Amelogenesis Imperfecta (AI)

DEFINITION: *Amelogenesis imperfecta* (AI) is a heterogeneous group of inherited defects in dental enamel formation. The malformed enamel can be unusually thin, soft, rough and stained. The strict definition of AI includes only those cases where enamel defects occur in the absence of other, non oral, symptoms. Isolated enamel malformations are caused by defects in a number of different genes. X-linked, autosomal dominant, and autosomal recessive modes of inheritance are possible, with considerable variability in the character and appearance of the resulting enamel. Fourteen subtypes are recognized. *Amelogenesis imperfecta* has also been used to describe enamel defects associated with inherited syndromes. There are over 70 such conditions.
Synonyms: None

DIFFERENTIAL DIAGNOSIS: Dental fluorosis, enamel hypoplasia secondary to systemic disease, tetracycline staining, hypophosphatemia, dentinogenesis imperfecta (DGI), AI as part of a broader syndrome.

SIGNS & SYMPTOMS: The spectrum of enamel malformations that are observed in patients with *amelogenesis imperfecta* is divided into three groups based primarily upon the thickness and hardness of the dental enamel. Differences in these parameters are believed to reflect differences in the timing, during amelogenesis, when the disruption occurred. During tooth formation, enamel first appears on the surface of recently deposited dentin, at what becomes the dentino-enamel junction or DEJ. The thickness of the enamel layer as a whole increases primarily by the elongation of enamel crystallites. Flaws in the dentino-enamel junction can result in an enamel layer that shears easily from the underlying dentin. Insufficient crystal elongation leaves the enamel layer pathologically thin, or hypoplastic. The most severe form of hypoplastic AI is enamel *agenesis*, where there is almost no clinical or radiographic evidence of enamel. The teeth are yellowish brown in color, rough in texture, and widely spaced. When the enamel crystals achieve their final length (and the enamel layer itself achieves its final thickness), the organic matrix separating individual enamel crystallites is degraded and resorbed. The enamel layer then hardens or "matures" as mineral deposits on the sides of the crystals until adjacent crystallites contact. A failure to properly remove the organic matrix and promote the hardening of the enamel layer leads to pathologically soft or hypomaturation forms of AI. The dental crowns are of normal size and contact adjacent teeth, but the mottled, brownish-yellow enamel is soft and has a radiodensity approaching dentin. X-linked forms of hypoplastic and hypomaturation AI often show a distinctive phenotype in affected females, where the enamel displays alternating vertical bands of normal and defective enamel. This phenotype is called "Lyonization", and results from the alternative inactivation of either the normal or the defective X chromosome in different cohorts of enamel forming cells. In the third type, hypocalcified AI, the failure in mineralization is most extreme. The enamel layer may be of normal thickness, but is extremely soft and wears away quickly following tooth eruption. Patients with hypocalcified enamel form calculus rapidly and develop acute and chronic periodontitis.

CLASSIFICATION: Witkop Jr. CJ (1989). Amelogenesis imperfecta, dentinogenesis imperfecta and dentin dysplasia revisited: problems in classification. *J Oral Pathol* 17:547-53.

Hypoplastic: Enamel layer is thin, but hard

1. Autosomal dominant pitted hypoplastic *amelogenesis imperfecta*
2. Autosomal dominant local hypoplastic *amelogenesis imperfecta*
3. Autosomal dominant smooth hypoplastic *amelogenesis imperfecta*
4. Autosomal dominant rough hypoplastic *amelogenesis imperfecta*
5. Autosomal recessive rough *amelogenesis imperfecta* (enamel agenesis)
6. Autosomal recessive smooth hypoplastic *amelogenesis imperfecta*
7. X-linked (dominant) smooth hypoplastic *amelogenesis imperfecta*

Hypocalcification: Enamel is soft, may have normal thickness

8. Autosomal dominant hypocalcified *amelogenesis imperfecta*
9. Autosomal recessive hypocalcified *amelogenesis imperfecta*

Hypomaturation: Soft, brown enamel, normal thickness

10. X-linked (recessive) hypomaturation *amelogenesis imperfecta*
11. Autosomal recessive pigmented hypomaturation *amelogenesis imperfecta*
12. Snow-capped teeth

Hypomaturation-hypoplastic with taurodontism:

13. Autosomal dominant hypomaturation-hypoplastic *AI* with taurodontism
14. Autosomal dominant hypoplastic-hypomaturation *AI* with taurodontism

ETIOLOGY: *Amelogenesis imperfecta*, by the strict definition of inherited enamel defects in the absence of a generalized syndrome, occurs in approximately 1 out of every 14,000 people. X-linked *amelogenesis imperfecta*, which accounts for about 5% of all cases, is caused by defects in the amelogenin gene (Xp22.3-p22.1). Autosomal forms of AI have been shown to be caused by defects in the enamelin (ENAM, 4q13), enamelysin (MMP20, 11q), and kallikrein 4 (KLK4, 19q) genes. Not all of the genes that cause AI have been identified. The ameloblastin gene (AMBN, 4q) is also a prime candidate. It is likely that in the future the classification of AI will be according to the gene involved.

DIAGNOSIS: *Amelogenesis imperfecta* can be diagnosed by an oral examination with dental radiographs and a family history to draw and analyze a pedigree to determine the mode of inheritance. For information concerning how to determine the mode of inheritance from the distribution of affected status in a pedigree, please review:

http://www.merck.com/mrkshared/mmanual/section21/chapter286/286b.jsp

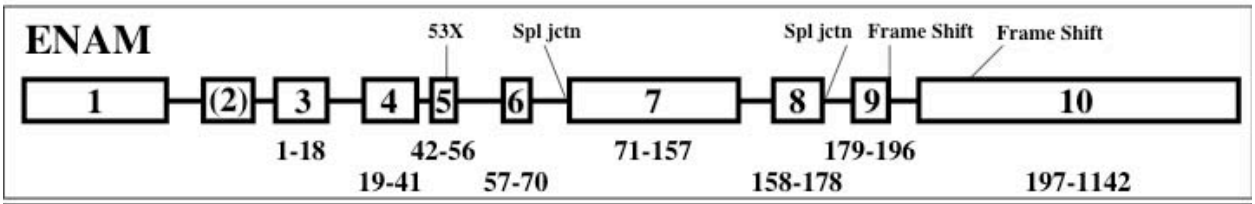
For information concerning the phenotypes observed in different types of amelogenesis imperfecta please review:

Witkop Jr. CJ, Sauk Jr. JJ (1976). Heritable defects of enamel. In: Oral Facial Genetics. RE Stewart and GH Prescott editors. St. Louis: C.V. Mosby Co., pp. 151-226.

TREATMENT: Diligent oral hygiene with frequent professional prophylactic scalings and extensive dental restorative and reconstructive procedures are often necessary. Hypomaturation and hypocalcified types may respond poorly to enamel bonding techniques. Dentin bonding is normal.

CASE REPORTS WITH MUTATION ANALYSES: Mutations in kindreds suffering from autosomal dominant (ADAI) and autosomal recessive (ARAI) have been identified in the ENAM, KLK4, and MMP20 genes. The oral phenotypes in some of these cases are provided. It is believed that phenotype and mode of inheritance will permit educated guesses as to which genes should be selected for mutation analyses.

I. Enamelin Gene (ENAM).



	Protein	cDNA	Gene	Diagnosis	References
Exon 5	p.K53X	c.157A>T	g:2382A>T	Local Hypoplastic	Mårdh et al. 2002
Intron 6	p.M71-Q157del		g.4806A>C	Hypoplastic	Kim et al. 2005
Intron 8	p.A158-Q178del		g.6395G>A	Smooth Hypoplastic	Rajpar et al. 2001
Intron 9	p.N197fsX277		g.8344delG	Pitted/smooth Hypoplastic	Kida et al. 2002 Hart et al. 2003a Kim et al. 2005
Exon 10	p.P422fsX448	c.1258_1259insAG	g.13185_13186insAG	Hypoplastic	Hart et al. 2003b

Figure 1a. Enamelin gene structure and mutations that cause ADAI. The structure of the human enamelin gene showing the positions of known mutations in AI kindreds is shown at the top. The exons are blocks numbered one through ten; the introns are lines. Below each exon is a range of numbers indicating the amino acids it encodes. The lower box shows the predicted effect of each mutation on the protein, the location of the mutation in the cDNA and gene, the type of enamel defect, and the reference(s) where each mutation are listed. Reference: Kim J-W, Seymen F, Lin BP-L, Kiziltan B, Gencay K, Simmer JP, Hu JC-C (2005). Two enamelin gene mutations in kindreds with autosomal dominant amelogenesis imperfecta. *J Dent Res*.

Case 1: Autosomal Dominant/Hotspot ENAM Mutation at the exon 9/intron 9 boundary.

Mutation: ENAM gene at the exon 9/intron 9 boundary, g.8344delG, p.N197fsX277. One of six Gs at the end of exon 9 was deleted, shifting the reading frame after Gly^{196}, and causing the synthesis of a chimeric protein predicted to have 196 amino acids of the wild-type protein (normally 1142 amino acids) followed by 80 novel amino acids, for a total of 276 amino acids (p.N197fsX277). This mutation was independently identified in three unrelated kindreds.

