfecta Gingival Fibromatosis Syndrome (ERS/AIGFS)

- Recessive mutations in the FAM20A gene
- Mutations were also identified as the cause of “Amelogenesis Imperfecta and Gingival Fibromatosis Syndrome”(AIGFS, MIM#614253).
- Dental phenotype in both cases is the same and that the kidney phenotype has not been investigated fully in AIGFS patients.
- Recessive FAM20A mutations lead to only one disease with distinctive oral phenotype frequently associated with renal calcification.

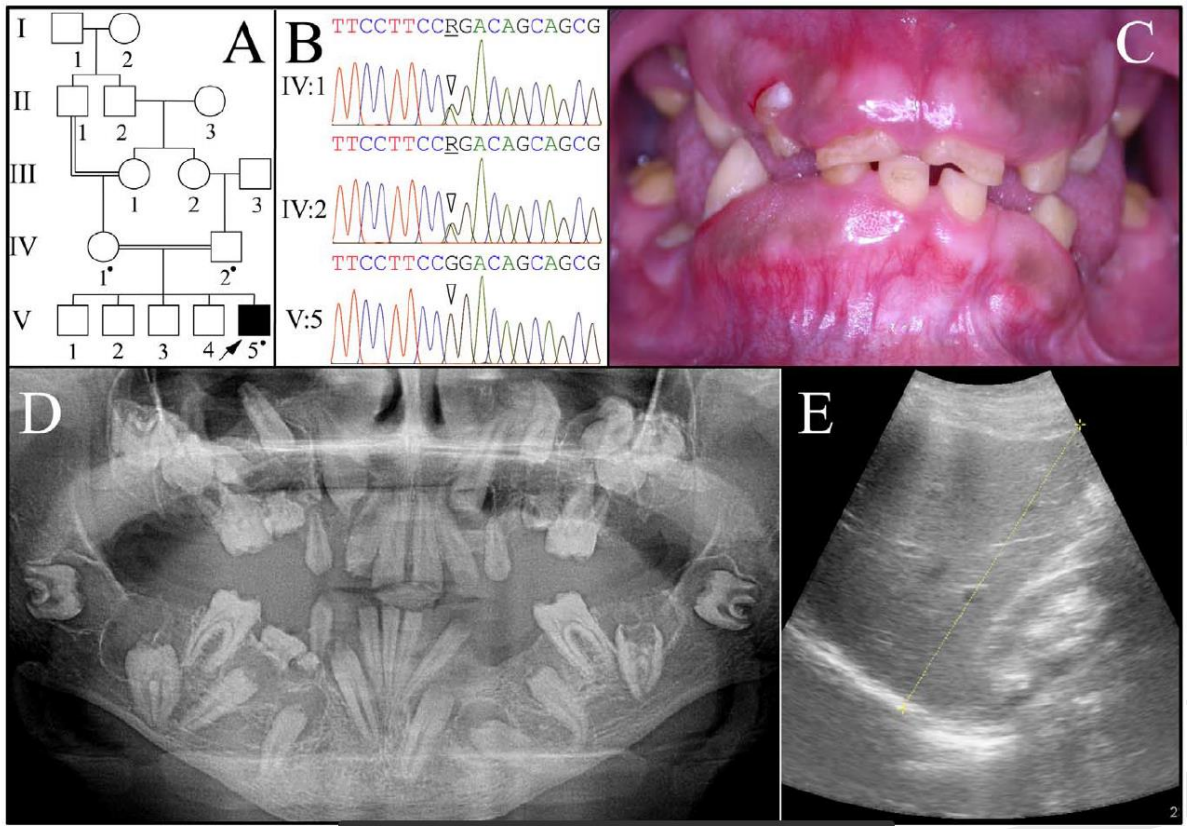


Etiology

- The FAM20 family includes FAM20A, FAM20B and FAM20C proteins. (“family with sequence similarity 20, member A.”)
- FAM20C is phylogenetically closer to FAM20A.
- FAM20C is a Golgi casein kinase that phosphorylates several secreted proteins implicated in biomineralization, including the SIBLING proteins (small integrin-binding ligand, N-linked glycoproteins). It is expressed by osteoblasts, ameloblasts (during secretion stage) and odontoblasts and plays an essential role in tooth development



Enamel Renal Syndrom/Amelogenesis Imperfecta Gingival Fibromatosis Syndrom (ERS/AIGFS)



Wang et al. PLoS Genet, 9(2):2013.

Renal/Metabolic Phenotype

- Bilateral medullary nephrocalcinosis on renal plain radiograph, ultrasound or CT imaging.
- Renal cortex biopsies reveal focal clusters of sclerosed glomeruli, marked periglomerular fibrosis with lymphocytic and plasma cell infiltration of the renal interstitium.
- Hypocalciuria and reduced citrate excretion are typical with hypophosphatemia present less frequently.
- Urine from affected patients promoted calcium oxalate (CaOx) crystal growth compared to controls.
- Values for serum urea, creatinine and serum electrolytes, as well as creatinine clearance, alkaline phosphatase, parathyroid hormone, vitamin D are typically within normal limits.

Differential Diagnosis

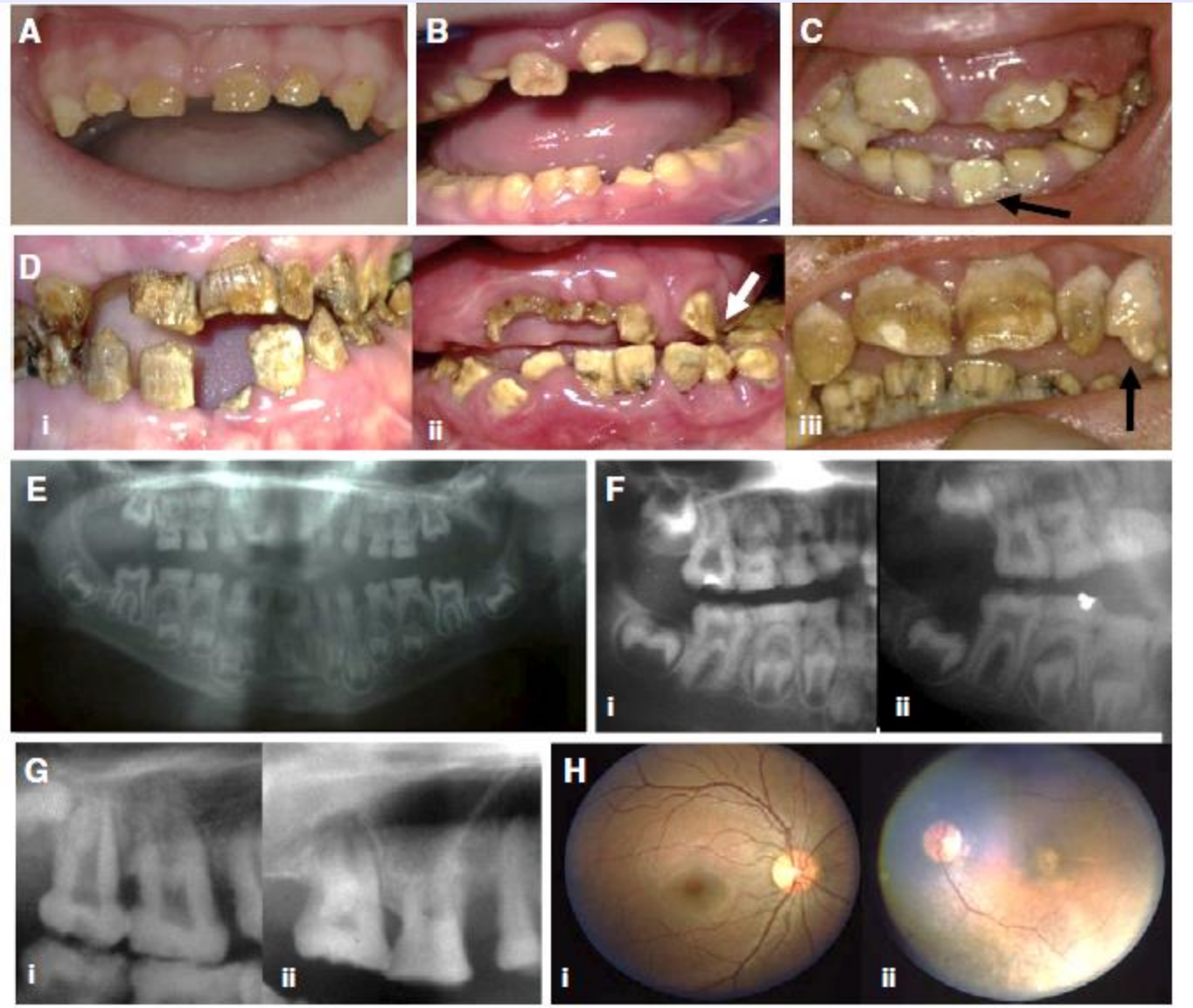
- AI occurs either in isolation or as part of a syndrome (such as Jalili syndrome, Raine syndrome, epidermolysis bullosa, tricho-dento-osseous syndrome).
- A review of literature published since 1972 shows several reports severe hypoplastic enamel constitutes the first element of differential diagnosis.
- **Hypomaturation or hypocalcified** AI have never been described in ERS. Multiple diagnostic features, as described above, should be present together.

Raine Syndrome (FAM20C)

- This gene encodes a member of the family of secreted protein kinases. The encoded protein binds calcium and phosphorylates proteins involved in bone mineralization
- a kinase that phosphorylates S-x-E/pS motifs on proteins in milk and in the extracellular matrix of bones and teeth.
- generates the majority of the extracellular phosphoproteome.
- 100 secreted phosphoproteins are genuine Fam20C substrates.
- functional annotations suggest roles for the kinase beyond biomineralization, including lipid homeostasis, wound healing, and cell migration and adhesion.

