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Molecular Basis of Human Enamel Defects

SUMMARY

During eruption of teeth in the oral cavity, the effect of gene variations and environmental factors can result in morphological and structural changes in teeth. Amelogenesis imperfecta is a failure which is detected on the enamel of the teeth and clinical picture varies by the severity and type of the disease. Classification of the types of amelogenesis imperfecta is determined by histological, genetic, clinical and radiographic criteria. Specifically, there are 4 types of amelogenesis imperfecta (according to Witkop): hypoplastic form, hypo-maturation form, hypo-calcified form, and hypo-maturation/hypoplasia form with taurodontism and 14 subcategories. The diagnosis and classification of amelogenesis imperfecta has traditionally been based on clinical presentation or phenotype and the inheritance pattern. Several genes can be mutated and cause the disease. Millions of genes, possibly more than 10,000 genes produce proteins that regulate synthesis of enamel. Some of the genes and gene products that are likely associated with amelogenesis imperfecta are: amelogenin (AMELX, AMELY genes), ameloblastin (AMBN gene), enamelin (ENAM gene), enamelysin (MMP20 gene), kalikryn 4 (KLK 4 gene), tuftelins (Tuftelin gene), FAM83H (FAM83H gene) and WDR72 (WDR72 gene). Particular attention should be given by the dentist in recognition and correlation of phenotypes with genotypes, in order to diagnose quickly and accurately such a possible disease and to prevent or treat it easily and quickly. Modern dentistry should restore these lesions in order to guarantee aesthetics and functionality, usually in collaboration with a group of dentists.

Keywords: Amelogenesis Imperfecta; Enamel; Phenotype; Genotype

Georgios Chatzopoulos, Dimitrios Tziafas

Aristotle University, School of Dentistry
Department of Endodontology
Thessaloniki, Greece

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Introduction

From the eruption of teeth in the oral cavity, until the completion of their formation, morphological as well as structural variations may occur. These variations are the result of genetic damage or a harmful environmental impact during dentinogenesis[1]. ***Amelogenesis imperfecta*** is a malformation group of enamel structure and its clinical image varies according to the type and the gravity of the condition. The prevalence of the condition has been studied in only a few population groups and it has been reported to range from 1/700 to 1/15,000, while it depends on the population groups on which the study is conducted and on the diagnostic criteria (1/700 in Sweden and 1/15,000 in the USA)[1-5]. The inherited developmental damage of enamel structure on primary and permanent teeth does not affect any other organs or systems of the human organism, since it is caused by a harmful agent during the process of amelogenesis in the primary stages of tooth development. In that way, enamel appears to be thinner, up to 1/8 of its normal thickness and it is brittle; so, as a result, it wears off quickly and reveals the underlying dentin. In other occasions enamel shows normal thickness, but looks like chalk and is very brittle[6].

Amelogenesis

Amelogenesis is the mechanism of enamel formation in the teeth that starts during the bell stage,

after dentinogenesis. During the whole process of dentinogenesis, epithelial cells of the inner enamel epithelium produce the components of pre-enamel under the effect of lateral mesenchymal cells[1]. Enamel development is studied in 5 distinct stages[7]. Some researchers suggest 3 stages[8]. In the first occasion that is adopted by most scientists, amelogenesis is divided in the following stages: pre-secretory stage, secretory stage, transition stage, maturation stage and post-maturation stage[7] (Tab. 1). In the second occasion, the following stages are proposed: pre-secretory stage, secretory stage and maturation stage[8].