References:

Kim J-W, Seymen F, Lin BP-L, Kiziltan B, Gencay K, Simmer JP, Hu JC-C (2005). Two enamelin gene mutations in kindreds with autosomal dominant amelogenesis imperfecta. *J Dent Res*.

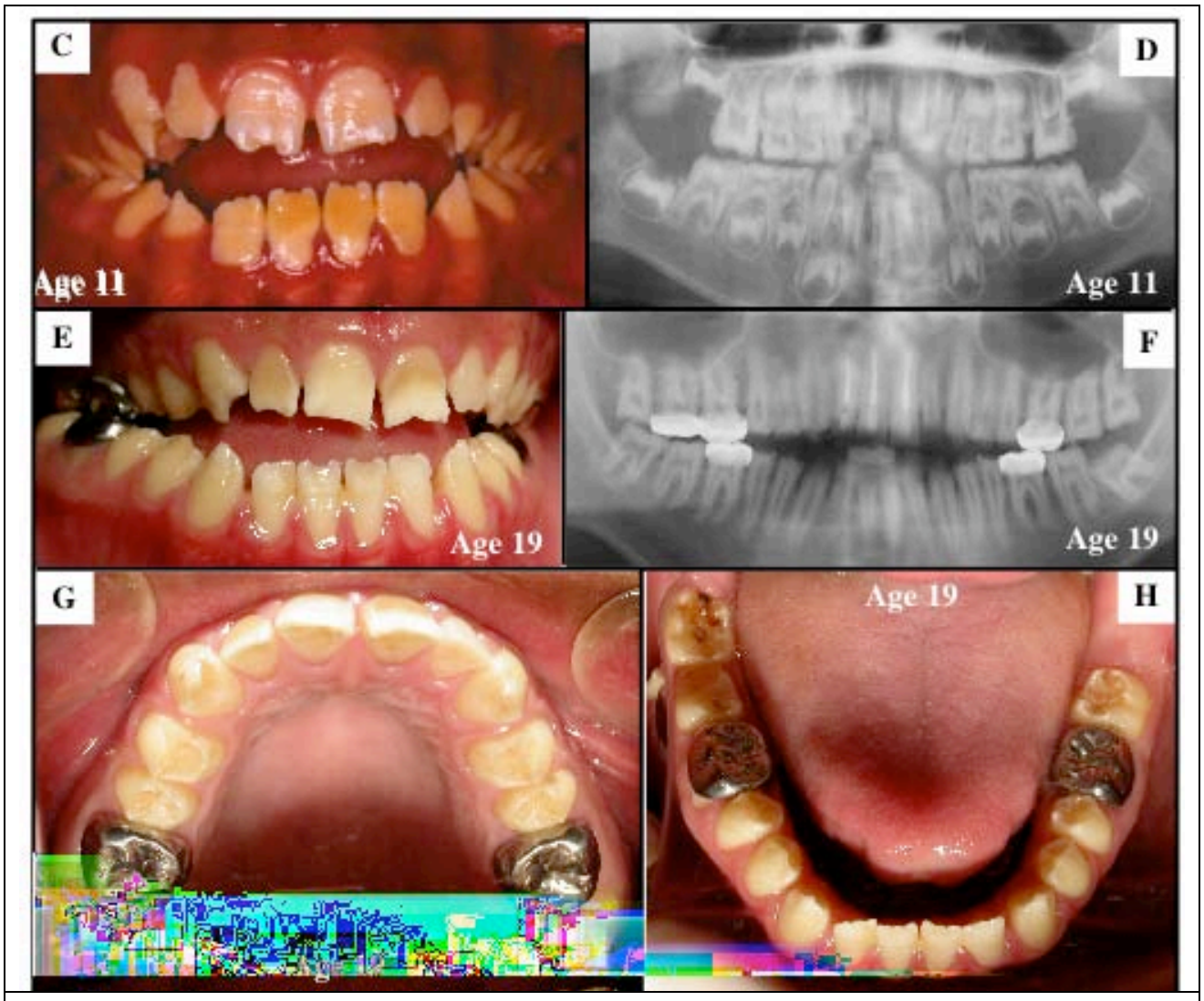


Figure 1b. Panels C and D show frontal photograph and a panorex radiograph for the proband taken at ages 11. Panel E through H show intraoral photographs and a panorex radiograph taken at ages 19. The upper anterior teeth were treated endodontically and restored with composite resin restorations. Kim *et al.*, (2005) J Dent Res.

Description: The proband was an 11-year-old male. Oral hygiene was poor and thick deposits of plaque and calculus were evident, even on the facial surfaces of the anterior teeth. The proband had an anterior openbite and the incisal edges were jagged and chipped easily. His teeth were sensitive to thermal changes. The enamel layer was unusually thin, with shallow horizontal grooves on the buccal middle 1/3 of anterior teeth. The enamel appeared most normal on the occlusal surfaces of the posterior teeth, especially near the cusp tips and on the marginal ridges, and at the incisal line angles of the anterior teeth. Outside of these areas, the teeth were yellow in color due to thinness. A traumatic injury to the anterior teeth resulted in endodontic treatment of 7, 8 and 9, which further altered the color of these teeth. Sealant and composite restorations were of normal durability after several years of follow-up. Mutational analyses revealed that one of seven Gs at the end of exon 9/beginning of intron 9 was deleted (g.8344delG).

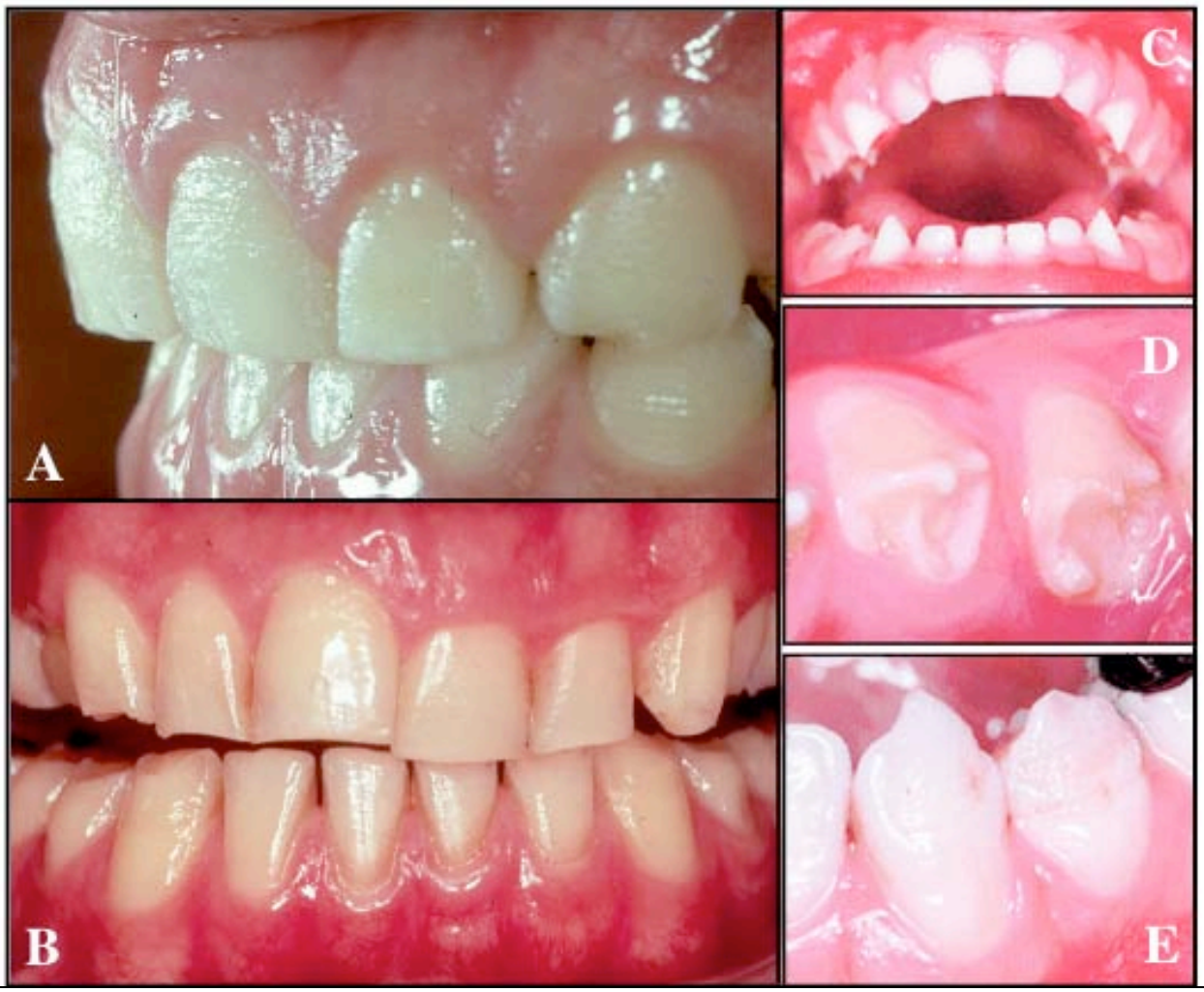


Figure 1c. Both affected Lebanese individuals (A & B) showed a generalized and severe thinning of the enamel. The dentition of the proband (A) shows horizontal furrows with pits while another dentition (B) appears to have been worn smooth. Radiographically the primary and permanent teeth showed little to no visible enamel. The visible enamel had a greater radiopacity compared with dentin suggesting the enamel had a greater mineral content than dentin. Histological examination of the teeth showed the dentin was normal. The enamel thickness did not exceed 40 μm and was often only 10—20 μm in thickness. This represents a 25—100-fold reduction in enamel thickness compared with normal (greater than 1mm). In a Japanese family with this mutation the male proband and his younger brother showed hypoplastic enamel in both their deciduous and permanent teeth (C & D) that resulted in hypersensitivity to cold stimuli. Anterior open bite was found in both of them in the primary dentition. Their father showed local hypoplastic enamel defects demonstrating a horizontal lesion involving primarily the middle third of the permanent teeth (E). In the molars, the lesion was further extended occlusally. In contrast to his sons, he showed normal sensitivity to cold stimuli in the affected teeth.