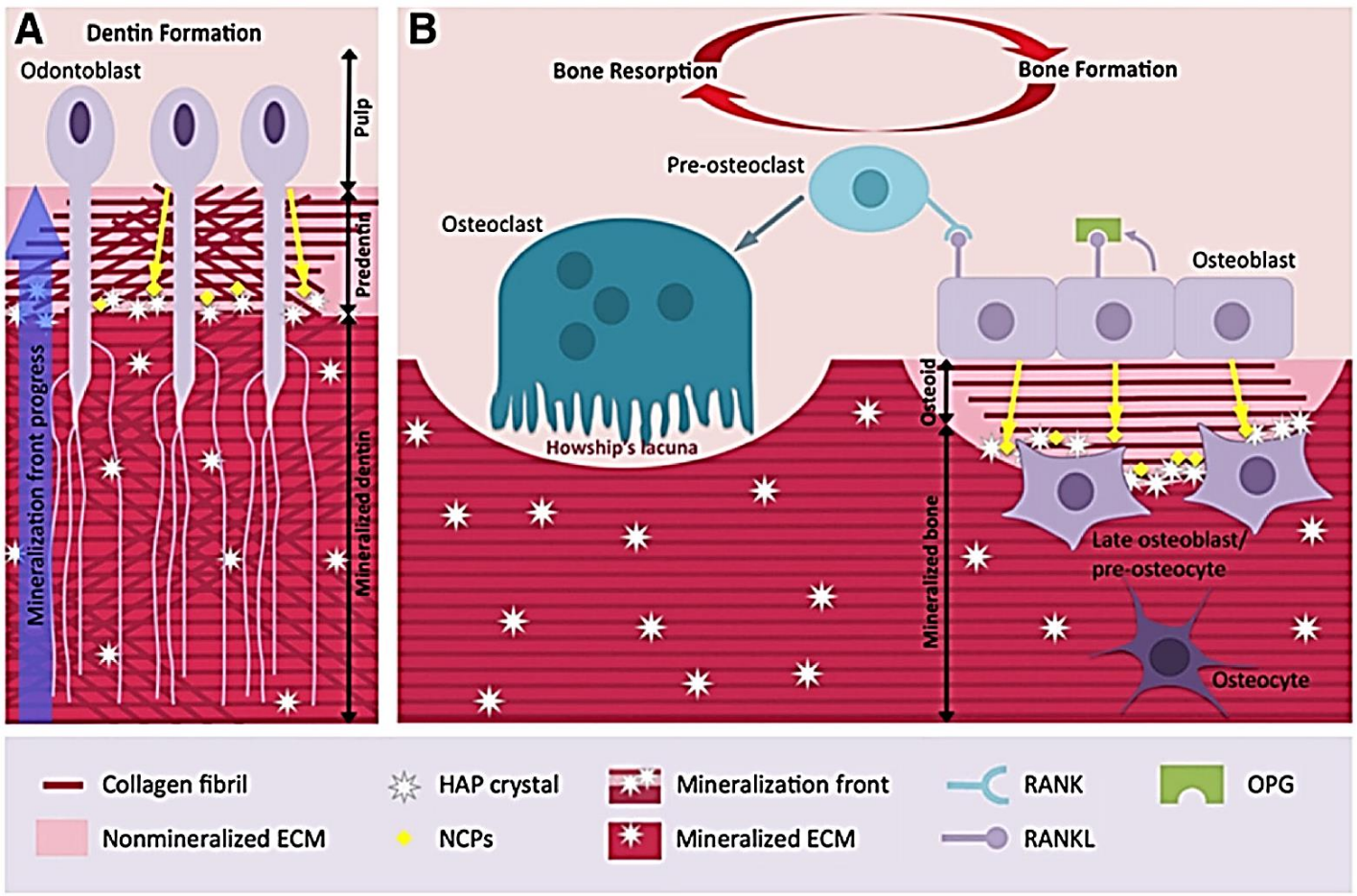
Cone-rod dystrophy and amelogenesis imperfecta (Jalili syndrome)

- Recessive amelogenesis imperfecta with cone-rod dystrophy.
- Mutations in the CNNM4 gene, encoding a putative metal magnesum transporter, accounting for the condition
- Cone-rod dystrophy(CRD[MIM120970]) usually manifests in childhood or early adulthood with predominant or equal loss of cone compared to rod photoreceptors, reduced visual acuity, color-visionabnormalities, photophobia,and visualfield loss.
- Mutations inABCA4 (MIM*601691), AIPL1(MIM*604392), CRX (MIM þ602225), GUCA1A (MIM *600364), GUCY2D (MIM *600179), PITPNM3 (MIM *608921), RIMS1 (MIM *606629), SEMA4A (MIM *6072920), RPGR (MIM *312610), PROM1 (MIM *604365), and UNC119 (MIM *604011) have been associated with CRD.
- CRD can be inherited in an autosomal-dominant, autosomal recessive, or X-linked manner (RetNet).



Parry DA, et al. Am J Hum Genet. 2009 Feb;84(2):266-73

Dentinogenesis/ Osteogenesis

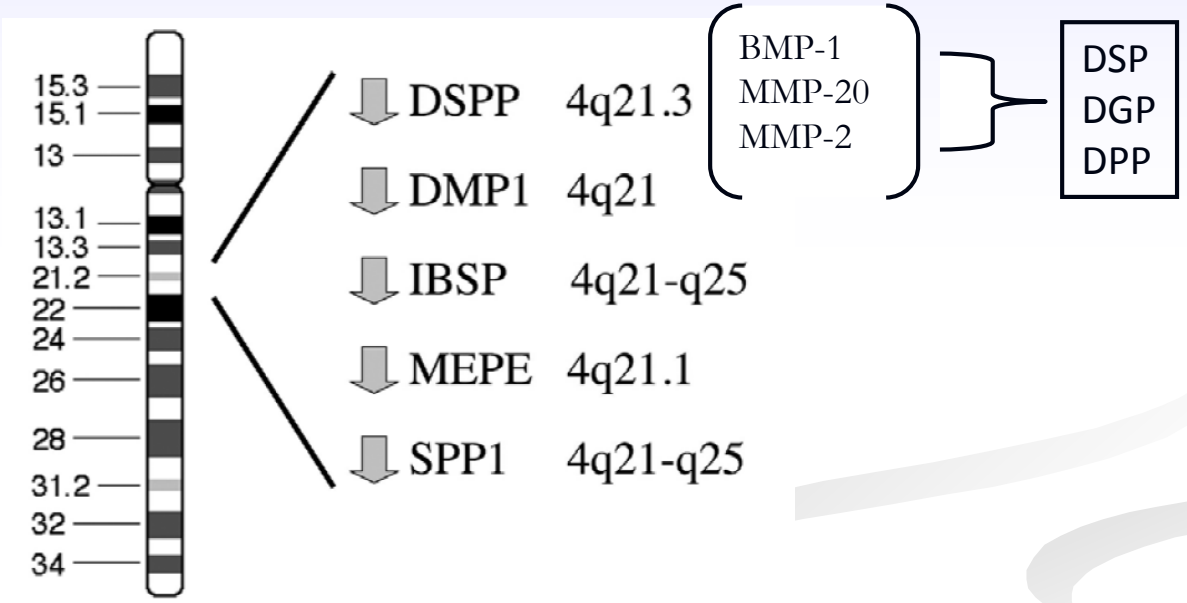


Dentinogenesis

Global composition of dentin extracellular matrix [ECM] molecules

Collagens 90%		**Type I Collagen (89%) + Type I trimer (11%)**	**+ 1–3% Type III and V Collagens**
Non-Collagenous Proteins (NCP) # 10%	Phosphorylated proteins	SIBLINGs (Small Integrin-Binding LIgand, N-linked Glycoproteins) [56]	**DSPP (Dentin Sialo Phospho Protein)** (Mw between 155 et 95kDa), after cleavage : • **DSP (Dentin sialo Protein)** (N-terminal-proteoglycan forming dimers) : 100–280kDa • **DGP (Dentin Glyco Protein)** : 19kDa • **DPP (Dentin Phospho Protein or dentin phosphoryn)** (C-terminal) 94kDa mineralization nucleator **DMP-1 (Dentin Matrix Protein-1)** : 61kDa, a proteoglycan, nucleator **BSP (Bone SialoProtein):** 95kDa, proteoglycan, nucleation & crystal growth. **OPN (Osteopontin)** : 44kDa glycoprotein (mineralization inhibitor). **MEPE (Matrix Extracellular Phospho glyco Protein)** 66kDa, glycoprotein (mineralization inhibitor)
	=	SLRPs (Small Leucine-Rich Proteoglycans)	Decorin (and possibly other SLRPs)

Dentinogenesis

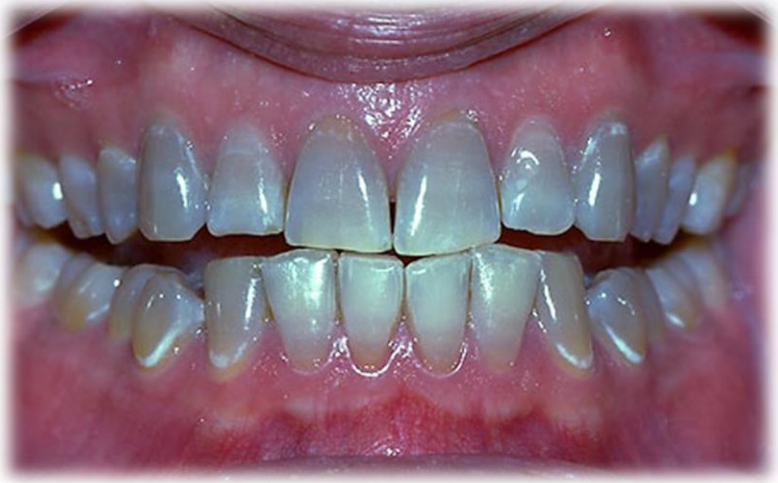


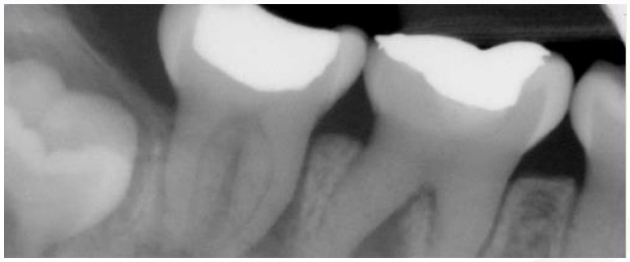
SIBLING genes on human chromosome 4. Key: Dentin sialophosphoprotein (DSPP), dentin matrix protein 1 (DMP1), integrinbinding sialoprotein (IBSP), matrix extracellular phosphoglycoprotein (MEPE), secreted phosphoprotein-1 (SPP1).

