Novel Mutations Associated with Amelogenesis Imperfecta- A Review

Vignesh P[1], Vijayashree Priyadharsini.J[2], Brundha M.P[3]

[1]Research Associate, Dental Research Cell, [2]Assistant Professor, Department of Microbiology, [3]Associate professor, Department of Pathology, Saveetha Dental College, Saveetha Institute of Medical and Technical Sciences, Chennai - TamilNadu, India

Abstract

Amelogenesis imperfecta [AI] is a congenital disorder that presents with a rare abnormal formation of the enamel, external layer of the crown of teeth, unrelated to any systemic or generalized Conditions. AI causes teeth to be usually small, discolored, pitted or grooved and prone to rapid wear and breakage. These defects which vary among affected individuals can affect both primary teeth and secondary teeth. About 14 forms of amelogenesis imperfecta have been described so far. They are distinguished by their specific dental abnormalities and by their pattern of inheritance. Additionally, amelogenesis imperfecta can occur alone without any other signs and symptoms or as a part of a syndrome that affects multiple parts of the body.

Keywords*: Amelogenesis imperfecta; gene mutation; enamel; dental.*

Introduction

Amelogenesis imperfecta [AI] is a congenital disorder that presents with a rare abnormal formation of the enamel, external layer of the crown of teeth, unrelated to any systemic or generalized conditions.[1,2] Tooth enamel is the most highly mineralized structure in the human body, with 85.1. of its volume involved by hydroxyapatite crystals[3]. The physical properties and physiological function of enamel are directly related to the orientation, disposition Composition, and morphology of the mineral components within the tissue[4]. During organogenesis, the enamel transitions from a pliable tissue, which is almost entirely devoid of proteins.[5] During genesis deflection of the unique molecular and cellular activities might be responsible for the patterns observed in amelogenesis imperfecta.[6]

Corresponding Author:
Vijayashree Priyadharsini.J
Assistant Professor, Department of Microbiology Saveetha Dental College, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, Chennai - TamilNadu, India - 600077
E-mail: vijayashreej.sdc@saveetha.com

The exact incidence of amelogenesis imperfecta is uncertain. Estimates vary wildly, from 1 in 700 people in northern Sweden to 1 in 14,000 people in the United states[7], among which hypoplastic AI represents 60 - 73% of all cases, hypomaturation AI represents 20-40%, and hypocalcification AI represents 7%[8]. A complex interplay of genes results in the formation of enamel, growth and enamel mineralization. The most severe type is mostly caused by truncating mutations in the *FAN83H* gene[9,10].

Classification of Amelogenesis Imperfecta

Amelogenesis imperfecta can be classified based on the phenotype[11], based on the clinical, microradiography and histopathological findings, and on the phenotype and mode of inheritance[12,13]. Most commonly accepted classification is the one being proposed by Witkop in the year 1988, which classified AI into mainly 4 types *viz.,* hypoplastic AI, hypomaturation AI and hypocalcified type based on developmental stages of enamel and hypoplastic-hypomaturation with taurodontism with several other subtypes under each type[14].

Table 1: Different types of amelogenesis imperfecta

Type 1 - Hypoplastic	IA hypoplastic, pitted autosomal dominant IB hypoplastic, local autosomal dominant IC hypoplastic, local autosomal recessive ID hypoplastic, smooth autosomal dominant IE hypoplastic, smooth X-linked dominant IF hypoplastic, rough autosomal dominant IG enamel agenesis, autosomal recessive
Type 2 - Hypomaturation	IIA hypomaturation pigmented autosomal recessive IIB hypomaturation IIC snow capped teeth, X-linked IID autosomal dominant
Type 3 - Hypocalcified	IIA autosomal dominant IIB autosomal recessive
Type 4 - Hypomature hypoplastic enamel with taurodontism	IVA hypomaturation - hypoplastic with taurodontism, autosomal dominant IVB hypoplastic - hypomaturation with taurodontism, autosomal dominant

1. Type 1 - Hypoplastic

The enamel of abnormal thickness due to malfunction in an enamel matrix formation. Enamel is extremely thin but hard & translucent and should have random pits & grooves. Condition is of an autosomal dominant, autosomal recessive, or x-linked pattern. Enamel differs in appearance from dentine radiographically as normal functional enamel.[15,16]

2. Type 2 - Hypomaturation

Enamel has a sound thickness, with a pitted appearance. It is less hard compared to normal enamel, and is prone to rapid wear, although not as intense as Type 3 AI.[17] Condition is of an autosomal dominant, autosomal recessive, or x-linked pattern. Enamel appears to be comparable to dentine in its radiodensity on radiographs.[18]

3. Type 3 - Hypocalcified

Enamel defect because of malfunction of enamel calcification, therefore enamel is of normal thickness but is extremely brittle, with an opaque/chalky presentation. Teeth are susceptible to staining and rapid wear, exposing dentin. Condition is of an autosomal dominant and autosomal recessive pattern. Enamel appears less radiopaque compared to dentine on radiographs.[20]

4. Type 4 - Hypomature hypoplastic enamel and taurodontism

Enamel has a variation in appearance, with mixed features from Type 1 and Type 2 AL. All Type 4 AI has taurodontism in common. Condition is of the autosomal dominant pattern. Other common features may include an anterior open bite,[19] taurodontism, the sensitivity of teeth. Differential diagnosis would include

dental fluorosis, molar-incisor hypomineralization, chronological disorders of tooth development.[20]