References: Hart PS, Michalec MD, Seow WK, Hart TC, Wright JT (2003). Identification of the enamelin (g.8344delG) mutation in a new kindred and presentation of a standardized ENAM nomenclature. *Arch Oral Biol* 48:589-596.

Kida M, Ariga T, Shirakawa T, Oguchi H, Sakiyama Y (2002). Autosomal-dominant Hypoplastic Form of Amelogenesis Imperfecta Caused by an Enamelin Gene Mutation at the Exon-Intron Boundary. *J Dent Res* 81:738-742.

Case 2: Autosomal Dominant Mutation in intron 6.

Mutation: Enamelin gene mutation (g.4806A>C, IVS6-2A>C), which alters the intron 6 splice acceptor site causing ADAI. Two defective splicing outcomes are probable for this mutation. The first is the inclusion of intron 6 (1615 bp). This would insert multiple, in-frame stop codons preceding the most 3' exon. Translation of this transcript would add 8 novel amino acids to 70 amino acids of the wild-type protein, with the first 39 amino acids constituting the signal peptide.

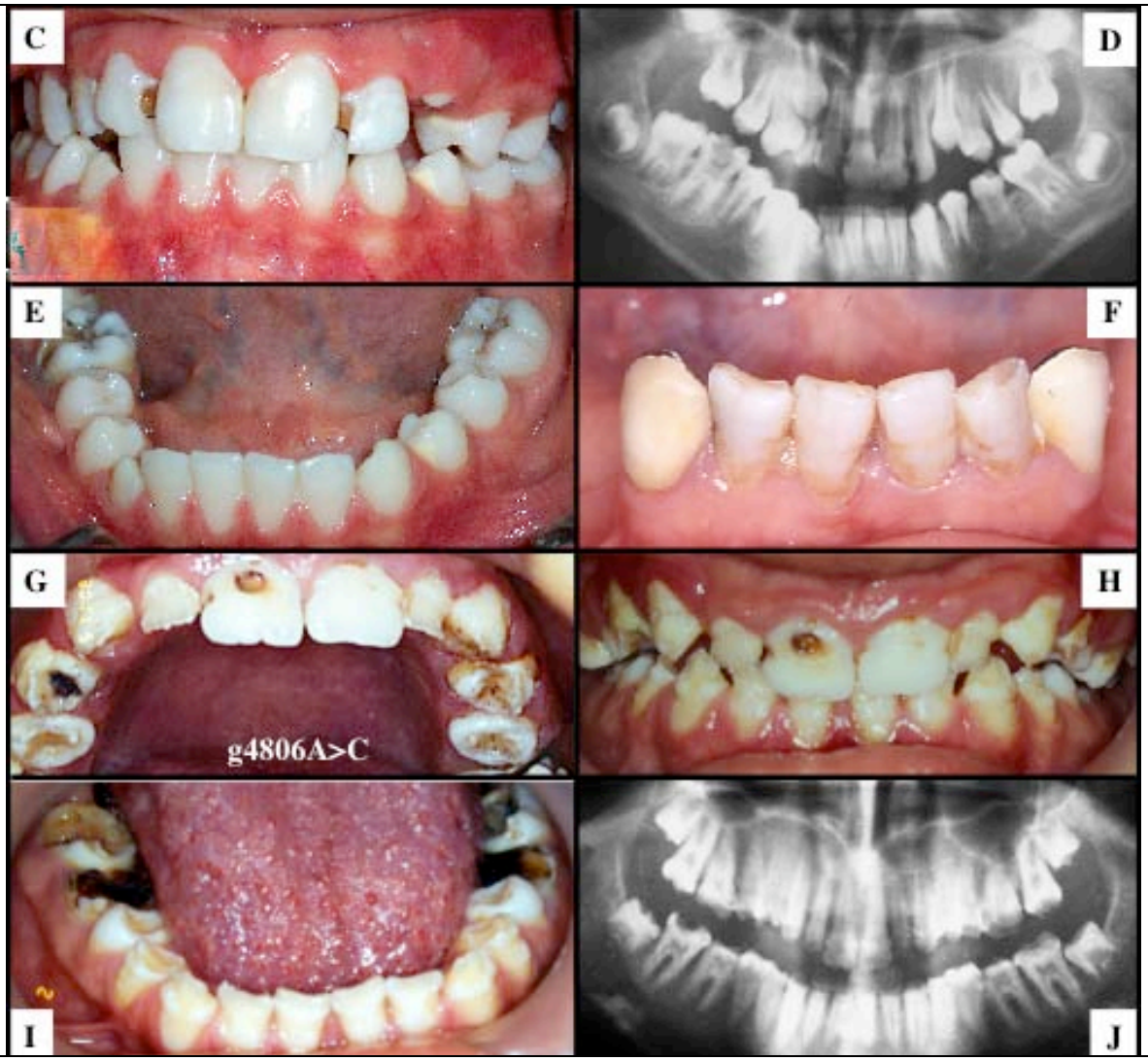


Figure 2. Panels C through E show intraoral photographs and a panorex of the proband's 11 yr old brother. Panel F shows photograph of proband's mother, taken at age 32. Panels G through J show intraoral photographs and a panorex of the proband, which were taken at age 12.5.

Description: The proband was a 12-year-old female patient in the Pediatric Dentistry Clinic at the University of Istanbul. The proband's teeth were sensitive to thermal changes. Oral hygiene was poor and several teeth showed cavitation from advanced dental caries. She had rough and thin enamel in general, which allowed the dentin show through and give the crowns a yellowish hue and horizontal grooves of severely hypoplastic enamel. The mother had several shallow hypoplastic horizontal grooves in the lower anterior teeth.

Reference: Kim J-W, Seymen F, Lin BP-L, Kiziltan B, Gencay K, Simmer JP, Hu JC-C (2005). Two enamelin gene mutations in kindreds with autosomal dominant amelogenesis imperfecta. *J Dent Res*.

Case 3: Autosomal Recessive/Dominant ENAM Mutation in Exon 10:

Mutation: *ENAM* g.13185_13186insAG, c.1258_1259insAG, p.P422fsX448.