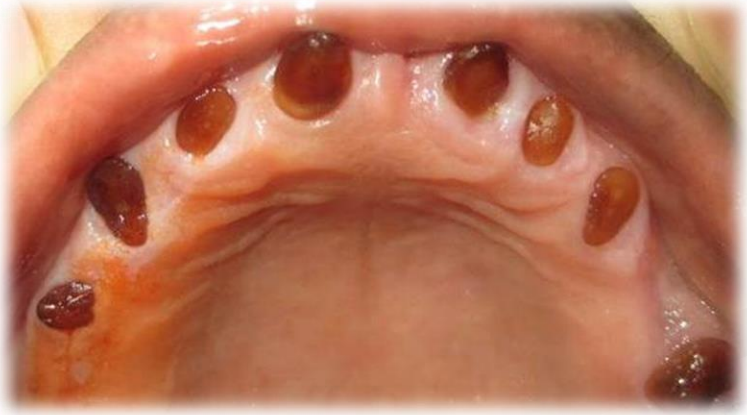
Dentinogenesis

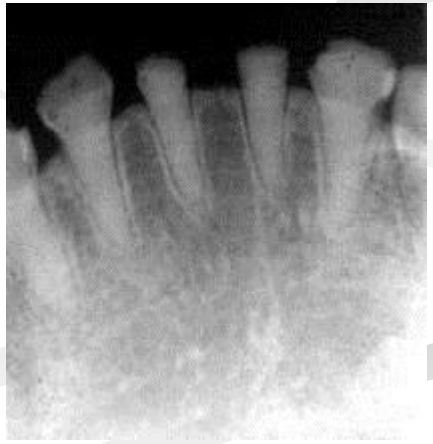
- Dentinogenesis imperfect type I-Col
- Dentinogenesis imperfect type II-DSPP
- Dentinogenesis imperfect type III-DSPP
- Dentin Dysplasia type I-UNK
- Dentin Dysplasia type II-DSPP

Dentinogenesis Imperfecta Type II

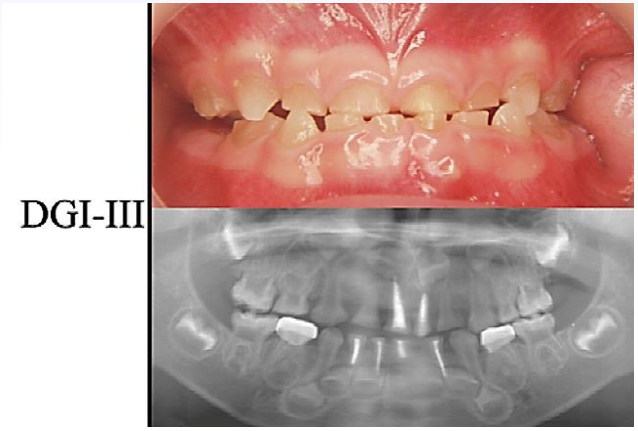


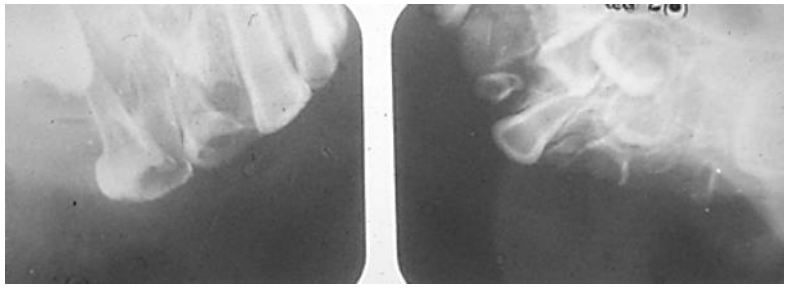






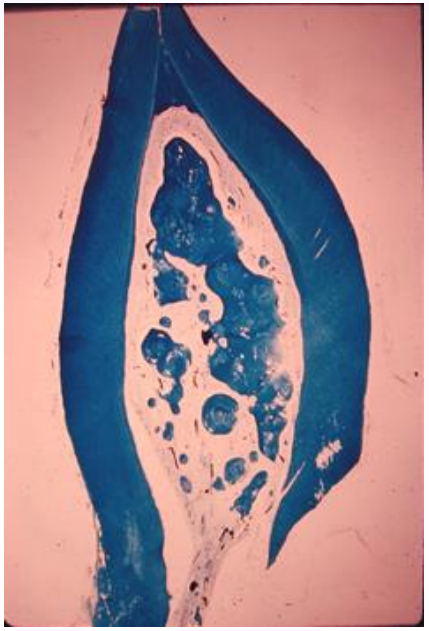
Dentinogenesis Imperfecta Type-III

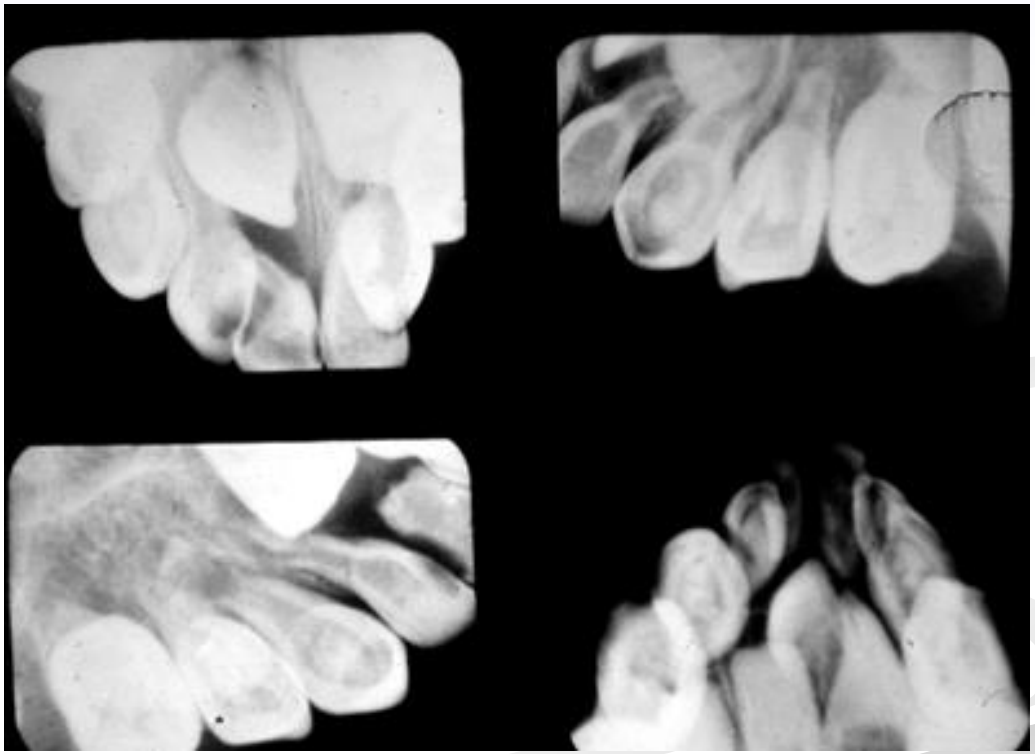




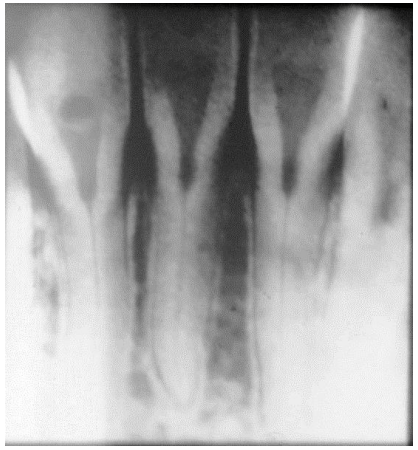
- Brandywine type of dentinogenesis imperfecta. Sometimes referred to as “shell teeth”

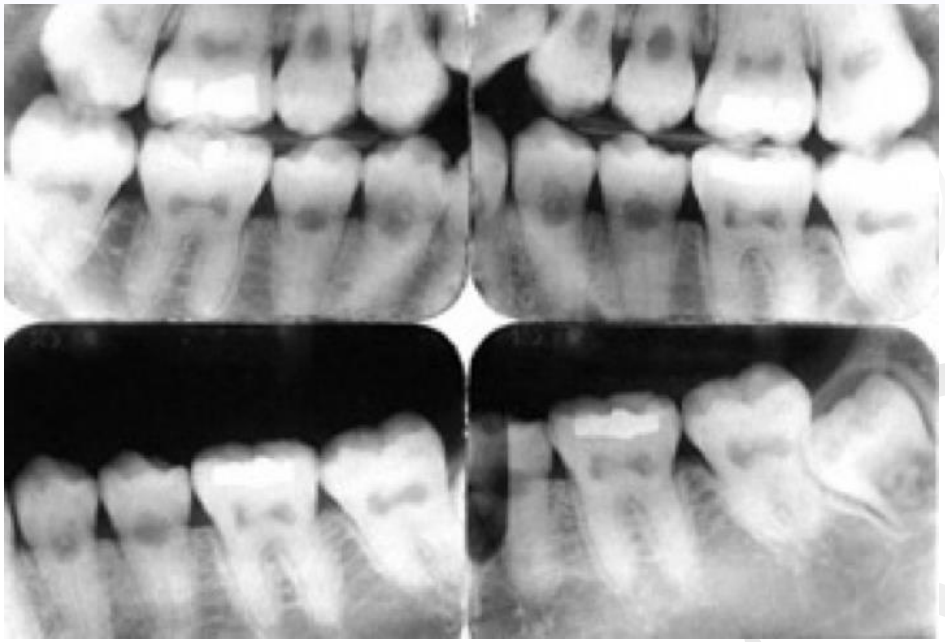
Coronal Dentin Dysplasia (Type II)