Table 1. Stages of amelogenesis7

PRE-SECRETORY STAGE	➢ Differentiation of pre-ameloblasts and pre-odontoblasts ➢ Basal lamina resorption
SECRETORY STAGE	➢ Deposition and partial mineralization of enamel thickness ➢ Ameloblasts compose and secrete proteinases ➢ Ameloblasts decompose proteins that are formed but cannot be secreted ➢ Ameloblasts absorb and destroy matrix proteins ➢ Ameloblasts retreat from recently formed dentine
TRANSITION STAGE	Extensive structural and functional variations
MATURATION STAGE	➢ Increased amounts of minerals ➢ Loss of protein and water bulk in the enamel matrix ➢ Mineral ions are added to the enamel plexus ➢ Mature enamel with 98% of minerals ➢ Cells become striated or have a ruffled borders
POST-MATURATION STAGE	➢ Enamel organ cells stop functioning and degenerate ➢ Enamel epithelium is reduced

The pre-secretory stage is the first stage of amelogenesis and it includes the part of the enamel organ before the secretion of enamel matrix. In that stage, the epithelial cells of the inner enamel epithelium that are initially cube-shaped, differentiate into pre-ameloblasts. 2 processes characterize this stage:

- ► Differentiation of pre-ameloblasts and pre-odontoblasts is interdependent and the right signal is required in order for the process to begin. So, the differentiation of mesenchymal cells into odontoblasts should be included in the studies on the differentiation mechanism of ameloblasts.
- ► The second characteristic is resorption of the basal lamina before the enamel matrix is created (Tab. 1).

The second stage of amelogenesis is the secretory stage. In this stage, deposition of the organic matrix (pre-enamel formation) and partial mineralization of the whole thickness of enamel are reported. Ameloblasts compose proteins of the organic matrix, as well as proteinases, which they secrete in the inside of the enamel matrix (Tab. 1). The proteins that are formed, their molecular genetic basis and the role they have been attributed with to date, are the following:

1. Amelogenin (product of AMELX, AMELY genes that are found in the X and Y chromosome) is the most abundant protein in developing enamel[9,10]. The exact role of amelogenin is not entirely determined, but it is claimed to play a special role in regulation of the size and shape of enamel crystallites. The water in the pre-enamel region is removed in order for the required space between amelogenins to be formed and for hydroxyapatite crystals to develop.
2. Ameloblastin (product of the AMBN gene that is found in chromosome 4, 4q21) is another enamel protein that appears to be the second most abundant enamel protein. Ameloblastins emigrate from the dentinoenamel junction to the outer surface of the tooth, where apoptosis occurs before tooth eruption[11]. Each ameloblastin creates an enamel rod that consists

of hydroxyapatite crystals[12]. The natural arrangement of enamel rods is crucial for enamel's strength.

3. Enamelin (product of ENAM gene that is found in chromosome 4) is secreted by ameloblasts in relatively small amounts. This protein could probably interact with amelogenin or other enamel proteins and its role is highly important for the development of the length of the enamel rods[13,14].
4. Enamelysin (MMP20 gene that is found in chromosome 11) is a proteinase related to amelogenin disintegration and is considered as the major proteinase involved in the processing of proteins of the enamel matrix[15,16].
5. Kallikrein 4 (KLK4 gene that is found in chromosome 19) is a proteinase that is secreted in the maturation stage of enamel development. It is an aggressive proteinase that could be responsible for disintegration of any protein that can't be disintegrated by enamelysin. Its removal during maturation is critical in order for enamel crystallites to develop and fully grow[17].
6. Tuftelins (tuftelin gene that is found in chromosome 1)[18] are protein molecules that belong to the enamelin family. These molecules are mainly found in some morphological enamel elements, enamel tufts and enamel spindles[1].

Secretory stage ameloblasts decompose matrix proteins as well as the ones that are formed, but cannot be secreted. In this stage, a retreat of ameloblasts from recently formed dentine is observed. In the end of this stage, the cells of the enamel organ undergo elaborate reorganization of their morphology that continues in the transition stage, which is the third stage of amelogenesis (Tab. 1).

In the transition stage, enamel cells undergo extensive structural as well as functional changes. Ameloblasts become shorter in length, from 60-70 μm in the secretory stage, they shrink and present with a length of 40 μm in this stage[7] (Tab. 1).