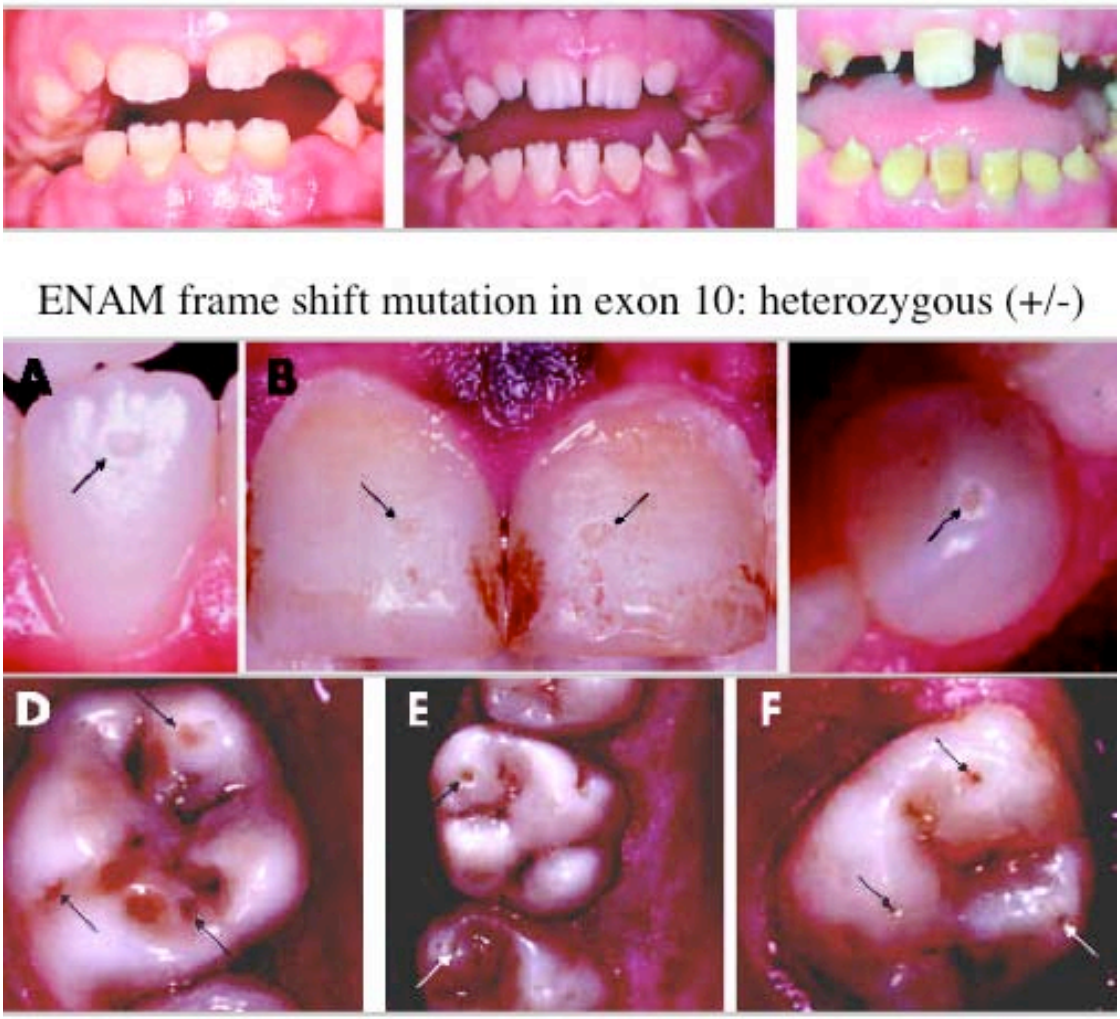


Figure 3. (Top panel) Photographs of all three probands show generalized hypoplastic enamel characteristic of hypoplastic amelogenesis imperfecta. The enamel has fractured from several teeth in the proband on the left. The posterior teeth are in occlusion in all cases, and the clinically

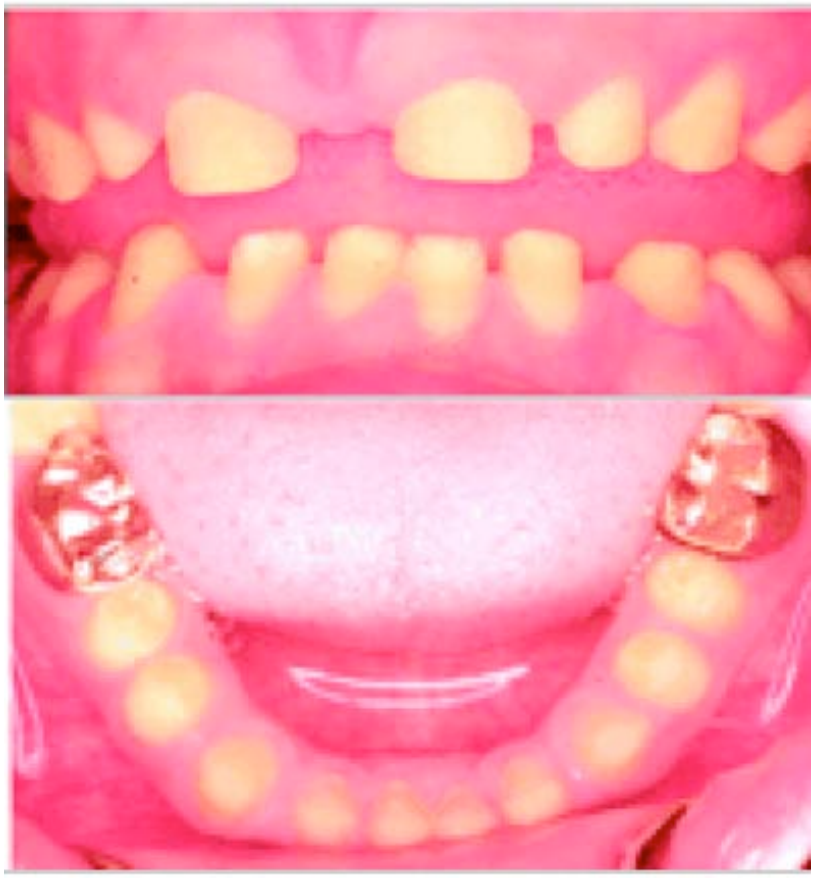
evident anterior openbite is seen in all three probands. Bottom panel: Local circumscribed enamel pitting present in heterozygous carriers of the ENAM g.13185_13186insAG mutation. (A) Enamel pit present on buccal surface of mandibular incisor. (B) Enamel pit present on buccal surfaces of maxillary incisors. (C) Enamel pit on mandibular cuspid. Multiple enamel pits present on occlusal surface of mandibular molar (D, E) and on maxillary molars.

Description: This case is particularly interesting because the pitting in the heterozygous condition would not have been considered to be AI. Thus sequence variations in the genes that participate in the etiology of AI may be cause sub-clinical defects that could conceivably result in increased susceptibility to dental diseases, such as caries.

Reference: Hart TC, Hart PS, Gorry MC, Michalec MD, Ryu OH, Uygur C, Ozdemir D, Firatli S, Aren G, Firatli E (2003). Novel ENAM mutation responsible for autosomal recessive amelogenesis imperfecta and localized enamel defects. *J Med Genet* 40:900-906.

Case 4: Mutation in intron 8: g.6395G>A

Figure 4. Autosomal-dominant smooth hypoplastic AI. Photographs of proband show small, smooth, yellow teeth that result from the enamel hypoplasia. All affected members of the family exhibited enamel hypoplasia in both the deciduous and permanent dentitions. Clinically, the teeth are small, thin and yellow due to a lack of enamel thickness.



Reference: Rajpar MH, Harley K, Laing C, Davies RM, Dixon MJ (2001). Mutation of the gene encoding the enamel-specific protein, enamelin, causes autosomal-dominant amelogenesis imperfecta. *Hum Mol Gen* 10:1673-7.

Case 5: *ENAM* mutation in exon 5 (p.K53X) introducing a translation termination codon at amino acid position 53.

Figure 5. Photographs showing the clinical manifestation of autosomal dominant local hypoplastic AI. The hypoplastic manifestation consists of a horizontal row of pits, grooves or a large hypoplastic area in the enamel. Apart from the variations in number and localization of the hypoplastic defects, the phenotype was consistent within and between the six affected families. from the same geographical area in Västerbotten County in Northern Sweden.

Reference: Mårdh CK, Backman B, Holmgren G, Hu JC, Simmer JP, Forsman-Semb K (2002). A nonsense mutation in the enamelin gene causes local hypoplastic autosomal dominant amelogenesis imperfecta (AIH2). *Hum Mol Gen* 11:1069-1074.

II. Mutations of the Enamelysin Gene.

Case 6: *MMP20* mutation (IVS6-2A>T) causing autosomal recessive pigmented hypomaturation amelogenesis imperfecta.

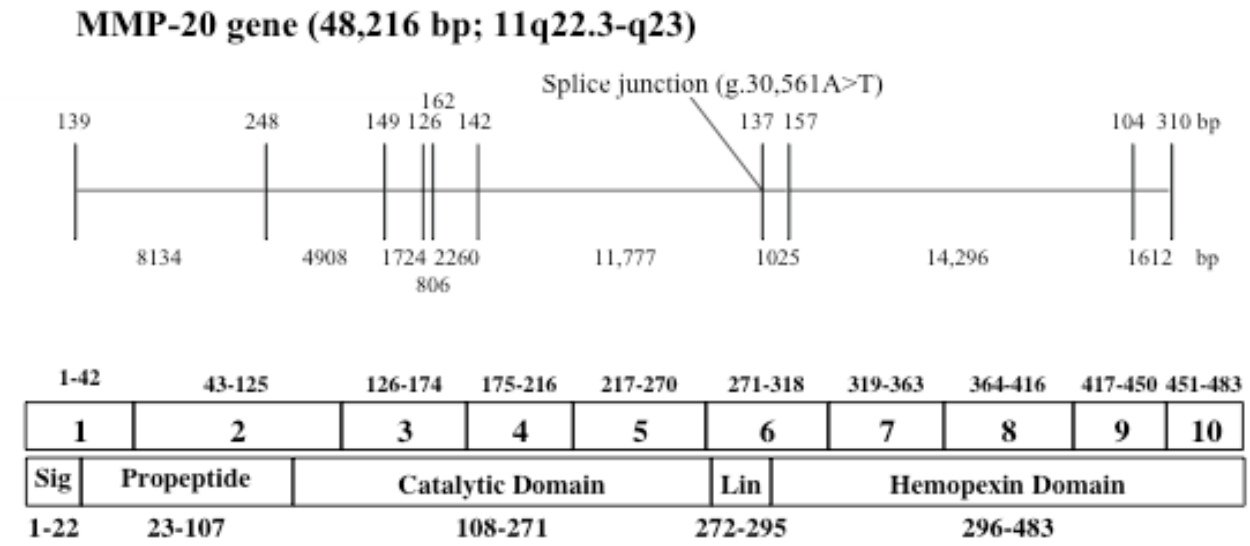


Figure 6a. Structure of the human enamelysin gene marking the position of the mutation associated with AI. The exons are indicated by the 10 vertical lines; the introns are horizontal lines. Above each exon and below each intron are numbers indicating its length in basepairs. Below the gene structure the 10 exons are aligned with a linear diagram of the MMP-20 structural domains. Above the exons are numbers indicating the range of amino acids encoded by each exon. Numbers beneath the protein structure indicate the range of amino acids in each structural domain.

