

Amelogenesis Imperfecta in Children: Review of Pathogenetic Aspect

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Abstract: *Amelogenesis imperfecta is an abnormal formation of the enamel. This anomaly associated with malformation of proteins, such as ameloblastin, enamelin, tuftelin and amelogenin. A few study report, mutation in the AMELX, ENAM, MMP20 and KLK-4 genes have been found to cause amelogenesis imperfecta. Mutations of AMELX, ENAM, MMP20 and KLK-4 genes will alter the structure of protein, that are essential for normal tooth development. People with amelogenesis imperfecta have teeth with abnormal color; yellow, brown or grey and have a higher risk for dental caries and hypersensitive to temperature changes. Incidence of amelogenesis imperfecta estimated 1 per 14,000 people in USA and 1 per 700 people in Northern Sweden. The purpose of this paper is to describe of pathology of amelogenesis imperfecta and its management. The treatment depends on severity of the problem. Full crowns will improve the appearance of the teeth and protect them from damage.*

Keywords: Amelogenesis Imperfecta, mutation genes, full crown

1. Introduction

Dental enamel is highest mineralized tissue in human body, consists of 85% hydroxyapatite crystals. This mineralized layer cannot be replaced or repaired. This crystals fulfill prism pattern given unique characteristic and fracture resistance properties for enamel. Development of unique mineral structure of enamel and its composition controlled by ameloblast. Ameloblast cells will disappear as tooth eruption. Enamel formation require some genes expression which record protein matrix and proteinase requirement for controlling growth process and mineralization of crystals.^{1,2}

X-linked amelogenesis imperfecta is a form of hereditary phenotypic damage which affects enamel development. This damage caused by gene mutation of human X chromosome. It is characterized by various phenotype in individual with hypoplastic damage and/or hypomineralization while enamel content decrease. Amelogenesis imperfecta associated with gene mutation identified for determining involvement of two molecules of extracellular matrix of enamel, they are amelogenin and enamelin. Amelogenin is protein that produce AMELX Xq22 and AMELY Yp11 genes which fulfill 90% of organic matrix in enamel development, this protein considered as main protein for structure and thickness of enamel. Enamelin is a protein produce ENAM gene in 4q21 chromosome, present in low number and undergo a series of proteolytic breakdown to generate various polypeptides that plays a role in nucleation, regulation, and enamel crystal extension. Allele mutation of gene code of amelogenin and enamelin associated with different phenotype of amelogenesis imperfect, showing that these proteins provide important function during enamel formation.^{1,2}

Besides ENAM and AMELX, the number of other genes important for enamel formation has been identified and considered as cause of amelogenesis imperfecta, includes ameloblastin, tuftelin, and two genes for enamel proteinase, i.e. enamelin (MMP-20) and kallikrein 4 (KLK-4). These

proteinase contribute to protein matrix regulation which provide enamel structure and composition. Abnormal proteolytic protein matrix generates enamel considered as principle of developmental mechanisms associated with autosomal inherited forms of hypomaturation amelogenesis imperfecta. Teeth with autosomal recessive hypomaturation amelogenesis imperfecta, show defense amelogenin protein that supports proteinase or protein damage. MMP-20 activity causes hypoplastic and hypomineralization of enamel.²

