

Human hereditary enamel abnormalities – molecular factors and genetic counselling

Andrei Kozma^{4,5,6,7}, Doriana Agop Forna², Viorica Radoi¹, Radu Ursu¹,
Agnes Katalin Lackner³, Laurentiu Camil Bohiltea¹, Horia Lazarescu⁵

¹“Carol Davila” University of Medicine and Pharmacy, Bucharest

²“Grigore T. Popa” University of Medicine and Pharmacy, Iasi

³Medical University Vienna, University Dental Clinic, Department of Pediatric Dentistry

⁴Research department in Social Pediatrics and Obstetrics,

“Alessandrescu-Russescu” National Institute for Mother and Child Health, Bucharest

⁵National Institute for Recovery, Physical Medicine and Balneoclimatology, Bucharest

⁶Academy of Romanian Scientists

⁷Romanian Academy of Medical Sciences

ABSTRACT

Defective enamel formation may result either from factors of environmental origin or from genetic abnormality. Such genetically determined enamel malformations have been described in patients with chromosomal anomalies and with inherited single gene defects. Enamel is a principal component of the dentition, and defects in this hard tissue are associated with a wide variety of diseases. Dental enamel is the epithelial-derived hard tissue covering the crowns of teeth. It is the most highly mineralized and hardest tissue in the body. Dental enamel is acellular and has no physiological means of repair. Amelogenesis imperfecta (AI) is a group of genetically and phenotypically diverse forms of defective tooth enamel development. Progress has been made regarding the definition of the genetic basis of AI, but the exact mechanism for the biomineralization process remains largely unknown. The list of genes associated with enamel defects has grown tremendously over the past decade. The molecular pathways involved in the development of enamel defects are diverse, and the functionality of the genes and gene products is heterogeneous. Syndrome-associated enamel defects are caused by many genes that affect other tissues, including eye, kidney, brain, and skin. As with enamel defects, early diagnosis and preventive care are essential for successful management of dentine defects. Patients who have a family history of dentine defects such as dentinogenesis imperfecta or those with medical conditions known to be associated with dentine defects such as hypophosphataemia and osteogenesis imperfecta should be screened early for dental problems.

Keywords: enamel, genetics, amelogenesis imperfecta

INTRODUCTION

Defective enamel formation may result either from factors of environmental origin or from genetic abnormality. Such genetically determined enamel malformations have been described in patients with chromosomal anomalies and with inherited single gene defects (1,2).

Enamel is a principal component of the dentition, and defects in this hard tissue are associated with a wide variety of diseases. Dental enamel is

the epithelial-derived hard tissue covering the crowns of teeth. It is the most highly mineralized and hardest tissue in the body. Dental enamel is acellular and has no physiological means of repair (2,3).

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,

Corresponding author:

Lecturer Viorica Radoi, MD, PhD

E-mail: viorica.radoi@yahoo.com

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while it depends on the population groups on which the study is conducted and on the diagnostic criteria (1,2,3).

The development of human enamel involves a complex series of events including the secretion and degradation of a unique extracellular matrix. Ameloblasts progress through a succession of cellular phenotypes executing specialized secretory and regulatory functions. When performing optimally, ameloblasts produce a highly structured and mineralized tissue (4,5,6). Given the elaborate developmental events required for normal enamel formation, it is not surprising that a variety of enamel malformations arise from defects in matrix synthesis, secretion and extracellular processing. Normal matrix secretion and post-secretory processing by ameloblasts can be affected by a variety of hereditary and environmental conditions (7,8,9,10).

Normal matrix secretion and post-secretory processing by ameloblasts can be affected by a variety of hereditary and environmental conditions. These disturbances can result in an abnormal amount and/or composition of matrix proteins, and subsequently, an altered enamel structure and/or mineral content (2,7,9).

This process of amelogenesis is accomplished through a temporally restricted and highly regulated series of events that include development of a specific extracellular matrix, matrix processing, and controlling the microenvironment of the developing enamel tissue (10,11). These processes are highly regulated at the molecular level, with amelogenesis ultimately involving thousands of genes and their products.

Amelogenesis imperfecta (AI) is a group of genetically and phenotypically diverse forms of defective tooth enamel development (11,12,13,14). Progress has been made regarding the definition of the genetic basis of AI, but the exact mechanism for the biomineralization process remains largely unknown.