Description: The proband first presented at age 6 yr. in the Pediatric Dentistry Clinic at the University of Michigan. The dental phenotype resembled the autosomal recessive pigmented hypomaturation type of amelogenesis imperfecta.[21] The teeth appeared normal in size, with some crowding. The enamel layer was pigmented, showing an agar-brown discoloration. The surface of the enamel was mottled and rough, but hard and brittle. Chunks of enamel had fractured away from several teeth, most notably on the lingual of the maxillary right canine (#6), and the buccals of the mandibular left canine (#22) and right first bicuspid (#28). Radiographically, the enamel layer was usually more opaque than the underlying dentin, but not in all areas, and was never as radiopaque as normal enamel. The proband had an anterior open bite. His teeth were generally not sensitive, except in response to extremes in temperature. Composites were placed, but required periodic repairs as the enamel at the restoration margins tended to chip off from the teeth. The father of the proband was reported to be affected, and is currently edentulous and wears maxillary and mandibular complete dentures.

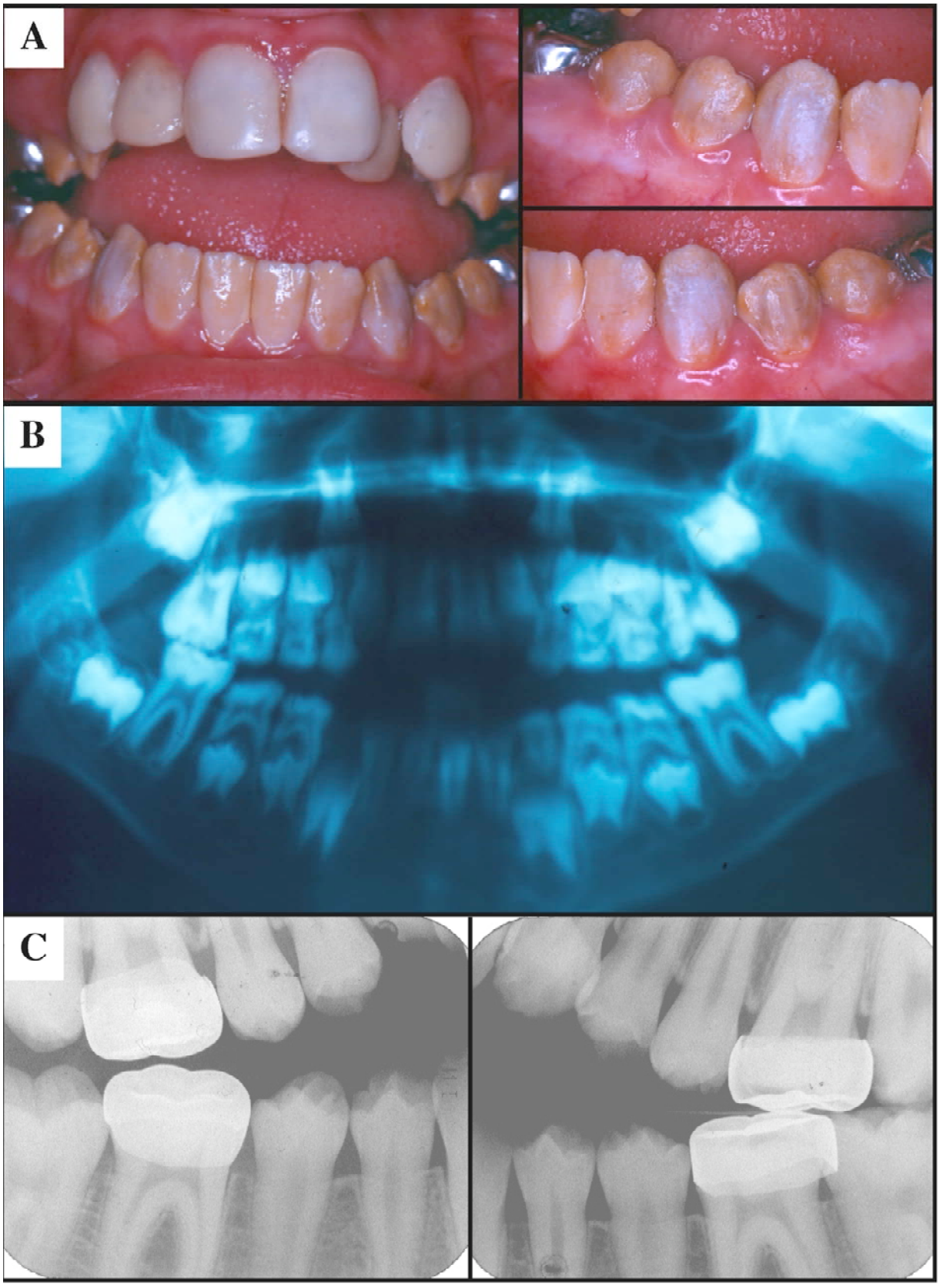

A
B
C

Figure 6b. Phenotype of proband. A. Photographs show frontal and lateral photographs of the proband at age 12 showing composite veneer restorations on the maxillary anterior teeth. The unrestored mandibular anterior teeth show the mottled appearance and irregular staining. **B**. Panorex radiograph of the same patient at age 6. The anterior openbite is evident. **C**. Bitewing radiographs of premolars and molars at age 12 show the lack of contrast between enamel and dentin, consistent with hypomaturation AI.

Reference: Kim J-W, Simmer JP, Hart TC, Hart PS, Bartlett JD, Hu JC-C (in press). MMP-20 mutation in autosomal recessive pigmented hypomaturation amelogenesis imperfecta. *J Med Genet*.

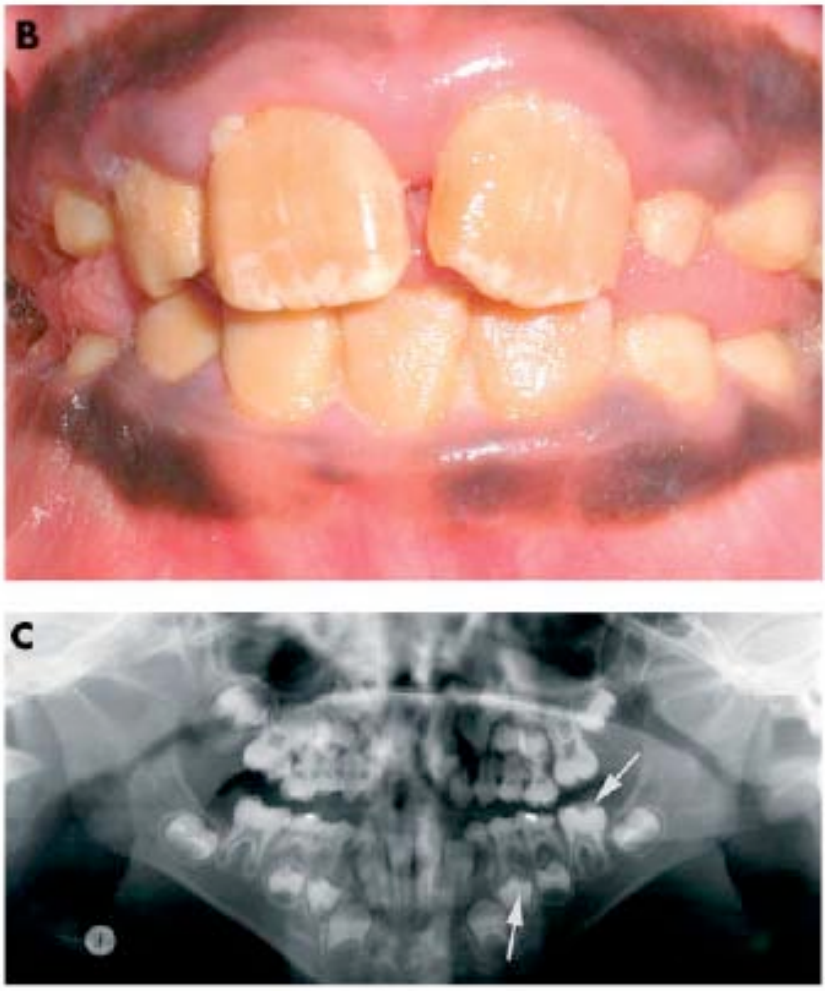
III. Mutations of the Kallikrein 4 (KLK4) Gene.