The next stage, the maturation stage of pre-enamel into enamel, is characterized by the increasing amounts of mineral contents, as well as by the final loss of protein and water bulk from the enamel matrix. Mineral ions are added to the pre-enamel plexus, while mature enamel that is formed consists of 98% of mineral contents and is an extremely hard substance. In the maturation stage, the ameloblast transfer substances are used in enamel formation, while microscopically, the most remarkable aspect of this stage is that these cells become striated or have a ruffled borders[7]. In the maturation stage, ameloblasts transfer some of the substances used in enamel formation from pre-enamel (Tab. 1). Most of those substances are proteins used for regulation of enamel calcification, as well as for the formation of its particular architectural structure. The proteins involved in this procedure are mainly amelogenins, enamelins, ameloblastins and tuftelins. Amelogenins gradually disappear and enamelins are the main enamel component. Enamel calcification will be completed by the end of this stage[1].

When enamel is fully developed, the enamel organ cells stop functioning and degenerate. In this way, amelogenesis processes to its final stage, the fifth, during which the enamel epithelium is reduced (Tab. 1).

Classification of Amelogenesis Imperfecta

Classification of amelogenesis imperfecta is based on histological, genetic, clinical and radiographic criteria. The types of amelogenesis imperfecta, as reported by Witkop[6] are presented in Tab. 2. Amelogenesis imperfecta is generally subdivided into 4 main types based on enamel damage and it is further divided into 14 distinct subtypes based on clinical appearance (phenotype) and the mode of inheritance. Although a lot of genes that have been accused of causing amelogenesis imperfecta have been identified since 1990, most of its types do not yet have a distinct molecular basis[6].

Table 2. Types of amelogenesis imperfecta6

1) Hypoplastic (Type I)
2) Hypo-maturation (Type II)
3) Hypo-calcified (Type III)
4) Hypo-maturation/ Hypoplasia/ Taurodontism (Type IV)

► TYPE I- Hypoplastic form

This type concerns the differentiation degree or the cycle of life of ameloblastins, while the condition that appears causes their low biosynthetic activity. All subcategories (7 subcategories) of hypoplastic amelogenesis imperfecta are characterized by the primary feature of deficient amount of enamel. The deficient amount of enamel varies in each subcategory and may be characterized by enamel with canals, enamel with large missing areas, very thin enamel as well as surrounding enamel with normal thickness, or finally very thin enamel throughout the whole extent of the crown of the tooth. The mode of inheritance of the hypoplastic form of amelogenesis imperfecta may be either autosomal dominant, autosomal recessive, or X-linked (Tab. 3)[6].

► TYPE II- Hypo-mature form

This type concerns damage in the architectural structure of enamel prisms and of the prism membrane. The reduced strength of enamel increases fracture risk on its surface in case of intense chewing forces, the result being the instant collapse of its mass[1]. The hereditary character of hypo-mature amelogenesis imperfecta may be autosomal dominant, autosomal recessive or X-linked, just like the previous type[19].

Table 3. Clinical, radiographic and hereditary characteristics of 4 main types of amelogenesis imperfecta6,19

Type	Clinical Appearance	Enamel Thickness	Radiographic Appearance	Inheritance
Hypoplastic (Type I)	• Colour: varies from yellow-brown to white • Smooth • Glossy, shiny • Rough	• Varies from thin to normal thickness • Grooves • Rows	• Varies from normal to slightly reduced contrast	• Autosomal dominant • Autosomal recessive • X-linked
Hypo-maturation (Type II)	• Colour: varies from opaque white to opaque yellow • Mottled yellow • Mottled brown • Soft	• Normal thickness	• Males: slightly reduced contrast between enamel and dentin • Females: no defects are observed • Unerupted teeth: normal morphology	• Autosomal dominant • Autosomal recessive • X-linked
Hypo-calcified (Type III)	• Unerupted teeth: light yellow-brown to orange colour • Brown to black • Friable • Soft • Sensitive to temperature changes	• Normal thickness	• Enamel is less radiopaque than the dentin	• Autosomal dominant • Autosomal recessive
Hypo-maturation/ Hypoplastic with taurodontism (Type IV)	• Mottled brown-yellow-white	• Reduced thickness	• The same or slightly greater radiodensity than dentin • Enlarged pulp chambers	• Autosomal dominant

► TYPE III- Hypo-calcified form

This type concerns disorders in the rate and the degree of pre-enamel calcification, where its composition appears to be normal. Chewing forces on enamel of soft composition result in wearing of its surface. That is the most frequent manifestation of amelogenesis imperfecta. Studies have shown that teeth with hypo-calcified amelogenesis imperfecta showed up to 30% less minerals than normal enamel[1]. The autosomal dominant, as well as the autosomal recessive type of inheritance, are the types of inheritance of hypo-calcified amelogenesis imperfecta[9] (Tab. 3).