Amelogenin is expressed in pre-ameloblasts, ameloblasts and in the epithelial root sheath remnants. A low level of amelogenin expression has been recently reported in odontoblasts. The various isoforms of amelogenin that are involved in the formation of the enamel matrix prior to enamel mineralization represent about 90% of the enamel

matrix (2,3,15,15). ENAM is expressed predominantly by the enamel organ and at a low level in odontoblasts. Genetic alterations also can affect enamel formation through secondary actions or distresses that do not involve ameloblast dysfunction caused by gene expression of the ameloblast (14,15,16). Through a variety of diverse processes, genes that are transiently or not expressed by ameloblasts can result in altered enamel development. Genes expressed by the ectomesenchyme or its derived odontoblast cells appear to be critical for signaling the ameloblasts, and abnormalities in this process could result in aberrant ameloblast function (14,17). This may well occur in certain cases of dentinogenesis imperfecta type II (OMIM 125490) caused by DSPP mutations that display enamel defects in addition to the more typical dentin defects. Interrogation of databases of human mutations can provide insights into the molecular etiologies associated with developmental defects of human teeth.

The list of genes associated with enamel defects has grown tremendously over the past decade. The molecular pathways involved in the development of enamel defects are diverse, and the functionality of the genes and gene products is heterogeneous. Syndrome-associated enamel defects are caused by many genes that affect other tissues, including eye, kidney, brain, and skin, to name just a few. Identification of the genes associated with developmental defects of enamel has been extremely informative in helping advance our knowledge of the molecular control of enamel formation and how genes and gene products can have diverse functions in different tissues.

Molecular-genetic basis of amelogenesis imperfecta

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. Amelogenin AMELX Xq22 and AMELYyp11 genes are critical for normal thickness and structure. About 14 mutations, 5 nucleotide substitutions, 7 small deletions, and 2 gross deletions have reported in amelogenin gene. The mutation destroys the normal functions of amelogenin, producing enamel of normal thickness

but poorly mineralized and discolored. Enamelin The largest extracellular matrix protein produced by ameloblast is enamelin (4,8). The enamel gene mutation occurs in autosomal dominant forms of hypoplastic Amelogenesis imperfecta

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.

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 enamel gene has 10 exons, 8 of which are encoded 14

Enamelysin (MMP20 gene found in chromosome 11). Enamel mutations are associated with the autosomal recessive type of inheritance of amelogenesis imperfecta (8,11)

Kallikrein 4 (KLK4 gene found in chromosome 19). Mutation of kallikrein 4 is associated with autosomal recessive mode of inheritance of amelogenesis imperfecta

FAM83H (product of FAM83H gene found in chromosome 8q24): mutations on this gene may cause a disorder in mineralized enamel elements It is found in chromosome 8q24 and has been identified as causative of type III amelogenesis imperfecta in an autosomal dominant mode (11,14)

A novel ADAI locus was mapped to a 2.1 Mb interval on chromosome 8q24.3 region. There are 60 known genes in this interval, and 32 hypothetical genes and expressed sequenced tags. Several

strong candidate genes in this region included EPPK1, LOC392275, GRINA, SLC39A4, GPAA1, COMMD5, VPS28, FOXH1, ZNF34 and ZNF517. The gene LOC392275 seemed like a strong candidate since a deletion of the related Smpd3 gene in the mouse resulted in osteogenesis and dentinogenesis imperfecta (18)

The clinical significance of enamel and dentine defects is well known but the pathogenesis of the defects is still being studied. While the range of environmental insults that can damage the enamel organ have been identified, the relative susceptibility of the enamel organ at the various stages of development have not been well researched (11,17,19).

CONCLUSIONS

As with enamel defects, early diagnosis and preventive care are essential for successful management of dentine defects. Patients who have a family history of dentine defects such as dentinogenesis imperfecta or those with medical conditions known to be associated with dentine defects such as hypophosphataemia and osteogenesis imperfecta should be screened early for dental problems. Enamel research is a multidisciplinary field, and one idea that was discussed was a platform where data and resources could be shared in a more efficient way.