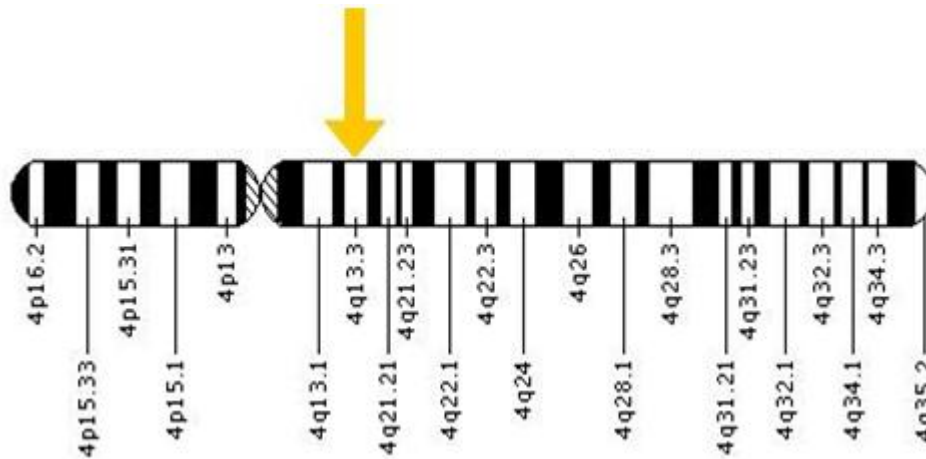
2. Literature Review

Amelogenesis imperfecta (amelo: formation of enamel, imperfecta: imperfecta) is a disorder of tooth development, relatively rare inherited disorder group with abnormal formation of enamel. This condition causes tooth become small, discolored and damaged. These disorders vary among affected individuals, can influence deciduous and permanent teeth.³ Enamel disorder amelogenesis imperfecta widely vary and classified as hypoplasia (abnormality in amount of enamel), hypomaturation (abnormalities in growth and maturation of the enamel crystal), and hypocalcification (abnormalities in initial crystal formation followed by growth disturbance). Enamel both in amelogenesis imperfecta of hypomaturation and hypocalcification types not mineralized to normal level of enamel and can be described as hypomineralization. Amelogenesis imperfecta can be inherited as an autosomal recessive X-linked or autosomal dominant. Incidence of amelogenesis imperfecta is uncertain, with widely vary estimates, 1 in 700 people in northern Sweden, to 1 in 14,000 people in the United States.⁴

Mutations of AMELX, ENAM, and MMP20 genes cause amelogenesis imperfecta. AMELX, ENAM, MMP20 give instructions in forming essential protein for tooth development. This protein is involved in enamel formation which is hard material, rich in calcium, forming protective outer layer of each tooth. Mutations in one gene alter the structure of this protein, consequently enamel becomes

abnormal, thin or soft that color yellow or brown.³ AMELX or by other name amelogenin X-link, AIH1, ALGN, AMG, AMGL, AMGX. This gene provides instructions for production of protein called amelogenin, which essential for normal tooth development. Amelogenin involved in enamel formation containing crystals that give strength and resistance. At least 15 mutations in AMELX gene that have been identified in humans with a form of X-link from amelogenesis imperfecta (X-linked disorder caused by a mutation on X chromosome genes). Some mutations of AMELX cause abnormal production of amelogenin proteins

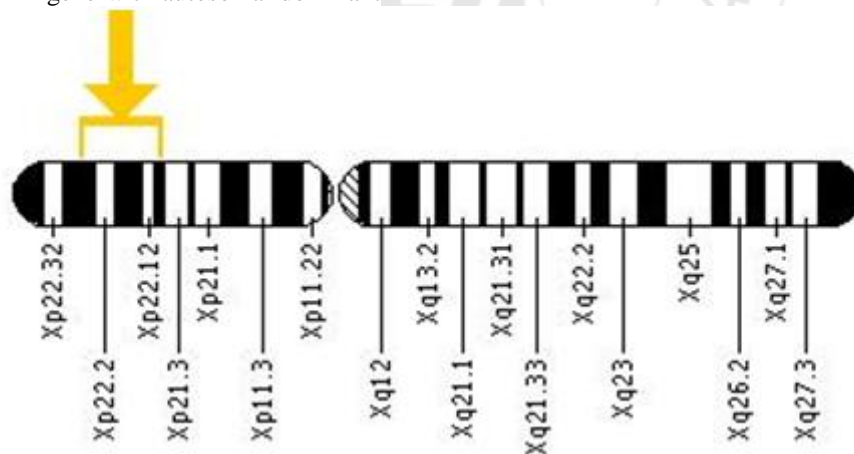
which can disrupt enamel crystal formation. Enamel can not be formed properly without sufficient amount of amelogenin. A copy of the amelogenin gene is located on each sex chromosomes (X and Y chromosomes) AMELX gene, located in X chromosome, makes almost all of amelogenin body. Amelogenin gene copies in Y chromosome, AMELY, make very little amelogenin and not required for enamel formation. AMELX gene located in X chromosome molecular location of the base pair 11,311,532 to 11,318,880.³



This AMELX gene located in short arm of chromosome between 22.31 and 22.1 position.