► TYPE IV- Hypo-mature/ Hypoplastic form with taurodontism

In this type, enamel presents with white, yellow and brown marks on its surface, while its thickness is reduced. The tooth that shows the specific type of amelogenesis imperfecta looks small clinically and lacks proximal contact. The type of inheritance is characterized as autosomal dominant[19] (Tab. 3).

Molecular-Genetic Basis of Amelogenesis Imperfecta

Phenotype variety in the 4 types and their subcategories is due to the large number of genes that can mutate and cause the condition. The genes involved in enamel formation are thousands, probably more than 10,000. Genes produce proteins that regulate gene expression for enamel formation and cell function. They can be secreted by ameloblasts in order to create the pattern for enamel development. Some of the proteins secreted by ameloblasts regulate the size, the shape and the orientation of the developing enamel crystallites, contributing to its final structure and formation.

Various genes and gene products that are known or suspected to be associated with amelogenesis imperfecta are mentioned below:

► ***Amelogenin*** (product of AMELX, AMELY genes found in X and Y chromosomes). Multiple mutations in the AMELX gene in humans are connected to amelogenesis imperfecta. 15 mutations of this gene have been reported. The variety of enamel phenotypes is undoubtedly related to the site of mutation in the gene[20]. On the other hand, there are no known mutations on the AMELY gene. Research on genes and their mutations that cause amelogenesis imperfecta might prove helpful in correlating genotypes with phenotypes, as well as genotypes with the corresponding gene therapy, aiming at the prevention and treatment of the condition[18]. In a research conducted in 2001 on a transgenic mouse that does not express the AMELX gene, a very thin enamel overlay lacking prism structure, similar in its appearance to that of some people that have mutations on the AMELX gene, was found on the teeth of the mouse[21].

► ***Ameloblastin*** (product of AMBN gene found in chromosome 4, 4q21). The AMBN gene is another candidate gene for the autosomal dominant type of amelogenesis imperfecta. Its involvement in the abnormality in humans is not yet entirely verified. It has not yet been associated with a phenotype of amelogenesis imperfecta in humans, while it is associated to the hypoplastic enamel phenotype according to a research conducted on mice[22].

► ***Enamelin*** (product of ENAM gene found in chromosome 4). Mutations of the ENAM gene are associated with the autosomal type of inheritance of amelogenesis imperfecta[13,14]. The enamelin gene has 10 exons, 8 of which are encoded[14]. The clinical appearance ranges from relatively small local cavities to a serious type of its hypoplasia[23,24]. The condition may be to a large extent mild and not clinically perceivable. It is frequently manifested in an indirect way, since those people present with high tooth caries rate[25].

► ***Enamelysin*** (MMP20 gene found in chromosome 11)[15]. Enamel mutations are associated with the autosomal recessive type of inheritance of amelogenesis imperfecta and the phenotype that accrues is the hypo-mature type.

► ***Kallikrein 4*** (KLK4 gene found in chromosome 19). Mutation of kallikrein 4 is associated with autosomal recessive mode of inheritance of amelogenesis imperfecta, the hypo-mature type to be specific. The enamel produced from the mutation is characterized by reduced concentration of mineralized substances[17].

► ***Tuftelins*** (tuftelin gene found in chromosome 1)[18]. Mutations of these genes have been reported to be associated with amelogenesis imperfecta[26].

► ***FAM83H*** (product of FAM83H gene found in chromosome 8q24): mutations on this gene may cause a disorder in mineralized enamel elements.