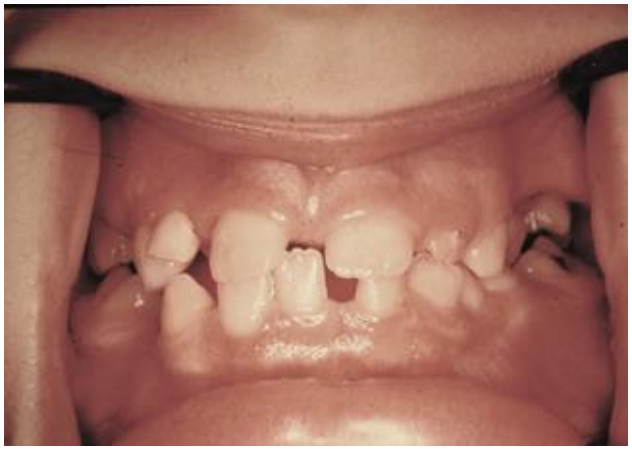


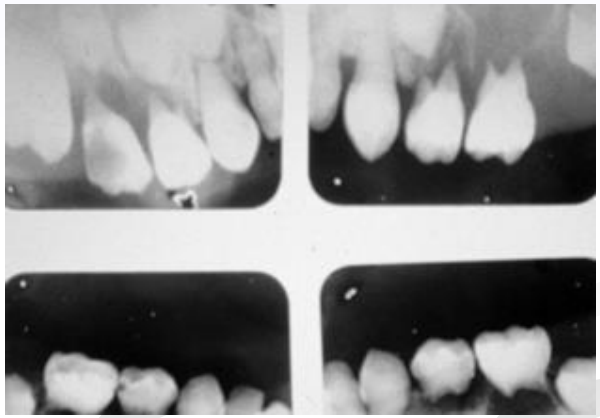
Dentin Dysplasia Type II

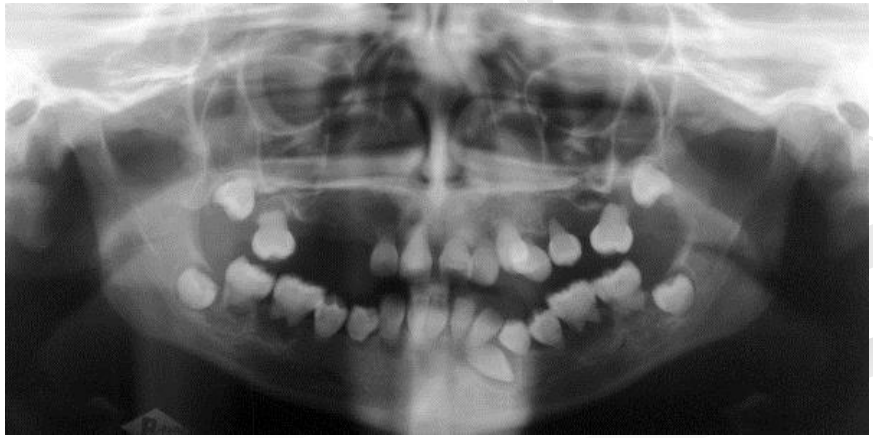




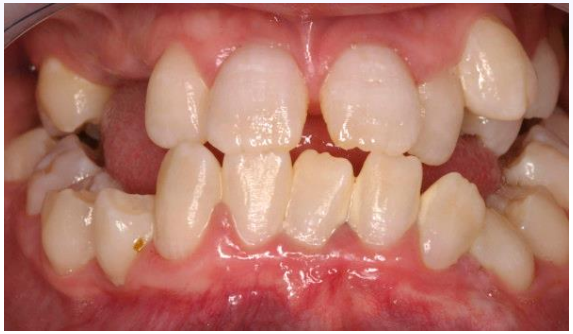
Dentin Dysplasia Type I

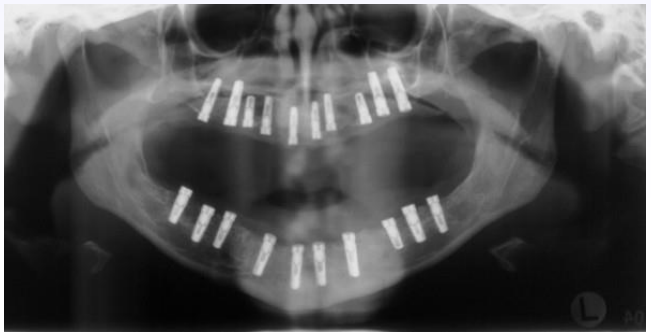


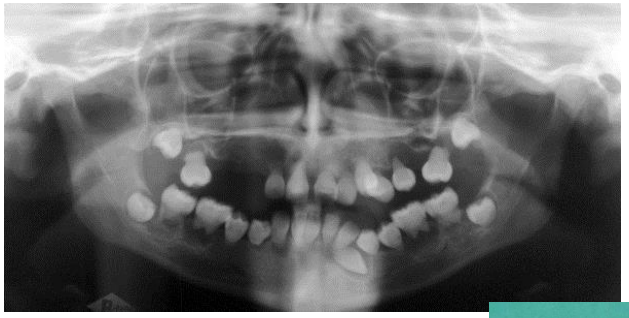


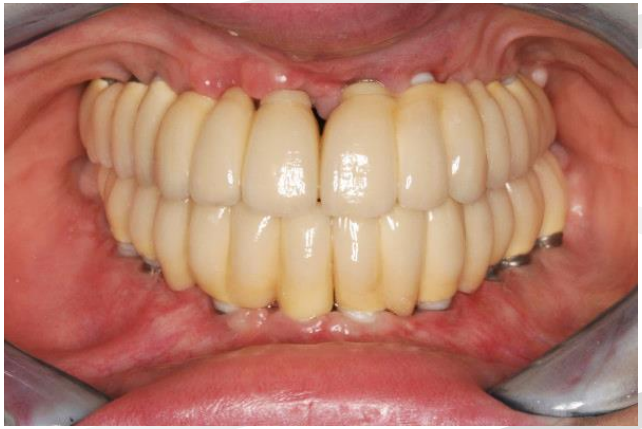


Dentin dysplasia type I: a challenge for treatment with dental implants.









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Depprich RA et al. Head Face Med., 2007

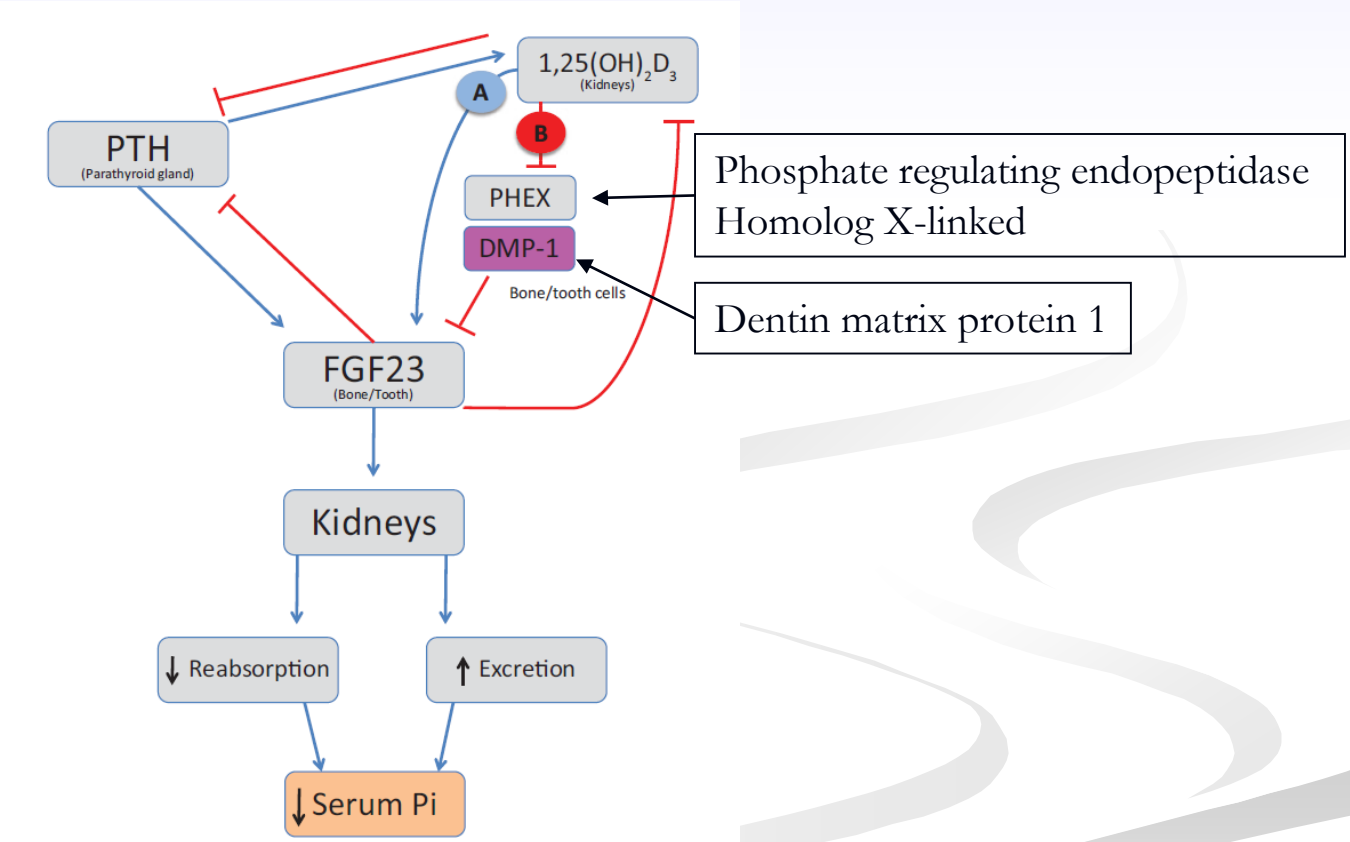
Syndromes involving dentin annomalies

- Hyperphosphatemic famialial tumoral calcinosis (HFTC)
- Familial hypophosphatemic vitamin D-resistant rickets

Phosphate Regulation and Related Conditions

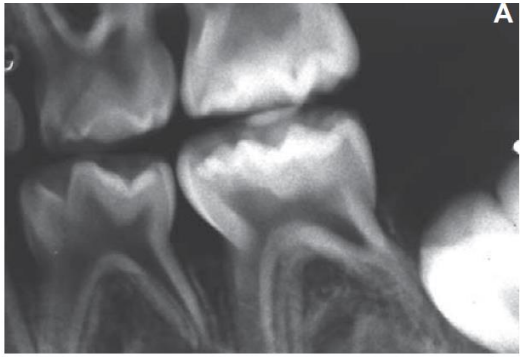
- Parathyroid hormone, 1,25-dihydroxyvitamin D and fibroblast-growth-factor 23 (FGF23).
- X-linked hypophosphatemia (XLH), autosomal dominant HR (ADHR), and autosomal recessive HR (ARHR) are examples of hereditary forms of Hypophosphatemia Rickets.
- Mutations in the phosphate regulating endopeptidase homolog, X-linked (*PHEX*), *FGF23,* and, dentin matrix protein-1 (*DMP1*) and ecto-nucleotide pyro phosphatase/phosphodiesterase 1 (*ENPP1*) genes, respectively are believed to cause elevation of circulating FGF23 protein. Increase in FGF23 disrupts phosphate homeostasis, leading to HR.

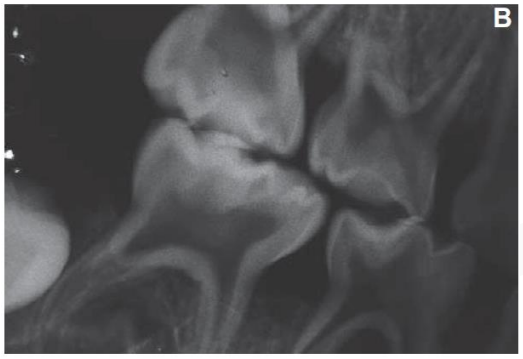
Model for hypothesized 1α,25(OH)2D3 (1,25D) regulation of FGF23 expression



Nociti FH, Jr. et al. J Dent Res, 2014: 93(2) 148-54.