Case 7: *KLK4* mutation (g.2142G>A, p.W153X) causing autosomal recessive pigmented hypomaturation amelogenesis imperfecta.

Mutation: KLK4 mutation (g.2142G>A, p.W153X) would truncate the kallikrein 4 protein.

Description. The proband had one sibling who was also affected with a nearly identical dental phenotype (A). Both the primary and permanent dentitions in the proband and sibling (ages 9 and 10 years) were similarly affected showing a yellow brown discoloration (B). The teeth were excessively sensitive to hot and cold, making it painful to masticate. Radiographically the teeth appeared morphologically normal in shape indicating that the enamel was of normal thickness (C). The enamel showed only a slightly increased opacity compared with the dentin, indicative of a decreased enamel mineral content. Enamel of the affected children had fractured from the occlusal surfaces of the primary molars, which is consistent with a decreased mineral content. One affected child had an anterior dental open bite while the other child did not.

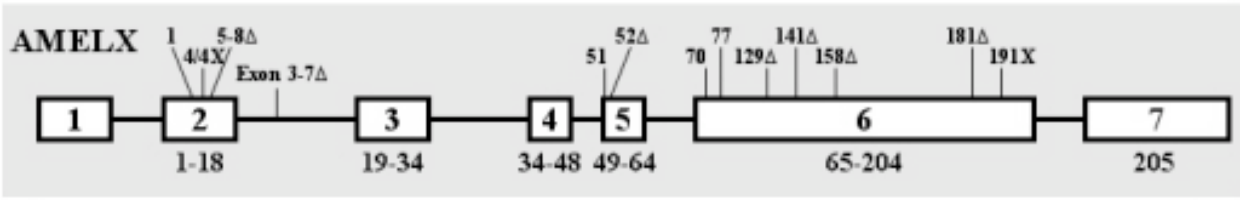
Figure 7. The family pedigree had two affected female children born to two unaffected adults. The dentition of both affected children was normal in morphology but had a generally yellow brown color (B) that affected both the primary and permanent teeth. Panographic radiography (C) revealed worn and fractured enamel on the posterior teeth and enamel that had a reduced opacity that was only slightly greater than the underlying dentin (arrows), indicative of enamel hypomineralization.



Reference: Hart PS, Hart TC, Michalec MD, Ryu OH, Simmons D, Hong S, Wright JT (2004). Mutation in kallikrein 4 causes autosomal recessive hypomaturation amelogenesis imperfecta. *J Med Genet* 41:545-549.

IV. Mutations of the amelogenin gene on the X-chromosome

Disease-causing mutation in the Amelogenin (AMELX) Gene



1	p.W4X	Sekiguchi et al. 2001a
2	p.I5-A8delinsT	Lagerström-Fermer et al. 1995
3	p.0	Lagerström et al. 1991
4	p.T51I	Lench and Winter 1995
5	p.P52fsX53	Aldred et al. 1992; Lench et al. 1994
6	p.P70T	Collier et al. 1997; Hart et al. 2000 Ravassipour et al. 2000
7	p.H77L	Hart et al. 2002
8	p.H129fsX187	Sekiguchi et al. 2001b
9	p.Y141fsX187	Greene et al. 2000
10	p.P158fsX187	Lench and Winter 1995
11	p.L181fsX187	Kindelan et al. 2000; Hart et al. 2002
12	p.E191X	Lench and Winter 1995
13	p.W4S	Kim et al. 2004
14	p.M1T	Kim et al. 2004

Figure 8a . Structures of the human amelogenin gene on the X-chromosome (AMELX) showing the sites of mutations known to cause X-linked AI. Exons are indicated by numbered boxes, introns by a line. The numbers below each exon show the range of amino acids encoded by that exon. The numbers with lines pointing to sites in the genes indicate the codon number that was affected by mutation. A deletion mutation is indicated by "Δ". An "X" indicates that the mutation created a stop codon.

X Inactivation (Lyonization)

In mammals, X chromosome expression is balanced in females (XX), and males (XY). by the random inactivation one of the two X chromosomes in each daughter cell during embryonic development. As a consequence, during tooth development some ameloblasts will express amelogenin from the maternal X-chromosome and some will express amelogenin from the paternal X-chromosome. When AMELX is defective on one X-chromosome in females (X*X), the enamel phenotype will be less severe than in affected males (X*Y) and will often be manifested as alternative vertical bands of defective and normal enamel on the crowns of the teeth.

Case 8: AMELX mutation p.W4S

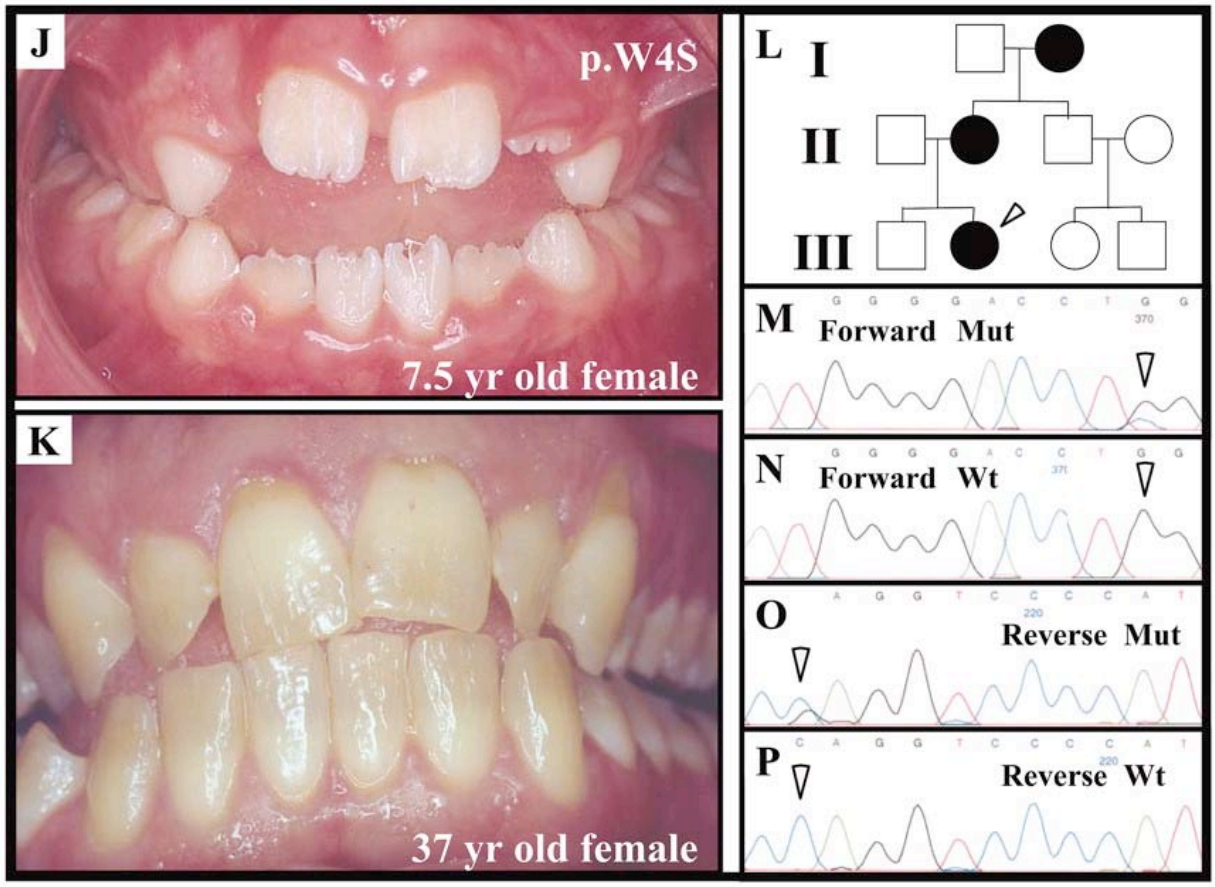


Figure 8b. Oral photographs of the proband (J, III-2) and her mother (K, II-2), who were both affected; pedigree of the family (L); and DNA sequencing chromatograms from the proband showing the mutation in the fourth codon of exon 2 (M-P), which changed the wild-type tryptophan codon (TGG) into a serine (TCG) codon. A pattern of alternative vertical bands of normal and hypoplastic enamel is evident.

Reference: Kim J-W, Simmer JP, Hu YY, Lin BP-L, Boyd C, Wright JT, Yamada CJM, Rayes SK, Feigal RJ, Hu JC-C (2004). Amelogenin p.M1T and p.W4S mutations underlying hypoplastic X-linked amelogenesis imperfecta. *J Dent Res* 83:378-83.