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REFERENCES

1. Tziafas D. Biology of dental tissues. Development, structure and function. Chap. 2 Odontogenesis: formation of coronal tooth. Thessaloniki: University Studio Press, 1999; pp 45-50.
2. Backman B. Amelogenesis imperfecta-clinical manifestations in 51 families in a northern Swedish country. *Scand J Dent Res*, 1988; 96:505-516.
3. Witkop CJ. Hereditary defects in enamel and dentin. *Acta Genet Stat Med*, 1957; 7:236-239.
4. Chosack A, Eidelman E, Wisotski I, Cohen T. Amelogenesis imperfecta among Israeli Jews and the description of a new type of local hypoplastic autosomal recessive amelogenesis imperfecta. *Oral Surg Oral Med Oral Pathol*, 1979; 47:148-156.
5. Sundell S. Hereditary amelogenesis imperfecta. An epidemiological, genetic and clinical study in a Swedish child population. *Swed Dent J*, 1986; 31(Suppl):1-38.
6. Witkop CJ Jr. Amelogenesis imperfecta, dentinogenesis imperfecta and dentin dysplasia revisited. Problems in classification. *J Oral Pathol*, 1988; 17:547-553.
7. Adaimy L, Chouery E, Megarbane H, Mroueh S, Delague V, Nicolas E, Belguith H, de Mazancourt P, Megarbane A. Mutation in WNT10A is associated with an autosomal recessive ectodermal dysplasia: The odonto-onycho-dermal dysplasia. *Am J Human Genet*, 2007. 81(4):821-828.
8. Aldred MJ, Savarirayan R, Crawford PJ. Amelogenesis imperfecta: A classification and catalogue for the 21st century. *Oral Dis*, 2003. 9(1):19-23.
9. Arquitt CK, Boyd C, Wright JT. Cystic fibrosis transmembrane regulator gene (CFTR) is associated with abnormal enamel formation. *J Dent Res*, 2002. 81(7):492-496.)
10. Ferrazzano GF, Sangianantoni G, Cantile T, Amato I, Orlando S, Ingenito A. Dental enamel defects in Italian children with cystic fibrosis: an observational study. *Community Dent Health*, 2012. 29(1):106-109.
11. Gasse B, Karayigit E, Mathieu E, Jung S, Garret A, Huckert M, Morkmued S, Schneider C, Vidal L, Hemmerlé J et al. Homozygous and compound heterozygous MMP20 mutations in amelogenesis imperfecta. *J Dent Res*, 2013. 92(7):598-603.

12. Hart PS, Hart TC, Michalec MD, Ryu OH, Simmons D, Hong S, Wright JT. Mutation in kallikrein 4 causes autosomal recessive hypomaturation amelogenesis imperfecta. *J Med Genet*, 2004. 41(7):545–549.
13. He P, Zhang Y, Kim SO, Radlanski RJ, Butcher K, Schneider RA, DenBesten PK. Ameloblast differentiation in the human developing tooth: effects of extracellular matrices. *Matrix Biol*, 2010. 29(5):411–419.
14. Hu JC, Yamakoshi Y. Enamelin and autosomal-dominant amelogenesis imperfecta. *Crit Rev Oral Biol Med*, 2003. 14(6):387–398.
15. Klein H. Dental fluorosis associated with hereditary diabetes insipidus. *Oral Surg Oral Med Oral Pathol*, 1975. 40(6):736–741.
16. Koster MI. p63 in skin development and ectodermal dysplasias. *J Invest Dermatol*, 2010. 130(10):2352–2358.
17. Lacruz RS, Smith CE, Chen YB, Hubbard MJ, Hacia JG, Paine ML. Gene expression analysis of early and late maturation stage rat enamel organ. *Eur J Oral Sci*, 2011. 119(Suppl 1):149–157.
18. Lacruz RS, Smith CE, Moffatt P, Chang EH, Bromage TG, Bringas P, Jr, Nanci A, Baniwal SK, Zabner J, Welsh MJ et al. Requirements for ion and solute transport, and pH regulation during enamel maturation. *J Cell Physiol*, 2012. 227(4):1776–1785.
19. Lagerstrom-Fermer M, Nilsson M, Bäckman B, Salido E, Shapiro L, Pettersson U, Landegren U. Amelogenin signal peptide mutation: correlation between mutations in the amelogenin gene (AMGX) and manifestations of X-linked amelogenesis imperfecta. *Genomics*, 1995. 26(1):159–162.