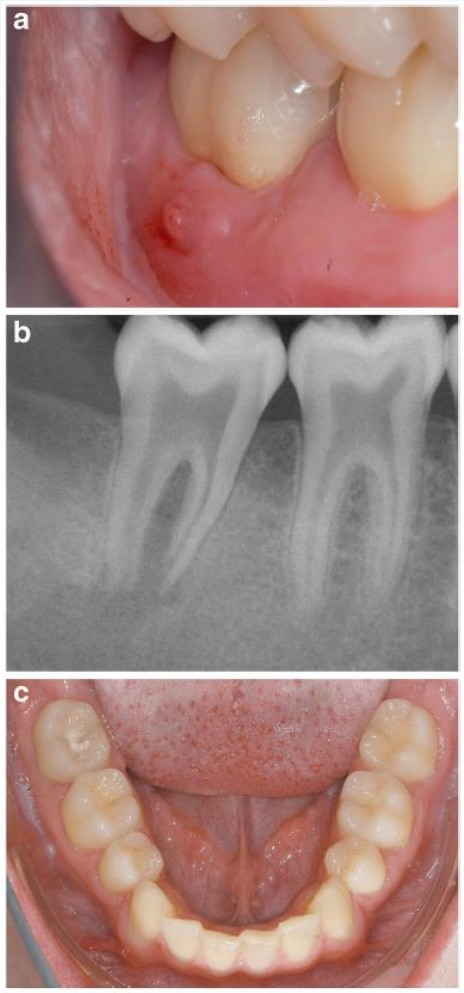
Hypophosphatemic Rickets

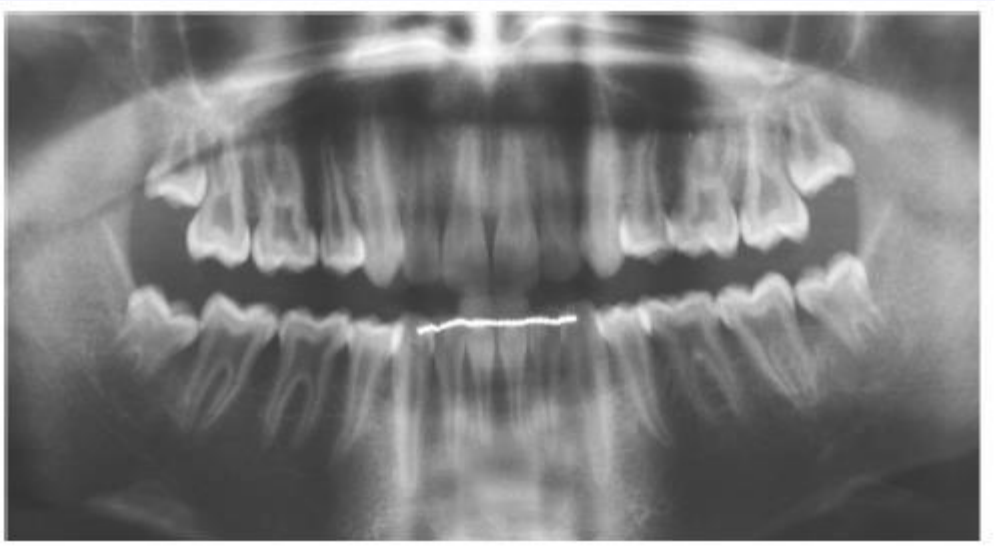


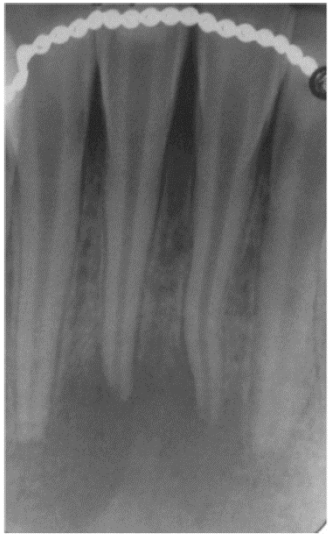


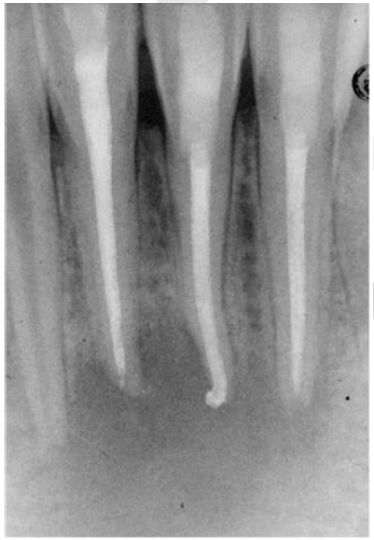
Souza AP et al. J Appl Oral Sci, 2013

Hypophosphatemic Rickets



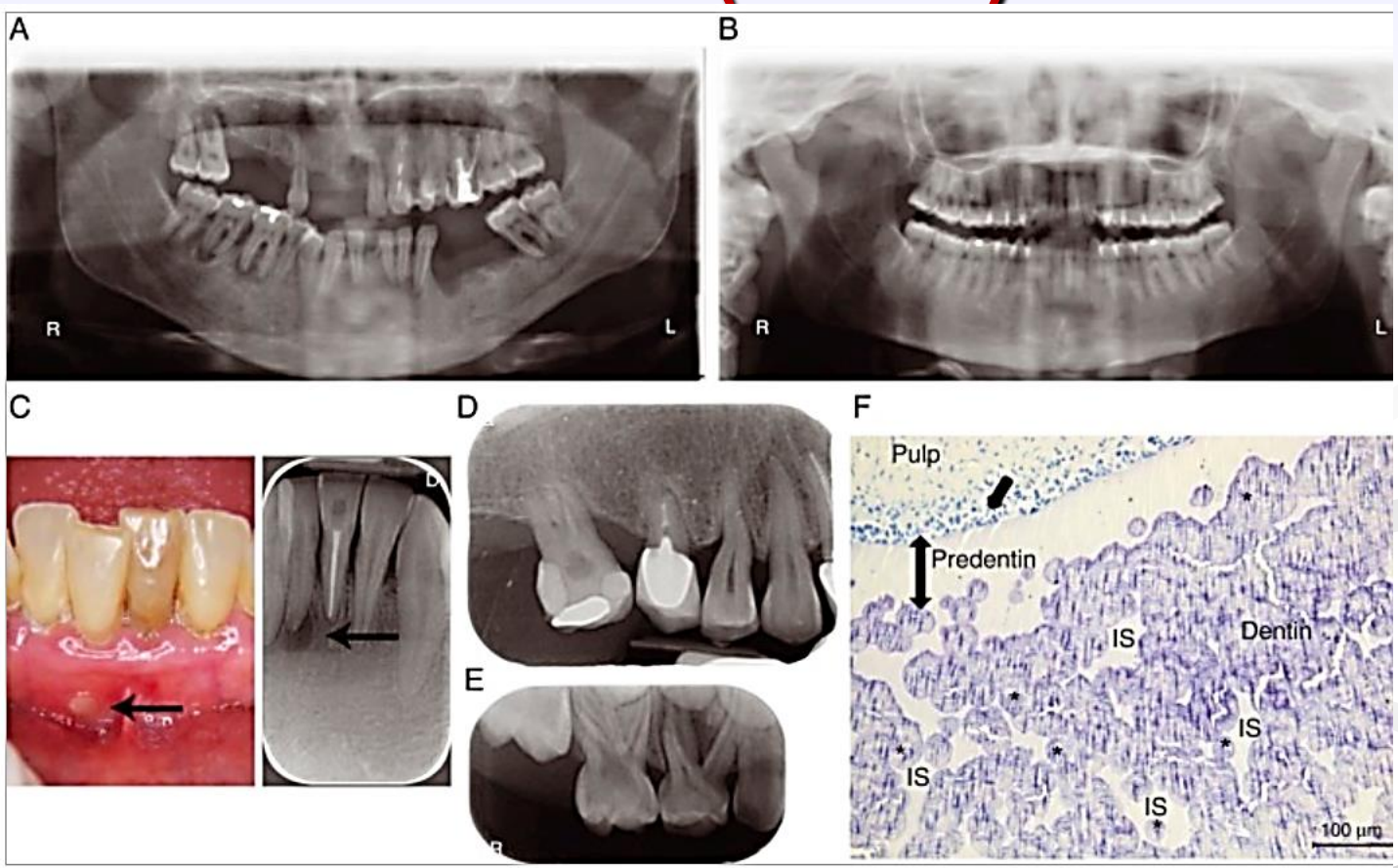






Martin et al. Clin Oral Invest (2015) 19:759-768)

X-linked hypophosphataemic rickets (XLHR)