Case 9: AMELX mutation p.M1T

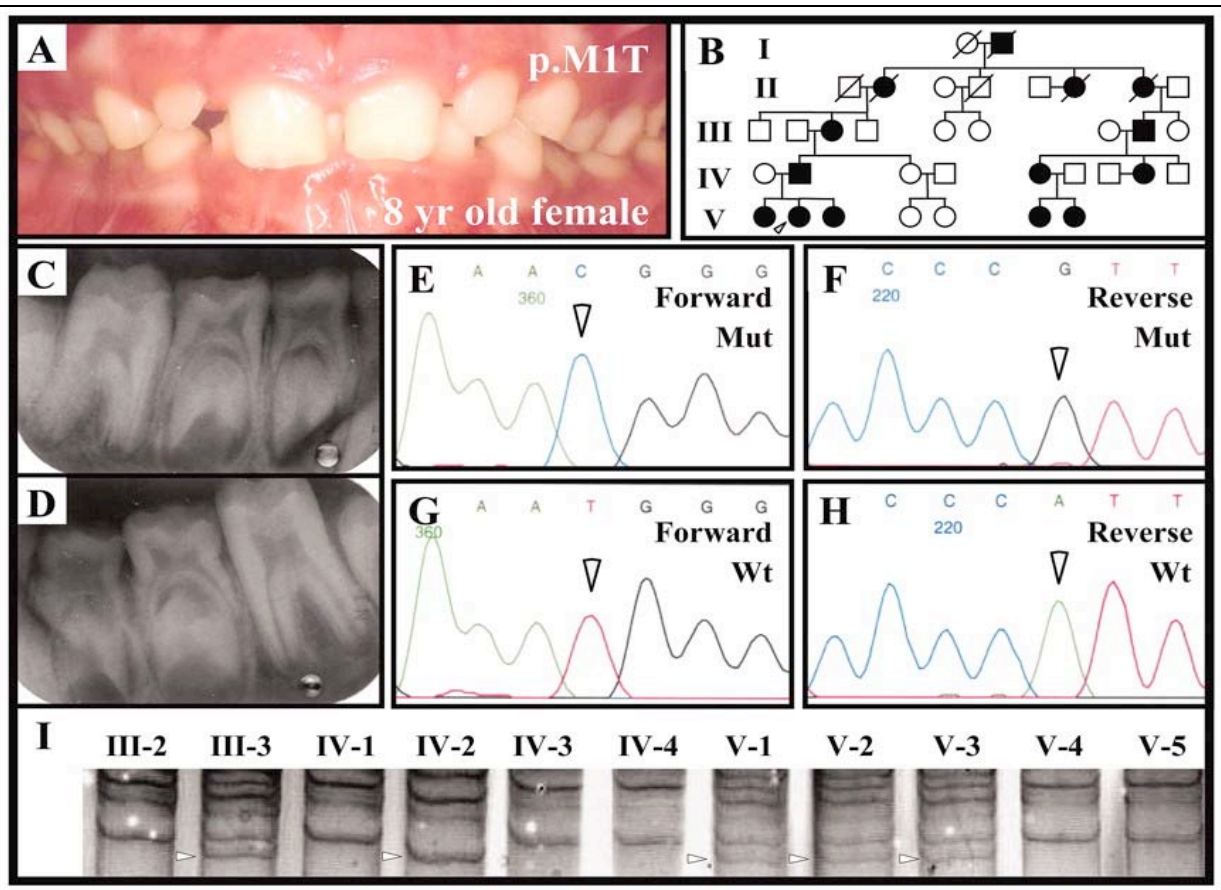


Figure 9. Oral photograph of the proband (A), pedigree (B), and bitewing radiographs of the proband showing the thin enamel layer is only evident radiographically on the cusp tips (C, D), DNA sequencing chromatograms (E-H) of exon 2 from an affected male member (IV-2) showing the mutation (Mut) that changed the ATG of the wild-type (Wt) start codon into an ACG, which is normally a threonine codon, and single stranded conformational polymorphism (SSCP) analysis of exon 2 with arrowheads pointing to the band that correlates with affection status (I).

Description: The teeth of the proband had sharp, thin incisal edges that fractured easily in both the maxillary and mandibular anterior teeth. The anterior incisors had diastemas, and the enamel layer was extremely thin and slightly rough. The underlying dentin appeared to show through the thin enamel covering, and gave the teeth a yellowish shade. On dental radiographs, the enamel layer was more radio-opaque than dentin but was difficult to delineate because of its thinness. The enamel did not appear to wear well, as some occlusal attrition was evident. No vertical banding pattern was evident in the enamel of affected females. The only affected male recruited from this kindred had crowns covering all of his teeth, but his panorex from age 27 taken before the full-mouth reconstruction, showed no evidence of enamel on any of the teeth (based upon radiodensity and the contour of the crowns).

Reference: Kim J-W, Simmer JP, Hu YY, Lin BP-L, Boyd C, Wright JT, Yamada CJM, Rayes SK, Feigal RJ, Hu JC-C (2004). Amelogenin p.M1T and p.W4S mutations underlying hypoplastic X-linked amelogenesis imperfecta. *J Dent Res* 83:378-83.

Case 10: AMELX mutation p.L181fsX187

Mutation: Deletion of a C-nucleotide exon 6 causing a frameshift alteration of the next six codons, and a premature stop codon resulting in truncation of the protein 18 amino acids shorter than the wild-type (g.4114delC, c.541delC, p.L181fsX187).

Description: The affected males had small teeth, with spacing and lack of contact points due to enamel hypoplasia. The enamel present was similar in color to normal and was hard on probing. Heterozygous females in this family had teeth of normal color and lucency, but the contour of the enamel surface was altered by a series of vertical grooves affecting all the teeth. Their enamel felt hard on probing and was impenetrable to a dental explorer. This family was therefore characterized by enamel that was of apparently normal mineral content but of reduced thickness.

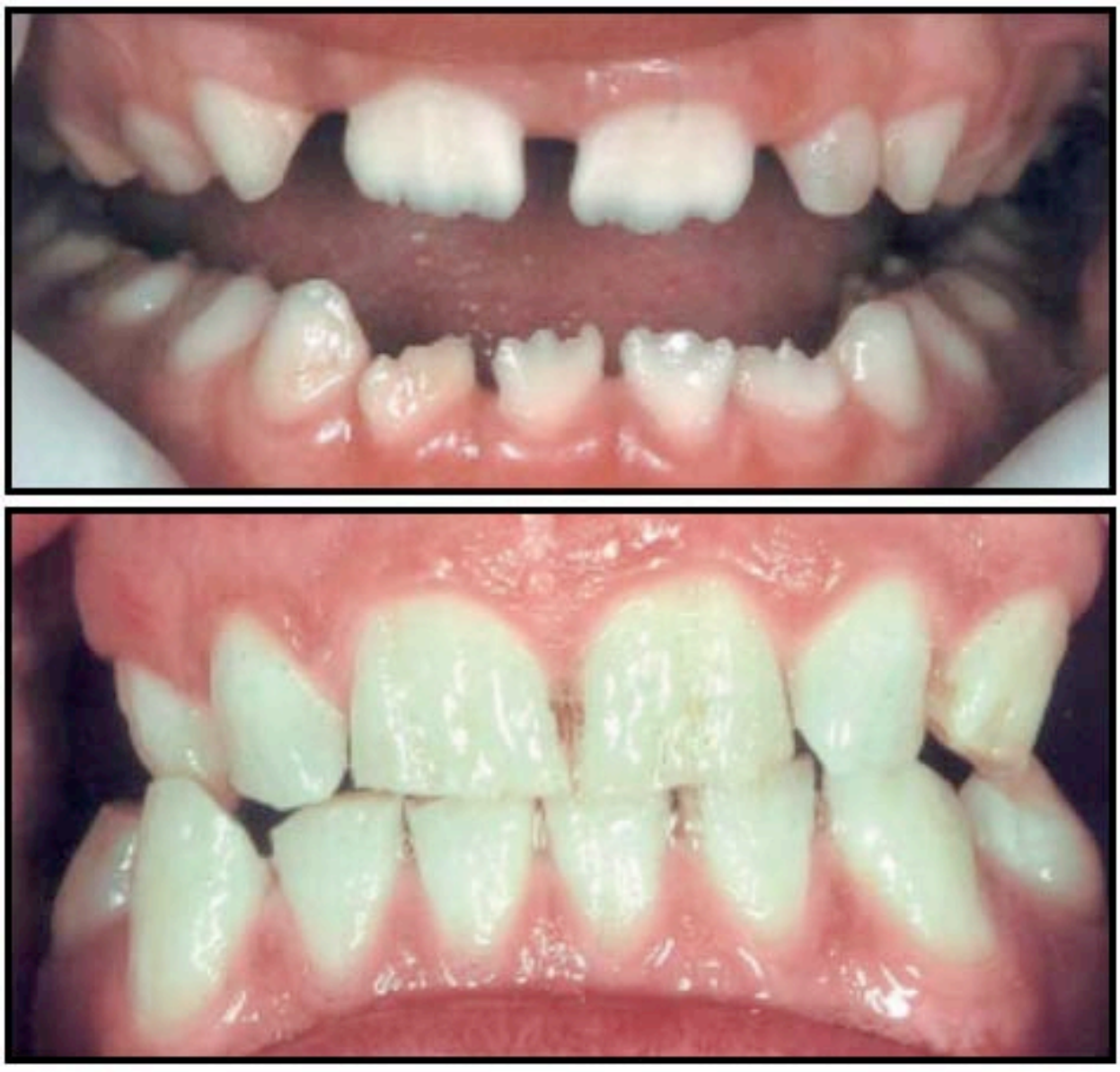


Figure 10. (Top) An affected male: both primary and permanent teeth have thin, lucent enamel of uniform contour and thickness. (Bottom) A heterozygous female: a series of alternating vertical ridges and grooves affects the maxillary central incisors and mandibular teeth; maxillary lateral incisors are also affected but more subtly. The enamel is of normal color and lucency. The slightly darker grooves on the maxillary left central incisor are interpreted as underlying dentine showing through a thin layer of enamel rather than a mineralization defect in the enamel itself.