Apart from the damage appearing on the surface of enamel, it has been verified that amelogenesis imperfecta leads to a series of other conditions as they are reported in table 4.

Table 4. Conditions presented because of amelogenesis imperfecta

Condition	Reference
1. Increased probability of impacted teeth	73, 74
2. Abnormalities on tooth eruption	73, 74, 75
3. Congenitally missing teeth	73, 74, 75
4. Skeletal open bite	73
5. Pulp calcifications	74, 75
6. Dental malformations	74
7. Crown-root absorption	73, 74
8. Taurodontism	74, 76

Research has revealed 6 genes that undergo mutations and cause this condition. Those genes are AMELX, enam, KLK4, MMP20, FAM83H and WDR72. The mutation of gene DLX3 has been reported to be associated with the tricho-dento-osseous syndrome, and it causes hypo-mature amelogenesis imperfecta with taurodontism[27].

The development of genetics has given an opportunity for lots of mutations to be associated with various types of amelogenesis imperfecta, in order to help diagnose the different types. In reality, clinical examination cannot on its own lead to definite conclusions; for example, verification of the type of the condition. Identification and association of the clinical phenotype of each subcategory of amelogenesis imperfecta with genetic mutation would be of great importance in preventing undesirable conditions, such as skeletal open bite and calculus formation by immediate implementation of the most adequate treatment.

► AMELX GENE

More than 15 mutations have been reported in the AMELX gene, each presenting with a different phenotype according to its effect on the enamel protein. Mutations on the specific gene may be loss of the C-terminus of the protein, loss of the N-terminus of the protein, large base deletions and mutations on the signal peptide coding region.

► The first mutation to be associated with amelogenesis imperfecta was reported by Lagerstrom et al in 1991. A 5 Kb deletion was found from exon 3 to a part of exon 7 (g. 1148_47del) (large deletion)[28].

► 4 mutations of the AMELX gene have been found to include a part of the N-terminus of amelogenin. The first mutation was a frame shift, which is the result of a substitution in exon 5 that leads to a stop codon. The result of this mutation will be an amelogenin with 36 amino acids in length. The phenotype will be hypo-mature enamel hypoplasia of various degrees. Variation between the phenotypes of the 2 sexes is also reported (loss of the N-terminus)[29,30].

► There are also 5 different mutations that introduce a stop codon and reduce the C-terminus of amelogenin. 4 of these mutations are the result of the deletion of a single nucleotide at various positions in exon 6. They all introduce a premature stop codon in the position of amino acid 187. The products of the 4 mutations are almost the same, since 18 amino acids are absent in the C-terminus of the protein. The phenotype differs according to the degree and the type of the amino acid changes that occur from the swift point to the stop codon[31,32,33,34]. Despite their differences, they all cause reduction of enamel thickness and its hypoplastic appearance. According to Shaw[35], the C-terminus plays an important role in the formation

and the direction of enamel crystallites, as well as in amelogenin connection during enamel development (loss of the C-terminus of the protein).

The AMELX gene mutations are presented extensively in table 5, as they have been detected during time.