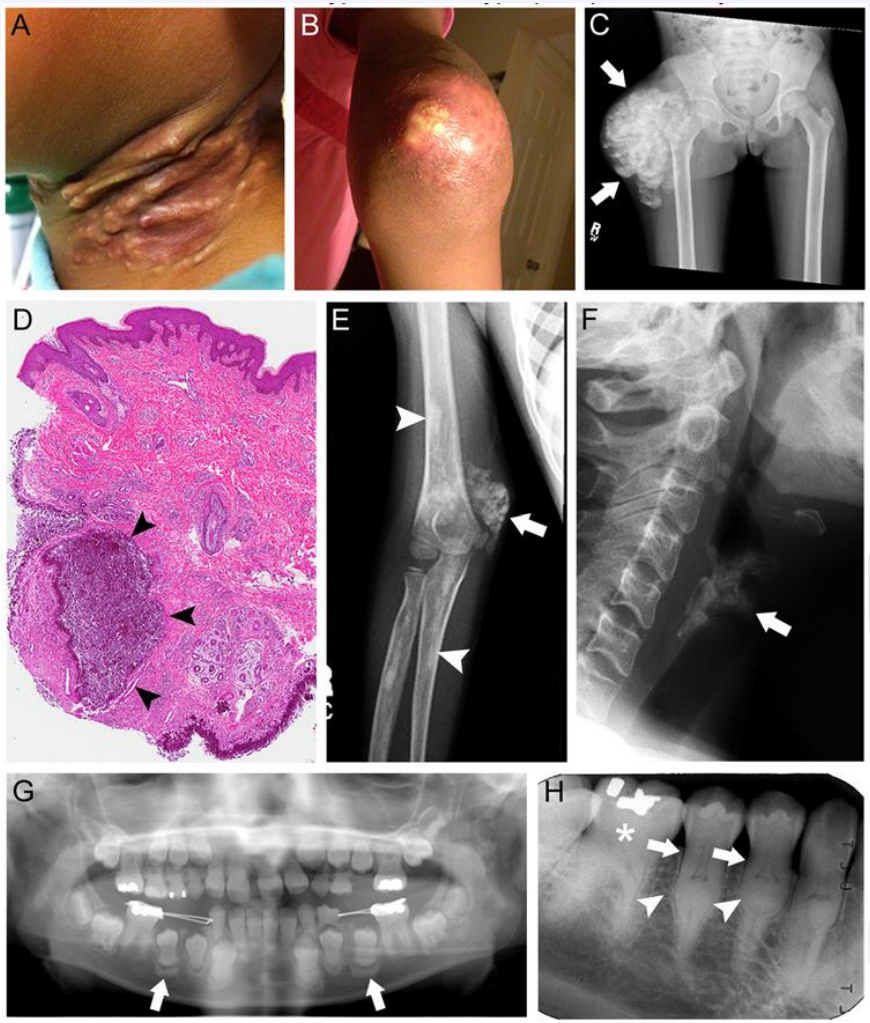


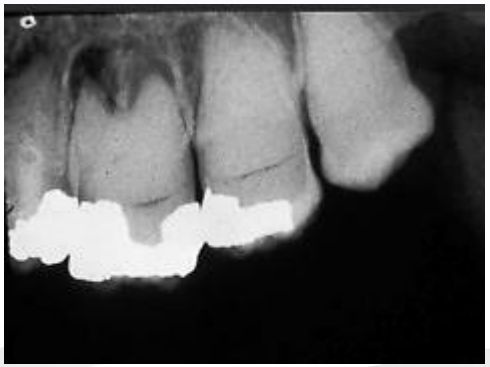
Linglart A et al. Endocr Connect. 2014 Mar 1; 3(1): R13–R30.

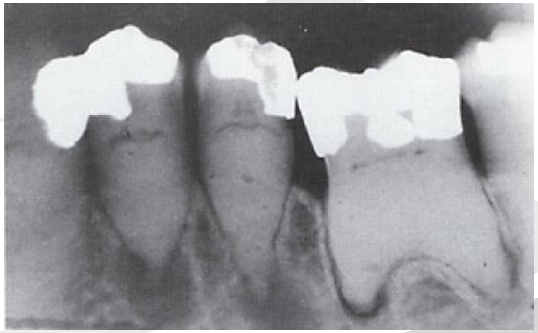
Familial Tumoral Calcinosis/Hyperostosis-Hyperphosphatemia Syndrome

- Familial tumoral calcinosis/hyperostosis-hyperphosphatemia syndrome (FTC/HHS; MIM 211900) is an autosomal-recessive disorder arising from functional deficiency of intact fibroblast growth factor 23 (iFGF23)
- Clinical manifestations include periarticular, subcutaneous, and soft-tissue calcifications that tend to occur in areas of trauma.
- Ectopic calcifications, radiographs often reveal cortical hyperostosis, which may cause diaphyseal pain of the long bones.

Familial Tumoral Calcinosis/Hyperostosis-Hyperphosphatemia Syndrome





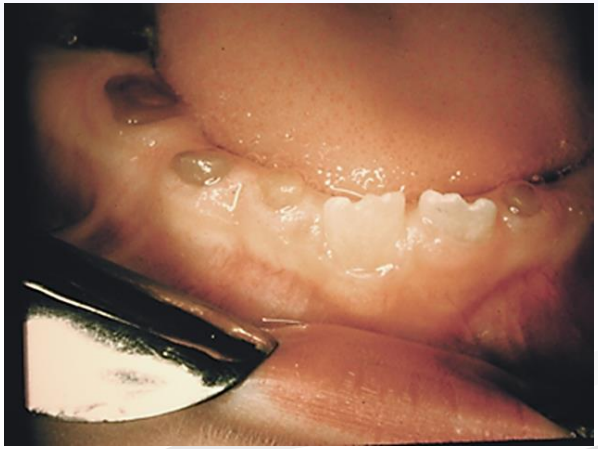


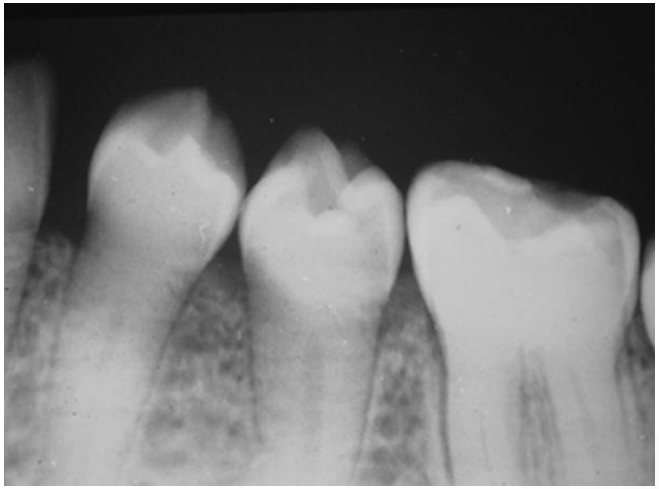
Foster BL et al. J Dent Res. 2014 Jul; 93(7 Suppl): 7S–19S.

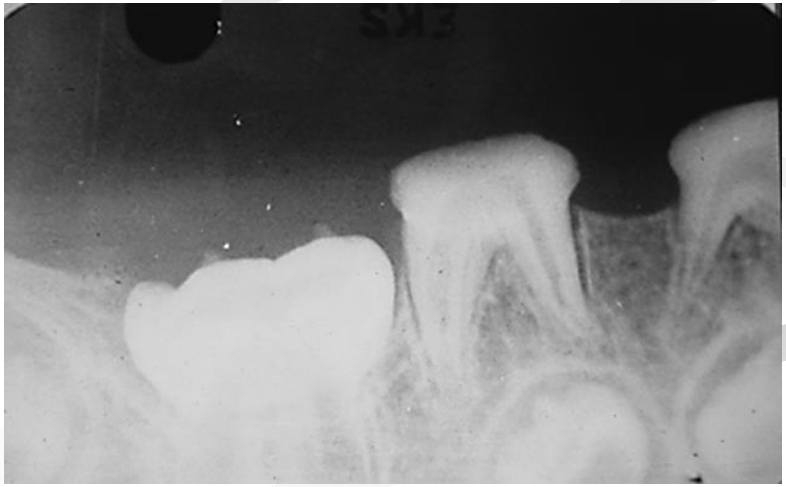
Syndromic forms of Dentinogenesis Imperfecta (DGI)

- Syndrome associated with DGI with a collagen mutation.
  - Osteogenesis Imperfecta
  - Ehlers-Danlos syndrome
  - Goldblatt syndrome
- Syndromes Associated without a collagen mutation.
  - Schimke Immunoosseous dysplasia (SIOD)