INHERITANCE PATTERNS OF AI

AI may be inherited in three manners which are X-linked form, autosomal dominant, or autosomal recessive trait. Apparently molecular genetic tools will allow more precise diagnosis. [21,22]Different genes are related to different forms of inheritance, located at different genomic sites. *AMELX* is associated with X-linked form which displays disorganized hypoplastic enamel.[23] Another gene shows both autosomal dominant and autosomal recessive inheritance patterns within the 4q13.3. has been identified as being allocated with on autosomal recessive inheritance.[24]

1. X-linked forms of amelogenesis imperfecta

X-linked amelogenesis imperfecta (XAI) shows the typical pattern of X-linked inheritance. Heterozygous females can transfer the mutant gene to children of either sex with the danger of this being 50% The condition affects males and females in strikingly different ways. Males show the trait fully [25]. They may have teeth that have only a thin layer of enamel of normal color and translucency, or the enamel may be of normal thickness but poorly mineralized with loss of translucency and/or a yellow-brown discoloration[26]

2. Autosomal dominant amelogenesis imperfecta

Autosomal dominant AI (ADAI) typically affects one or more individuals in each generation of a family.[27] There may be consistency in the clinical manifestations in every affected individual or there may be the variable expression, resulting in substantial or subtle differences between different affected individuals in the same family[28]. The phenotype in ADAI could also be predominantly or exclusively hypoplastic, manifested by thin enamel and spacing between the teeth, or in some pedigrees by rough, irregular, or randomly pitted enamel.[29,30] If the prime defect is in the amount of enamel matrix produced, the enamel will be hard, normally translucent, and not subject to significant attrition.[31]

3. Autosomal recessive amelogenesis imperfecta

Autosomal recessive AI (ARAI) should be considered if there is known consanguinity in a family with an affected individual. This may be more often encountered in certain ethnic and cultural groups where intermarriage within the family may be more common (for example, AI in association with cone rod dystrophy, a syndromic condition[32,33]. ARAI will also be more prevalent where there is a high frequency of the mutant gene in a population, such as in some Polynesian communities [34]

NOVEL MUTATION ASSOCIATED WITH AI

The first AI causing mutation was identified in the gene encoding the enamel matrix protein known to make up the bulk of the secreted enamel organic matrix [32][TABLE 2]. The EMP gene evolved from a standard ancestral gene and formed a part of the secretory calcium-binding phosphate gene cluster. The enamel matrix protein include amelogenin [*AMELX*] which makes up around 90%, of the EMD, [33] secrete *AMELX* last with remaining ameloblastin (AMBN) and *ENAM* [34]

GENE	Mode of inheritance
FAM83H	Autosomal dominant
FAM20A	Autosomal recessive
AMELX	X-linked form
ENAM	Autosomal dominant
MMP20	Autosomal recessive
KLK-4	Autosomal recessive
WDR72	Autosomal recessive
SLC4A4	Autosomal recessive
LAMB3	Autosomal dominant
ITGB6	Autosomal recessive

Table 2: Different gene mutation reported in AI

Enamel is a highly mineralized structure in the body with 85% of its volume occupied by hydroxyapatite crystals.[35] During the organogenesis, the enamel metamorphoses to form soft, pliable time to its final form which is almost devoid of protein.The final composition of enamel is a reflection of its unique molecular and cellular activity that happens during its genesis[36] deviation from this pattern may lead to amelogenesis imperfecta (AI)[37]. With an underlying genetic cause, the etiology of AI includes febrile illness or vitamin deficiency, local infection or trauma, fluoride ingestion congenital syphilis, birth defects or idiopathic factors[38]. *ENAM* and *AMELX* encode extracellular matrix proteins of the developing enamel and *KLK-4* and *MMP20* encode proteases that help corrupt organic matter from the enamel matrix during the development phase of amelogenesis[39]. *SLC24A4* encodes a calcium transporter that intervenes calcium transport to develop enamel during tooth development. Less is thought about the function of other genes implicated in amelogenesis imperfecta.[40]

MANAGEMENT OF AI

The management of individuals affected by AI has been described in three phases viz., temporary phase, transcriptional phase and permanent phase. The first phase of management is directed during primary and mixed dentition.[35] The transcriptional phase occurs during the period of tooth eruption and continues till adulthood and the final stage or permanent phase occurs in adulthood. In primary dentition, the dental treatment of affected children aims to ensure favorable conditions for the eruption of the permanent teeth as well as for the normal growth of the facial bones and TMJ.[36] In the mixed dentition, the treatment goals are to preserve tooth structure, maintain Tooth Vitality, decrease tooth sensitivity, vertical dimension, and Improve esthetics. when permanent first molars and anterior teeth erupt orthodontic and prosthetic assessment is essential.[37] However, rehabilitation in the mixed dentition is complex, since teeth have different eruption sequence, and definitive treatment cannot be rendered until the complete eruption of permanent dentition.[38] In the permanent dentition, the final treatment objective is to diminish tooth sensitivity and to restore the vertical dimension of occlusion, the function of well as esthetic is the final treatment often starts is soon in the clinical height of the crown and gingival tissue have been stabilizes and the pulp time has reduced.[39]

Conclusion

Amelogenesis imperfecta is a hereditary disorder affecting enamel often leading to physiological stress in patients resulting in poor aesthetics. One of the greatest challenges faced by the clinician in the total rehabilitation.[40–42] The treatment plan with respect to Al patients may be influenced by factors such as age, socioeconomic status and other comorbid conditions. Early plans for treatment, precise surgical procedure in order to meet the aesthetic and functional demands of patients with modern technology is warranted in the present scenario.[43,44]

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