Table 5. AMELX Mutations

Researcher	Year	Genomic DNA	Cdna	Protein	Phenotype	Reference
Simmer et al.	2004	g.2T>C	c.2T>C	p.M1T	AA (I) (normal mineralization)	36
Simmer et al.	2004	g.11G>C	c.11G>C	p.W4S	AA (I) (normal mineralization)	36
Sekiguchi et al.	2001	g.11G>A	c.11G>A	p.W4X	AA (I) (normal mineralization)	33
Lagerström-Fermer et al.	1995	g.14_22del	c.14_22del	p.I5_A8delinsT	AA (I) (normal mineralization)	37
Lagerström et al.	1991	g.1148_54del	c.55_54del	p.18del	AA (II) (some hypoplasia)	28
Lench και Winter	1995	g.3455C>T	c.152C>T	p.T51I	AA (II) (some hypoplasia)	31
Aldred et al. Lench et al.	1992 1994	g.3458delC	c.155delC	p.PS2fsX53	AA (II) (some hypoplasia)	29 30
Collier et al. Hart et al.	1997 2000	g.3781C>A	c.208C>A	p.P70T	AA (II) (some hypoplasia)	38 39
Hart et al.	2002	g.3803A>T	c.230A>T	p.77L	AA (II)	34
Sekiguchi et al.	2001	g.3958delC	c.385delC	p.H129fsX187	AA (I)	40
Greene et al.	2000	g.3993delC	c.420delC	p.Y141fsX187	AA (I)	41
Lench and Winter	1995	g.4046delC	c.473delC	p.P158fsX187	AA (I)	31
Kindelan et al. Hart et al.	2000 2001	g.4114delC	c.541delC	p.L181fsX187	AA (I) (some hypomineral.)	32
Lench and Winter	1995	g.4144G>T	c.571G>T	p.E191X	AA (I)	31
Kid et al.	2007	g.3458C>G		p.P52R	AA (I)	42

► ENAM GENE

The first clinical condition that was detected as amelogenesis imperfecta and is inherited in an autosomal mode was identified as a mutation on the enam gene that is found in chromosome 4q21[43]. Mutations on the enam gene are now known to be associated with at least 2 types of amelogenesis imperfecta. This character has been more frequently found to be transferred in an autosomal dominant mode, while it has also been found transferring as an autosomal recessive as well. 6 mutations that have been found resulting in loss of the largest part of the protein, such as protein K53X for example, result in regional hypoplastic damage. On the contrary, mutations that result in little loss of protein produce enamel with a generalized hypoplastic phenotype.

► MMP20 GENE

Mutations in the enamelysin proteinase that participates in enamel processing during its development are related to autosomal recessive type of inheritance. Enamel thickness is normal, but it shows reduced concentration of mineral content and increased concentration of proteins. The phenotype that results from these mutations is the hypo-mature type. Teeth have an orange-brown coloration, while enamel lacks its natural opacity and a slight contrast is presented in its comparison with dentine[48]. Mutations of the gene are presented in table 7.

► KLK4 GENE

Enamel phenotype is associated with the loss of function of the protein that regulates enamel

mineralization during its expression, because of the KLK4 gene mutation[50,51]. Affected people show an orange-brown coloration both on primary and on permanent teeth. In radiographs, teeth show normal enamel morphology with reduced density compared to normal teeth. Enamel crystallites are far from each other and enamel retains large amounts of amelogenin, which is a similar protein. The mutation of this gene is presented in table 8.

Table 6. ENAM Mutations

Researcher	Year	Genomic DNA	cDNA	Protein	Phenotype	Reference
Mardh	2002	g.2382A>T	c.157A>T	p.K53X	AA (I) localized	44
Rajpar	2001	g.6395G>A	IVS7+1G>A c.534+1G>A	p.A158_Q178del	AA (I) Generalized-thin	43
Kida	2002	g.8344delG	IVS8+1delGc.588+1delG	p.N197fsX277	AA (I) Generalized-thin	45
Hart	2003					46
Hart	2004	g.13185_13186insAG	c.1258_1259insAG	p.P422fsX448	AA (I) Generalized-thin	42
Ozdemir	2005	g.12663C>A	c.737C>A	p.S246X	AA (I)	47
Ozdemir	2005	g.12946_12947insAG TCAGTACCAGTAC TGTGTC/WT		p.V340_ M341insSQYQYCV	AA (I)	47

Table 7. MMP20 Mutations

Researcher	Year	Genomic DNA	cDNA	Protein	Phenotype	Reference
Kim et al.	2005	g.30561A>T	c.954-2A>T ή c.IVS6-2A-T	p.I319Fs338X ή p.I319X	AA (II) Decreased mineral contents	48
Hart et al.	2009	g.16250T>A	c.678T>A	p.H226Q	AA (II)	49

Table 8. KLK4 Mutations

Researcher	Year	Genomic DNA	cDNA	Protein	Phenotype	Reference
Hart et al.	2004	g.2142G>A	c.458G>A	p.W153X	AA (II) Decreased mineral contents	50