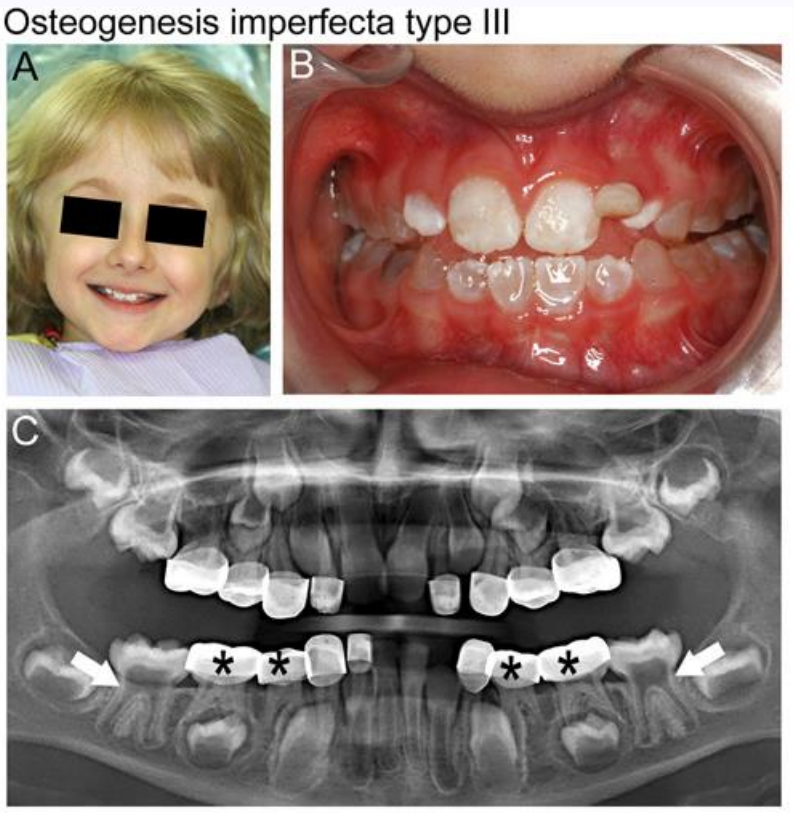
Dentinogenesis Imperfecta Type I

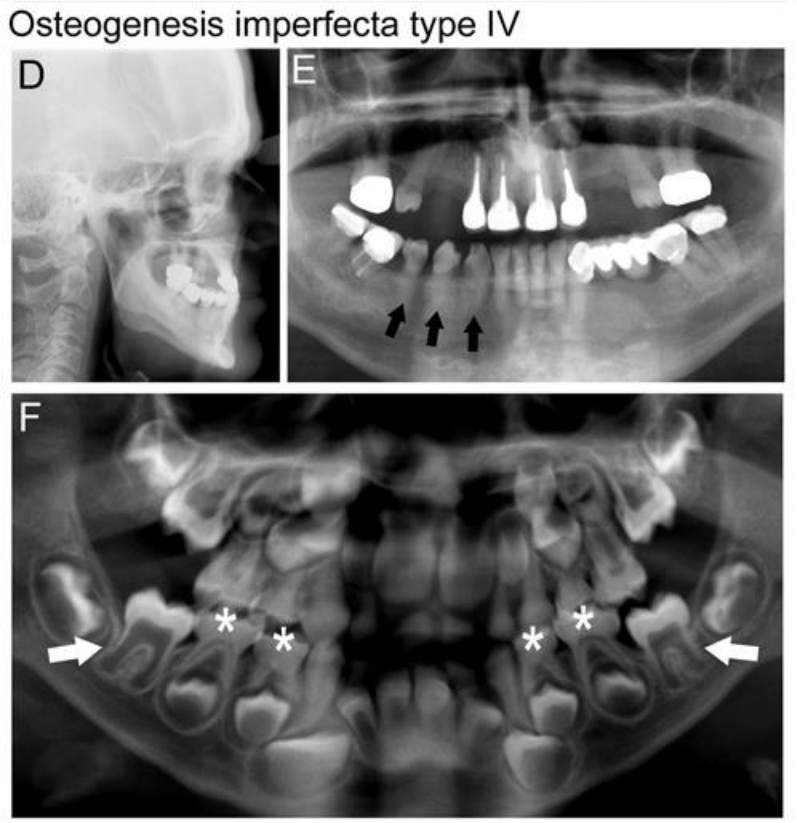






Ontogenesis Imperfecta





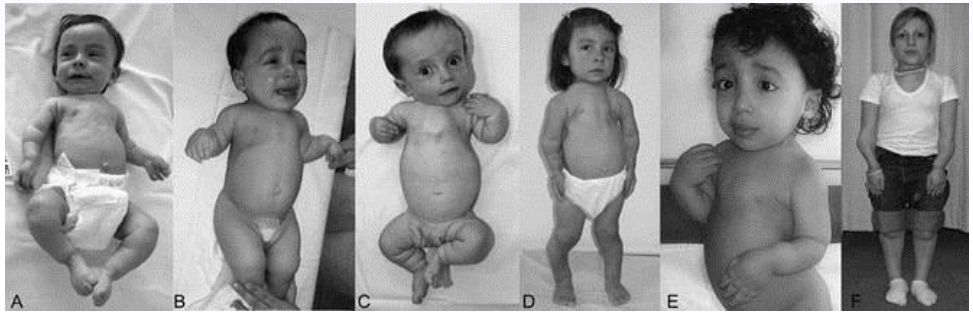
Goldblatt Syndrome
ODONTOCHONDRODYSPLASIA

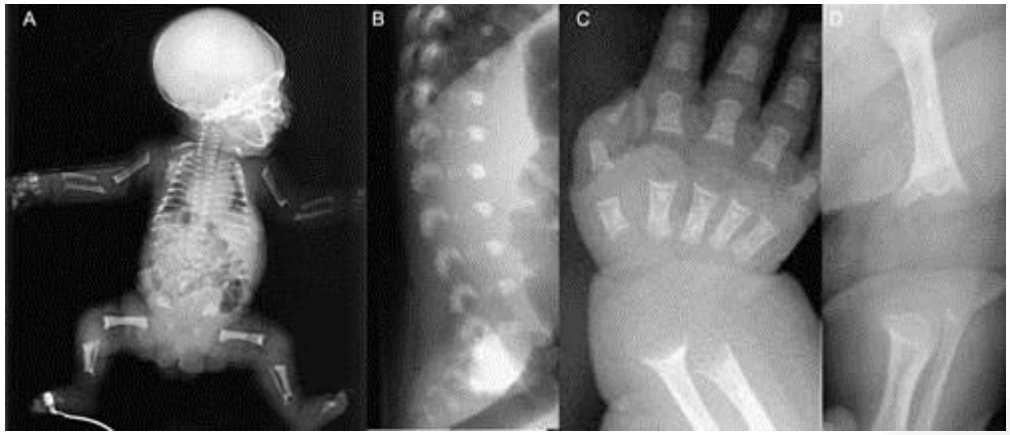
- This rare syndrome (OMIM184260) combines spondylometaphyseal dysplasia, joint laxity and DGI or dentin dysplasia type II.
- Deciduous teeth are opalescent whilst the permanent teeth are almost normal.
- decrease in synthesis of collagen type I (Alpha1 and Alpha 2), and a single-base substitution in the COL2A1 gene.
- This mutation has sequential effects on tissue-specific regulatory sequences that control the expression of type I collagen genes.
- Mutation analysis of *COL2A1* as well as of *COMP*, *FGFR3*, *RMRP*, and *SBDS* in one or more patients have given negative results, and the molecular etiology is as yet unknown.

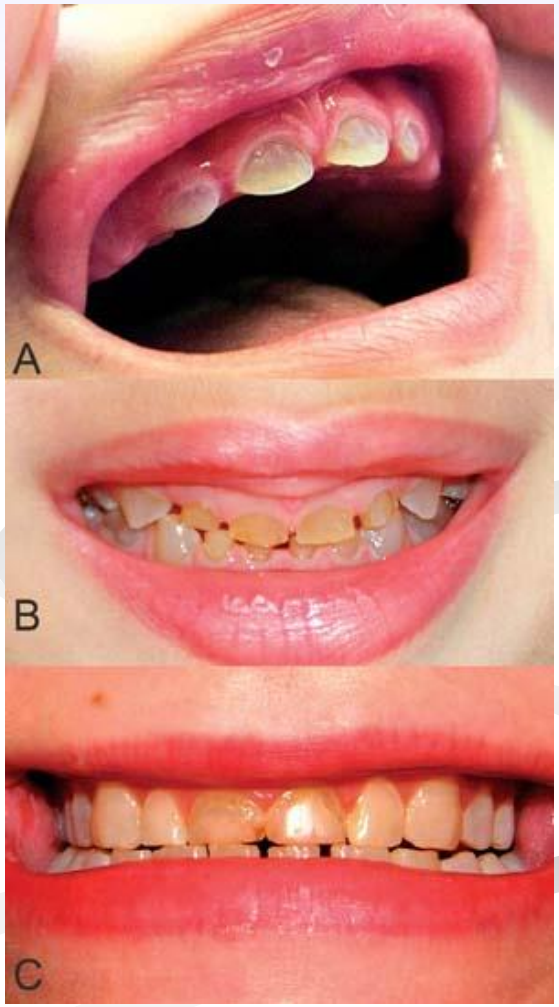
Goldblatt Syndrome
ODONTOCHONDRODYSPLASIA

- The main radiographic features are congenital platyspondyly with coronal clefts, severe metaphyseal changes particularly of the hands, wrists, and knees, mesomelic limb shortening, and coxa valga.
- The main physical signs are short stature, joint laxity, narrow chest, scoliosis, and DI.

Goldblatt Syndrome
ODONTOCHONDRODYSPLASIA







Unger S, et al. Am. J. Med. Genet. 146A:770-778, 2008

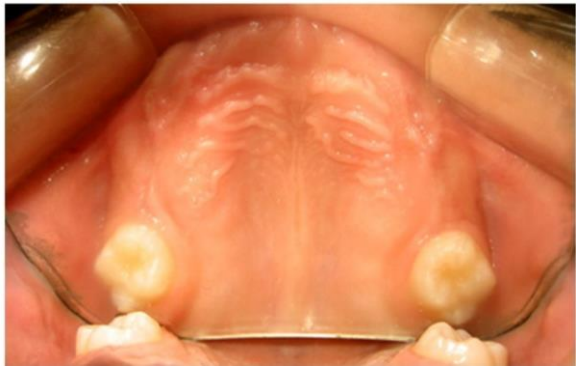
Ehlers Danlos Syndrome

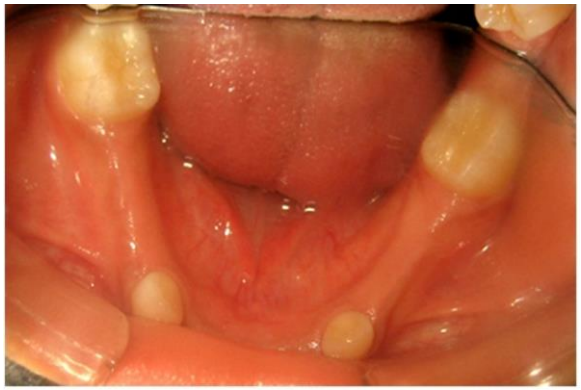
- Hypermobility of the joints.
- Hyperelasticity, fragility and softness of the skin.
- Deficient healing of wounds.
- Ecchymosis caused by minor traumas.
- Cardiovascular complications (such as aneurysms and mitral valve prolapse), gastrointestinal complications (hernias and gastrointestinal diverticulosis), and ocular defects

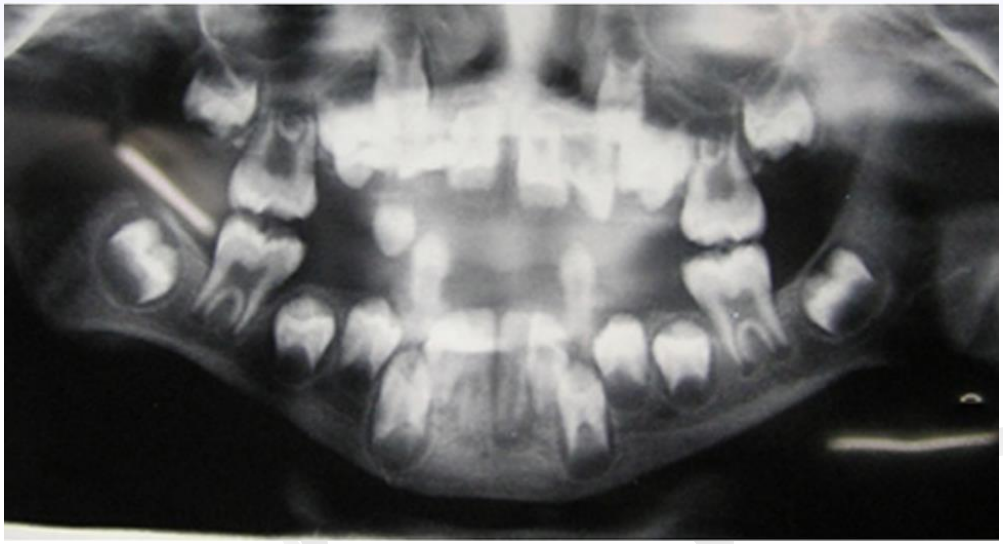
Ehlers Danlos Syndrome Type VIII

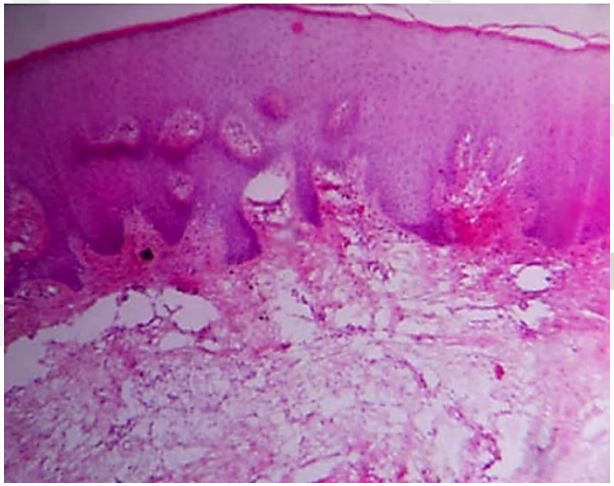
- Stewart and others in 1977
- Generalized early-onset periodontitis
- Large patches of scar tissue on the shins, similar to diabetic ulcers or varicose veins.
- The periodontal problems appear at puberty and usually lead to loss of the teeth before age 30.
- Type I and type III anomalies of collagen have been linked to EDS type VIII.