ENAM or enamelin, ADAI, AIH2, give instructions to make protein called enamelin, which essential for normal tooth development. At least seven mutations in the gene have been identified in humans ENAM gene with autosomal dominant

of amelogenesis imperfecta. Derivative autosomal dominant means that one copy of ENAM gene in each cell changed. Some mutations reduce amount of enamelin produced by gene, other mutations lead to abnormal production.³ ENAM located in chromosome 4: base pair 71,494,460 to 71,512,535.



ENAM gene located in long arm of chromosome 4, in 13.3 position

MMP-20, or matrix metalloproteinase 20, this gene provides instructions for making protein called enamelin, which essential for normal tooth development. Enamelin cut other proteins involved in enamel formation such as ameloblastin and amelogenin. These proteins division make amelogenin and ameloblastin easily removed when no longer needed.³ At least two mutations in MMP-20 gene have been identified in humans with autosomal recessive form of amelogenesis imperfecta. Each mutation is known changing

a single block of DNA (base pairs) in critical areas of MMP-20, preventing cells in producing functional enamelin. Without this protein, amelogenin and other proteins are not separating perfectly during enamel formation. The resulting enamel is soft and has abnormal crystal structure. Teeth with enamel defects such as abnormal roughness, discolored and prone to damage.³

Amelogenesis imperfecta (AI) is a group of developmental conditions, genomics, which affects clinical appearance and enamel structure and associated with morphological and biochemical changes in the body. Its prevalence varies from

1:700 to 1:14,000, according to study population. Enamel can be hypoplasia, hypomineralization or both, and affected teeth have abnormal color, sensitive or easily damaged. This can be either autosomal dominant, autosomal recessive, sex-linked inherited and inherited sporadic pattern. In families with X-linked has shown damage results from amelogenin gene mutations, AMLEX. Enamelin gene, ENAM, involved in pathogenesis of the dominant forms of AI.^{1,2,5}

During growth, the deciduous teeth can be protected by using metal crowns on posterior teeth. Long-term care includes the use of crowns, adhesive, or plastic restoration.⁵ There are four main types of amelogenesis imperfecta shown in the table below:⁴

Types	Clinical Features	Enamel Thickness	Radiographic Features	Inheritance
Hypoplastic (Type I)	Crown shapes vary from small to normal, small tooth, lack of proximal contact, colors vary from normal to white opaque-yellowish brown	Vary form thin and smooth to normal, the thickness grooved	Enamel appears normal to thin	Dominant autosomal, recessive, or X-linked
Hypomaturation (Type II)	Vary from opaque to yellow/brown, smooth and rough tooth surface, usually having tooth sensitivity, and open bite	Normal thickness with brittle enamel	Enamel has similar contrast or more than dentine, unerupted tooth crown	Dominant autosomal, recessive, or X-linked
Hypocalcification (Type III)	White opaque to yellowish brown, rough enamel surface, usually having tooth sensitivity and open bite, severe calculus formation	Normal thickness with brittle enamel	Enamel has similar contrast or more than dentine, unerupted tooth crown	Dominant autosomal, recessive
Hypomaturation/ Hypoplasia/ Taurodontism (Type IV)	Yellow/white, brown, mottled, tooth can appear small and lack of proximal contact	Reduced, hypomineralization area	Enamel has similar contrast or more than dentine, large pulp chamber	Dominant autosomal