Table 9. FAM83H Mutations

Researcher	Year	cDNA	Protein	Phenotype	Reference
Wright	2009	c.860C>A	p.S287X	Generalized	50
Lee	2008	c.891T>A	p.Y297X	Generalized	51
Wright	2009	c.923_924delTC	p.L308fsX323	Generalized	50
Kim	2008	c.973C/T	p.R325X	Generalized	48
Kim	2008	c.1192C/T	p.Q398X	Generalized	48
Lee	2008	c.1243G>T	p.E415X	Generalized	51
Hart	2009	c.1330C.T	p.Q444X	Generalized	49
Hart	2009	c.1366C.T	p.Q456X	Generalized	49
Lee	2008	c.1380G>A	p.W460X	Generalized	51
Wright	2009	c.1408C>T	p.Q470X	Generalized	50
Wright	2009	c.1872_1873delCC	p.L625fsX703	Localized	50
Lee	2008	c.2029C>T	p.Q677X	Generalized	51
Wright	2009	c.2080G>T	p.E694X	Localized	50
El-Sayed	2009	c.1374C>A	p.Y458X	Localized	52

► FAM83H GENE

FAM83H gene is the most recent gene found to be associated with amelogenesis imperfecta. It is found in chromosome 8q24 and has been identified as causative of type III amelogenesis imperfecta in an autosomal dominant mode[48,49,50]. The condition presents with reduction in the mineral content of enamel and as a result, hypo-calcification occurs.

The role of this gene and of the protein it produces is unknown to date, but we know that despite the fact that this gene is expressed in lots of tissues, the only mutations that have been detected cause enamel deficiencies.

The phenotype of the autosomal dominant type of amelogenesis imperfecta III shows diversity and is related with the type of the FAM83H gene mutation. The colour of enamel of the primary and permanent teeth is yellow-brown and the enamel is particularly thin and brittle. Mineral content of enamel are significantly reduced (from 40 up to 70% per volume), while enamel has an increased density in proteins poor in proline, as shown in hypo-mature types of amelogenesis imperfecta[50].

The 14 mutations of the FAM83H gene that have been found to date and cause hypo-calcified amelogenesis imperfecta that is inherited in an autosomal dominant mode are presented in table 9.

► WDR72 GENE

The WDR72 gene consists of 19 coding exons spanning around 250 kb encoding a protein of 1102 amino acid. Its functions are unknown[53]. The WDR72 protein is an intracellular protein with a predicted b-propeller structure that is expected to mediate in reversible interactions between proteins, while its structure could probably contribute to a number of various ways of amelinoblastin maturation. Gene mutations affect the late stages of enamel maturation[10]. WDR72 gene mutations are associated with type II autosomal recessive amelogenesis imperfecta and are presented in table 10.

Table 10. WDR72 Mutations

Researcher	Year	cDNA	Protein	Phenotype	Reference
W. Elsayed et al.	2009	c.2348C>G	p.S783X	AA (II)	53
W. Elsayed et al.	2009	c.2934G>A	p.W978X	AA (II)	53
W. Elsayed et al.	2009	c.2857Adel	p.S953V fs X20	AA (II)	53
W. Elsayed et al.	2011	c.2728C>T	p.R897X	AA (II)	54

Table 11. Candidate genes related to amelogenesis imperfecta (as reported in the literature)

Candidate gene	Researcher	Reported year	Reference
CNNM4	Parry et al.	2009	55
GJA1	Vitiello et al.	2005	56
SLC4A4	Igarashi et al. ; Urzua et al.	1991 ; 2011	57 ; 58
DLX3	Dong et al.	2005	59
ROGDI	Schossig et al.	2012	60
C4orf26	Parry et al.	2012	61
AMTN	Gasse et al.	2012	62
TP63	Kantaputra et al.	2011	63
FAM20A	Vogel et al.	2012	64
FAM20C	Vogel et al.	2012	64
TUFT1	Luo et al.	2004	65
AMBN	Paine et al.	2003	66

► OTHER GENES

Apart from those 6 genes that have been proved to be correlated with types of amelogenesis imperfecta, there are also candidate genes that could be integrated or not in the list of genes that cause amelogenesis imperfecta after research studies that will be conducted in the future. The candidate genes, the researcher that proposed them and the year when they were reported are presented in table 11.