Reference: Hart PS, Aldred MJ, Crawford PJ, Wright NJ, Hart TC, Wright JT (2002). Amelogenesis imperfecta phenotype-genotype correlations with two amelogenin gene mutations. *Arch Oral Biol* 47:261-265.

Case 11: AMELX mutation p.L77H

Mutation: A single basepair change of A to causing a His to Leu change (g.3803A>T, c.230A>T, p.H77L).

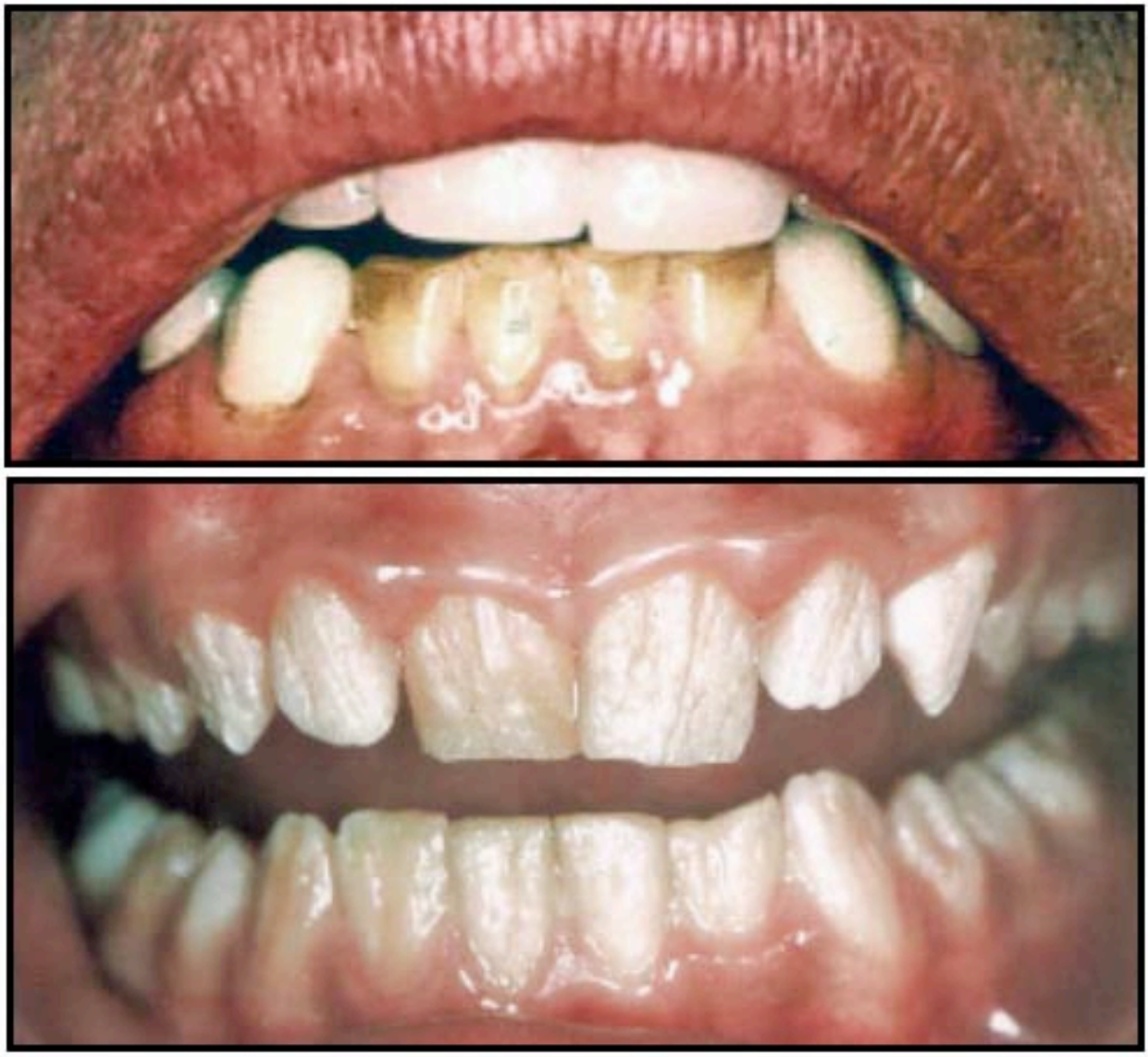


Figure 11. (Top) An affected male: lower incisors are darker than the remainder of the teeth, which have been crowned; there is moderate wear on the incisal edges of the lower incisors. (Bottom) A heterozygous female: incisors show vertical markings with alternating grooves and ridges; enamel forming the grooves is darker than that of the adjacent ridges.

Description: Most of the affected males had been rendered edentulous or had had extensive restorations, with full crowns on most teeth. Any uncrowned teeth were yellow-brown, with loss of the normal translucency of enamel, which had also been subject to excessive wear. Heterozygous females in family 1 had vertical ridges and grooves on the enamel surface, with discoloration. Generally, their teeth appeared yellow-brown, but closer examination showed that

the enamel in the grooves contributed most to the discoloration, with the enamel of the ridges being of more normal color and lucency. The phenotype in this family was therefore characterized clinically by enamel that was affected both in thickness and mineralization. The predominant effect in males appeared to be an alteration of mineral content (based on the clinical appearance of excessive wear and marked color change), with a relatively normal enamel thickness.

Reference: Hart PS, Aldred MJ, Crawford PJ, Wright NJ, Hart TC, Wright JT (2002). Amelogenesis imperfecta phenotype-genotype correlations with two amelogenin gene mutations. *Arch Oral Biol* 47:261-265.

Case 12: AMELX mutation p.P70T

Mutation: A single basepair change of C to A causing a His to Leu change in the amelogenin protein (g.3781C>A, c.208C>A, p.P70T).

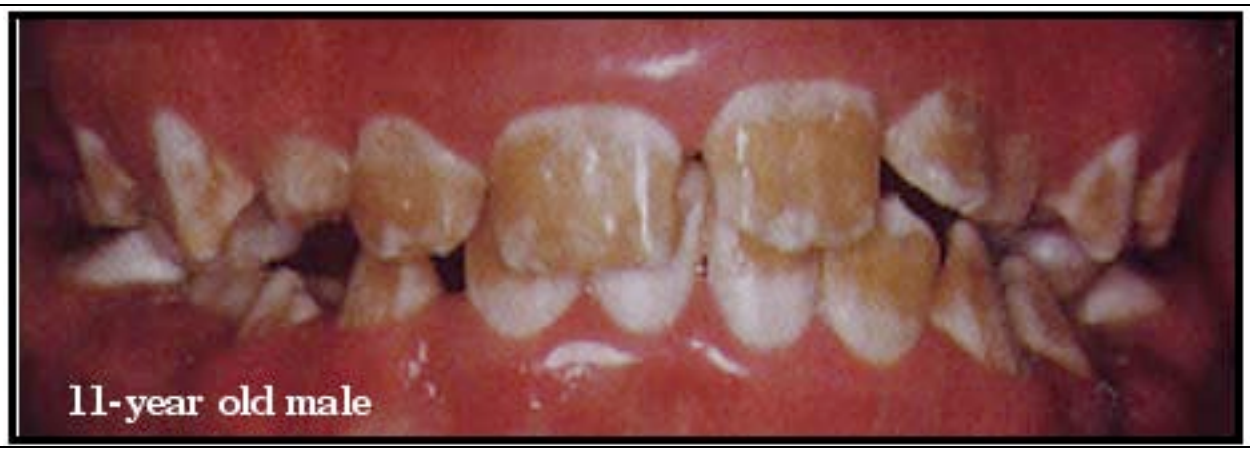


Figure 12. The teeth of this 11-year-old affected male show the characteristic yellow-brown coloration of the clinical crowns that becomes white-opaque at the cervical region.

Description: Clinically, enamel in affected males did not abrade easily and was yellow-brown, becoming opaque-white in the cervical one-fourth of the crown. In affected males, the tooth morphology was generally normal, with enamel of normal thickness. Radiographic examination revealed that the enamel of greater radiopacity than dentin, indicating a relatively normal mineral content. Females heterozygous for both the normal and mutant AMELX alleles showed a milder expression of the condition compared with hemizygous affected males with vertical bands of normal and affected enamel.

Reference: Ravassipour DB, Hart PS, Hart TC, Ritter AV, Yamauchi M, Gibson C, Wright JT (2000). Unique enamel phenotype associated with amelogenin gene (AMELX) codon 41 point mutation. *J Dent Res* 79:1476-81.

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