The enamel is a highly mineralized tissue by volume of more than 95% filled by an organized crystalline structure, called hydroxyapatite. The formation of these structures are strictly controlled in ameloblast through interaction of a number of organic matrix molecules include, enamel (ENAM; 4q21), amelogenin (AMELX; Xp22,3-P22,1), Ameloblastin (AMBN; 4q21), tuftelin (TUFT1; 1q21), and various enzymes such as kallikrein 4 (KLK-4; 19q13,3-q13,4) and matrix metalloproteinase 20 (MMP-20; 11q22,3-Q23). The patterns are different from inheritance according to different genomic sites. Xp22.3 - p22.1 (AMELX, AIH1) associated with X-linked form. 4q11-q21 (AIH2, ENAM 4q21) associated with both autosomal dominant and autosomal recessive inheritance pattern and in 4q13.3 have been identified as an autosomal recessive inheritance. Amelogenesis imperfecta affects enamel of all teeth in affected individuals. Enamel may be hypoplasia, hypomineralization or both, and the affected teeth become discolored, sensitive or prone to be damaged before or after eruption (idiopathic resorption). During tooth formation, there are two proteinases stored by ameloblast, they are enamelin (MMP-20) and kallikrein-4 (KLK-4). Enamelin is an initial proteinase, expressed by ameloblast through the secretory phase and part of maturation stage. KLK-4 is the next proteinase, expressed by ameloblast starting at transition stage and continuing in maturation stage.^{5,6}

Division of MMP-20 plays an important role in crystal elongation, dentino-enamel junction (DEJ) formation, and maintenance of enamel rods. Extracellular KLK-4 is considered to be predominant degradation enzyme that release enamel protein from matrix during maturation phase. Enamelin is metalloproteinase matrix (MMP). In humans, enamel expressed from gene on chromosome 11q22,3-q23 which has 10 exons (all codes). Enamelin protein has 483 amino acids, which include peptides, propeptides, catalytic, linker, and domain hemopeksin. Inherited

enamel malformation shows variation of phenotypes, grouped according to thickness and hardness of enamel and described as hypoplastic type, hypocalcification, or hypomaturation of amelogenesis imperfecta (AI).^{6,7}

Changes in human amelogenin (AMELX) gene responsible for X-linked AI, but only 5% of families with AI show the pattern of X-linked inheritance. Currently, AMELX mutation have been reported. Various enamel phenotype observed in families with X-linked AI is associated with mutations area code location of amelogenin. Genes known to form amelogenesis imperfecta are autosomal genes encodes enamel matrix protein, i.e. enamel and ameloblastin (4q11-q21), tuftelin (1q21-31), MMP-20 (11q22), and kallikrein-4 (19q13,3-q13, 4). First association of AI is autosomal dominant form of 4q chromosomes, in region containing ameloblastin and enamelin genes. Enamelin mutations cause autosomal dominant form of hypoplasia and autosomal recessive of AI.⁷

3. Discussion

Amelogenesis imperfecta (AI) is an inherited enamel defect. The pattern of genetic inheritance may be autosomal dominant, autosomal recessive or X-linked. This is an exclusive ectodermal disorder, while mesodermic component of teeth is not impaired. The etiology associated with changes in genes involved in the formation and maturation of enamel. Origin of autosomal genetic form is still unknown, although the cause of X-linked AI must be related to damage in amelogenin gene, which is the main protein in human tooth enamel formation. These genetic changes can be divided into three main types: hypoplasia, hypocalcification, and hypomaturation, according to clinical characteristics of enamel, which reflect formation stage in which the enamel affected. Hypoplasia type is characterized by reduce of enamel amount, can be seen clinically by