A correlation between amelogenesis imperfecta and the nephrocalcinosis syndrome has also been reported. Various researches have shown that people that present deficiencies in enamel surface, suffer from nephrocalcinosis syndrome, but lots of research steps are still needed in order for such a conclusion to be formed[67,68].

Discussion

The development of technologies as well as of scientists' abilities to detect gene mutations has decisively contributed in establishing a connection between amelogenesis imperfecta phenotypes and genotypes. It has contributed in the grouping of the phenotypes, the genes

involved, mutation types, the results on translated proteins and on the functions of these proteins.

To date, mutations on 6 genes have been verified: AMELX, enam, KLK4, MMP20, FAM83H and WDR72, and more than 42 different mutations have been reported in the literature. Although only these genes have been associated with amelogenesis imperfecta until now, there are probably more candidate genes that have yet to be associated. AMBN is the gene that composes ameloblastin, the second in concentration protein in enamel. This gene has not been associated with an amelogenesis imperfecta phenotype in humans, although it is associated with hypoplastic enamel phenotype in mice research. The results of this research show the crucial role of protein in enamel formation[22,69].

The dentist ought to know the phenotype and the mode of inheritance of the 4 main types of amelogenesis imperfecta in order to be able to diagnose such a probable condition and to help narrow the search for the candidate gene for determining molecular etiology. There are obvious differences in the phenotype of some mutations (as for example in mutations in the enam gene) that can be diagnosed and treated easily and quickly.

The knowledge of the mode of inheritance of the condition is also extremely important. In case there is no information on the mode of inheritance of the phenotype, there can't be an enlightening molecular study. More specifically, a type I amelogenesis imperfecta phenotype can be caused by X-linked, autosomal recessive or autosomal dominant mutation type. As research is developing and new genes related to amelogenesis imperfecta are being detected, phenotypes that will oversubscribe known phenotypes may occur, rendering molecular identification even more difficult.

The treatment of amelogenesis imperfecta depends on the gravity of the condition and it usually calls for the cooperation of a wide group of dentists that will contribute to the final rehabilitation. This group will include an orthodontist, an oral surgeon and a prosthodontist[70]. The purpose of rehabilitation is creation of an aesthetically and functionally acceptable chewing system with right vertical dimension of the jaws, and preservation of the right dimension of the dental arches[18]. The treatment of amelogenesis imperfecta depends on the social, economic and educational level of the family and of the child's will to cooperate with the dentist, like in every dental treatment. Of course, the parents' interest for their child's problem is a highly important factor. Differential diagnosis from other syndromes and systemic diseases with a clinical appearance similar to amelogenesis imperfecta plays a key role in its treatment. Such syndromes are chondral ectodermal dysplasia, Goltz syndrome, Albright syndrome, tricho-dento-osseous syndrome and hypovitaminosis D rachitis[63,64,71,72].

Conclusion

In conclusion, there are 6 genes that have been genetically proved to be causative of amelogenesis imperfecta. These genes are: AMEX, ENAM, MMP20, KLK4, FAM83H, and WDR72. Mutations that have been found to lead to the disorder in teeth enamel are mentioned in the literature. As genetics develop, more genes related to amelogenesis imperfecta cold be recognized, while there will be a possibility for further research. The 4 categories of amelogenesis imperfecta differ in their clinical appearance, their radiographic depiction and the mode of inheritance. The dentist ought to recognize and correlate the phenotype with the genotype in order to prevent or treat conditions.

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Correspondence and request for offprints to:

Chatzopoulos Georgios
8, Papapetrou str., Kalamaria, Thessaloniki
Telephone: 00306945675693
e-mail: gschatzo@dent.auth.gr