Type III





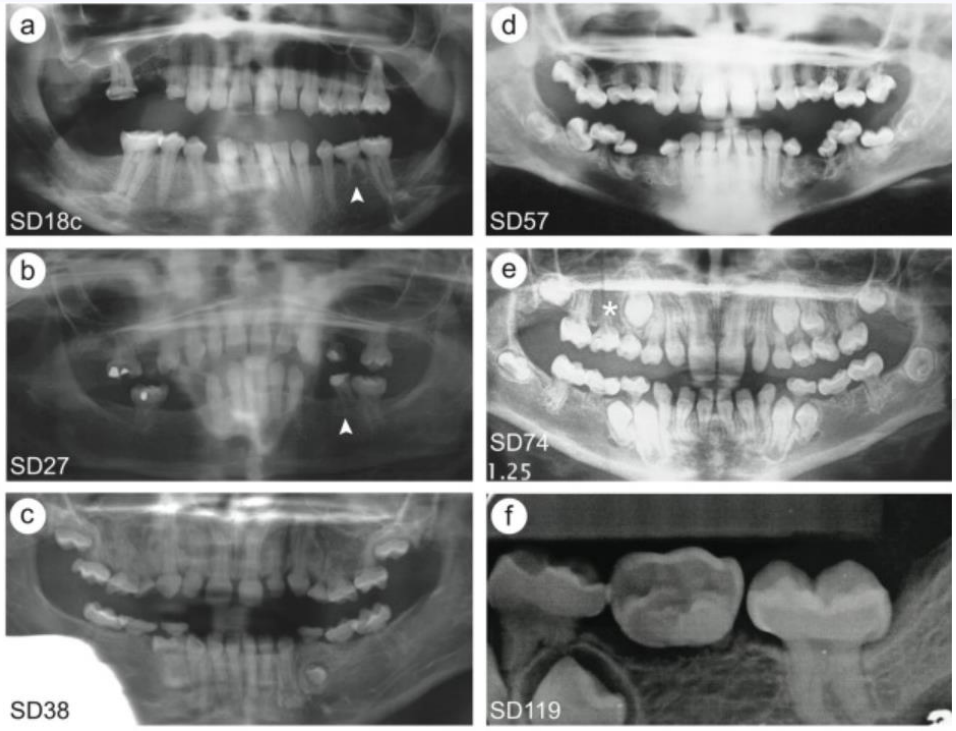




Kaurani P. et al. J Clin Diagn Res. 2014 Mar; 8(3): 256–258

Schimke immuno-osseous dysplasia

- Autosomal recessive disorder that results in spondyloepiphyseal dysplasia, renal dysfunction, immunodeficiency, facial dysmorphism and growth failure.
- Multisystem disorder that is caused by bi-allelic mutations of SMARCAL1, which encodes a DNA annealing helicase.



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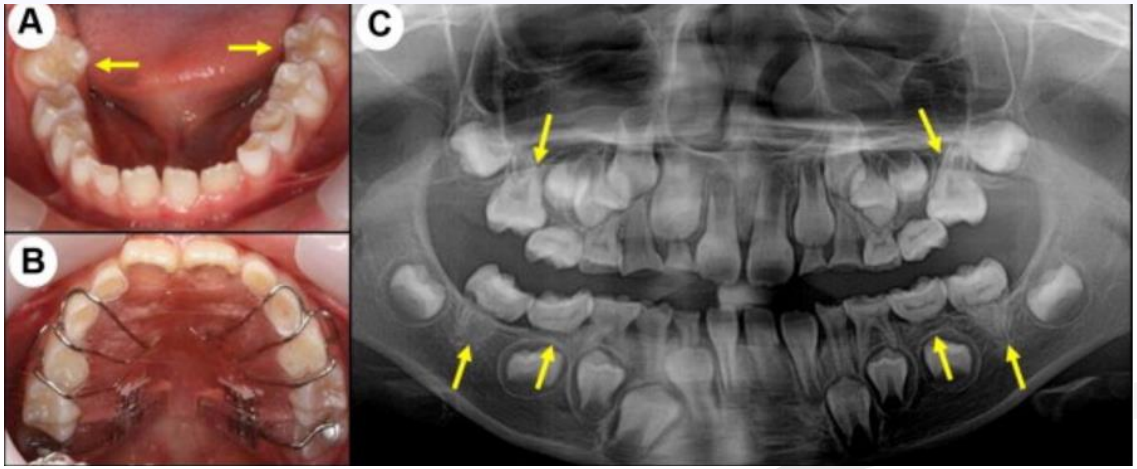
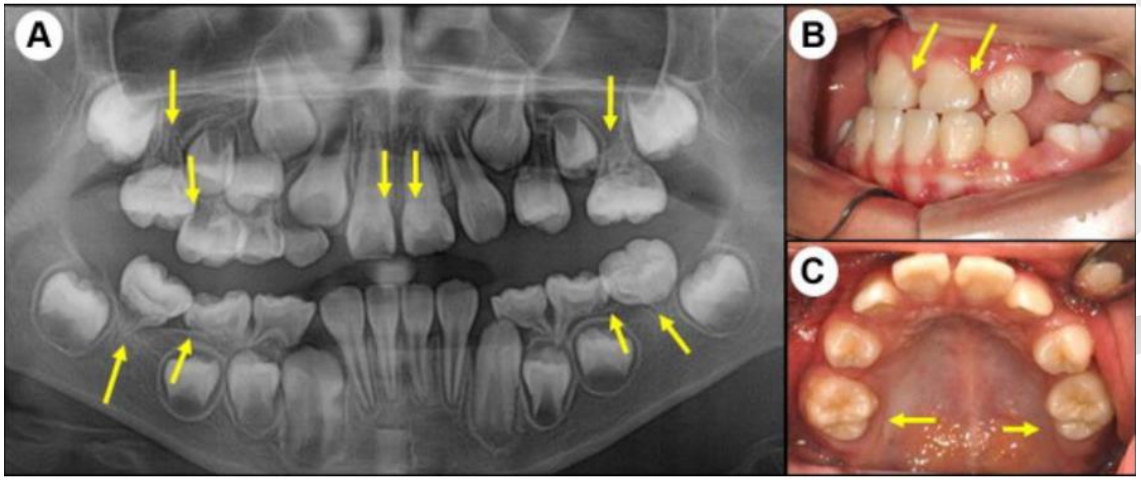
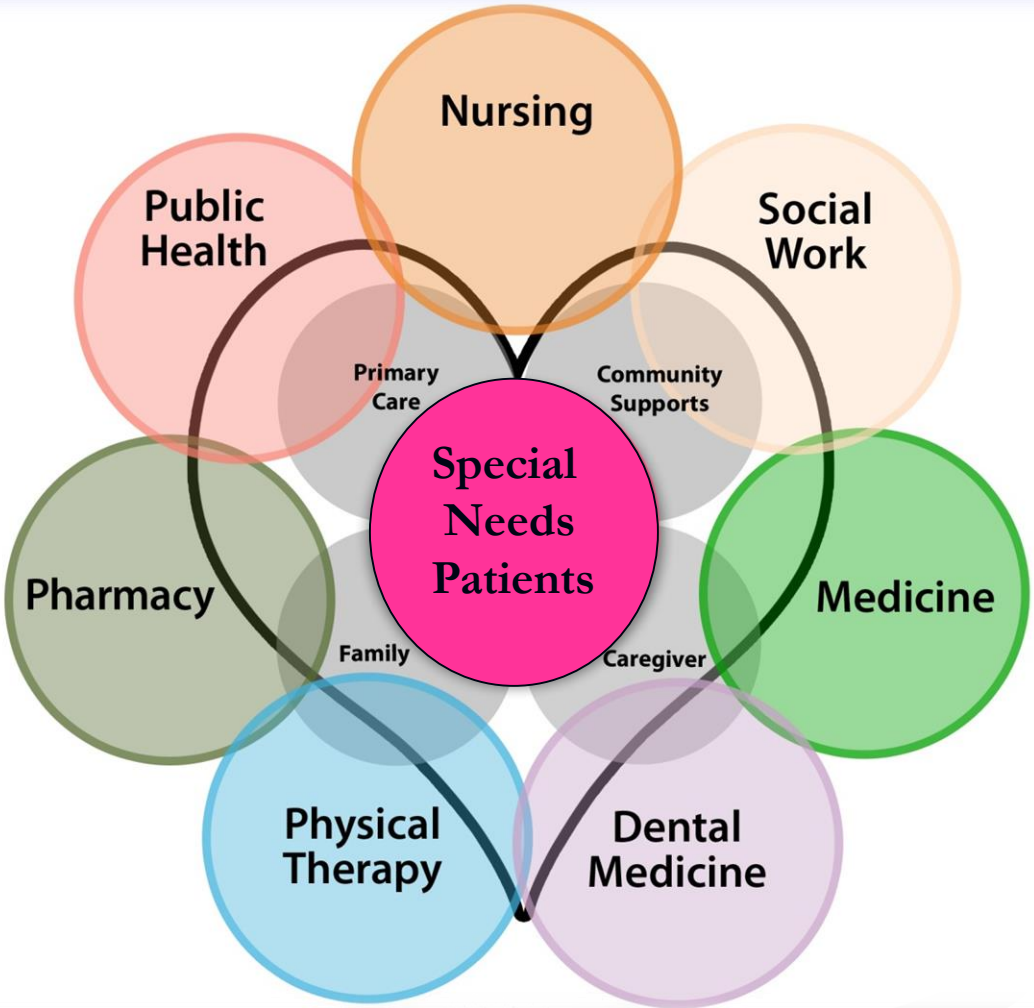
Schimke Immuno-osseous Dysplasia






Nursing
Public Health
Social Work
Primary Care
Community Supports
Special Needs Patients
Pharmacy
Medicine
Family
Caregiver
Physical Therapy
Dental Medicine

Interprofessional Education

How can they work together
if they don't learn together?

Special Needs is a Team Game!

Thank You!