smooth enamel, or grooves and holes on the surface. Hypocalcification type shows low mineralization enamel, clinically demonstrated enamel pigmentation, softens and easily removed. Hypomaturation type associated with anomalies of maturation phase during enamel formation, resulting in opaque and porous enamel.⁸ Amelogenin gene is specific dental gene expressed in pre-ameloblasts, ameloblasts, and the rest of root epithelium, while low-expression of amelogenin mRNA was recently shown in odontoblast. To date, there are 14 AMELX associated with AI mutations. Enamelin gene (ENAM) is a specific dental gene dominated by enamel organ, and odontoblast at low level. ENAM human gene located on chromosome 4 (4q13,3). One form of autosomal inherited, autosomal dominant namely amelogenesis imperfecta (ADAI), associated with 4q21 region. KLK-4 genes located close to telomere of chromosome 19 and considered members of human kallikrein gene networks. KLK-4 was expressed by ameloblasts and odontoblasts. In abnormal enzyme activity, enamel crystals grow at normal length, but its thickness is not complete. MMP-20 gene code for calcium-dependent proteinase, is member of matrix metalloproteinase (MMP). This gene is expressed by ameloblast, pre-ameloblasts and odontoblasts. Mutations in the MMP-20 gene located in 11q22.3-q23 region, has been associated with pigmented hypomaturation autosomal recessive form of amelogenesis imperfecta.⁹



Figure 1: Phenotype features of amelogenesis imperfecta. AI can be divided in clinical level into various form depending on damage type and disrupted stages of enamel formation.

Hypoplasia (a,b,c,d), demoralization (e,f), hypomaturation (g,h).

(Sumber: Crawford JM, Aldred M, Zupan AB.

Amelogenesis imperfecta. Orphanet J Rare Dis [internet] 2007 [cited 2001 March 01]; 2(17): about 12 p.]. Available from: URL: <http://www.ncbi.nlm.nih.gov> > Journal List > Orphanet J Rare Dis > v.2; 2007)⁵

Amelogenesis imperfecta is serious problem that could result in reduced oral health associated with quality of life and cause some psychological problems. Of these issues, individual with amelogenesis imperfecta requires extensive care. While treatment plan should also consider the patient's age and socioeconomic status, type and severity of damage.¹⁰

During growth, primary teeth could be protected by using metal crowns on posterior teeth. Caries removal should be performed with caution because the damaged dentin is softer than the normal dentine. It is because damaged dentine involving large areas and some involve subgingival area. It is difficult to obtain preparation by one impression. Therefore, double-cord technique required to provide better results. This is likely to cause patient discomfort. During the process, patient is given advice and motivation regarding oral hygiene and diet, so the periodontal tissues and caries problem for future can be avoided. This is done to get successful long-term treatment. Psychological health is also important in patients with amelogenesis imperfecta. With good restoration appearance, it can make happy with satisfactory masticatory system. In addition to objective problem as initiation of treatment, psychological factors also considered to boost patient's confidence.¹¹

Treatment of amelogenesis imperfecta also ranges from preventive using sealant and bonding for aesthetic to prosthetic reconstruction. AI type with enamel hypomineralization easily prone to fracture so conservative approach or bonding procedures can be performed. Extreme tooth sensitivity of heat stimuli, chemical, and mechanical, usually seen in AI with hypocalcification and hypomaturation, recommended for adequate oral hygiene procedures.⁴



Figure 2: Treatment of amelogenesis imperfecta will develop aesthetic and function of teeth

(sumber: Wright T.J. Developmental defect of the teeth. [internet] 2007 [cited 2011 March 12]. Available from: URL: <http://www.dentistry.unc.edu/research/defects>)⁴

4. Conclusion

Amelogenesis imperfecta (AI) is one form genomic breakdown of enamel, with pattern of inheritance may be autosomal dominant, autosomal recessive or X-linked. The aetiology associated with changes in genes known to play important role in enamel formation and maturation, such enamelin (ENAM; 4q21), amelogenin (AMELX; Xp22,3-p22,1), ameloblastin (AMBN; 4q21), tuftelin (TUFT1; 1q21), and various enzymes such kallikrein 4 (KLK-4; 19q13,3-q13,4) and matrix metalloproteinase 20 (MMP-20; 11q22,3-q23). Changes in organic matrix molecules will have impact on changes of enamel formation and maturation processl.
 1,2,3,4,5,6,7,8,9,10,11

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