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Amelogenesis Imperfecta Enamel Changes, Amelogenin, and Dental Caries Susceptibility

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There is great interest in identifying the subset of individuals in the population that are more susceptible to dental caries. We proposed that a portion of these particular individuals are more susceptible to dental caries due to changes in dental enamel that are related to amelogenin genomic variation. However, apparently amelogenin function can be impacted by inflammation, and this can lead to small changes in the structure of the dental enamel that later in life increases the risk of dental caries.

Keywords: dental caries, amelogenesis, inflammation, AMELX, amelogenin

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INTRODUCTION

Dental caries is highly preventable but continues to affect a large proportion of populations. Identification of risk factors for the disease that will allow for preventive strategies are of great interest. Aspects related to the individual have been less studied and are likely to provide the new insight needed. We believe that factors that cause deviations of normal dental enamel development should be the focus of future research that aims to unveil new targets for dental caries prevention.

DENTAL CARIES EPIDEMIOLOGY

The epidemiology of dental caries has changed, and it is common to be able to identify clusters of individuals that are caries-free. At the same time, certain individuals appear to have most of the disease of the population (1). It has become a need to be able to identify early these individuals who are at higher risk for dental caries. We have suggested that individual genetic variation may be a factor playing a role in these specific individuals that appear to have most of the burden of disease. One plausible gene that may influence individual risk to dental caries is amelogenin, which is mutated in X-linked forms of amelogenesis imperfecta and accounts for 5% of all cases of the condition (2). We and others have hypothesized that variation in enamel formation genes could explain in part individual susceptibility to dental caries (1, 3). Further, genetic variation in amelogenin was associated with caries experience (4–11), erosive tooth wear (12), variation in microscopic enamel structure (13), salivary calcium levels (14), and molar–incisor hypomineralization (MIH) (8) in a number of cohorts with distinct geographic origins, and with incisor enamel microhardness in amelogenin-impaired mouse models (15).

AMELOGENESIS IMPERFECTA

Amelogenesis imperfecta is a collective designation for the variety of inherited conditions displaying isolated enamel malformations. However, the designation of amelogenesis imperfecta is also used to indicate the presence of an enamel phenotype in syndromes (16). There is great

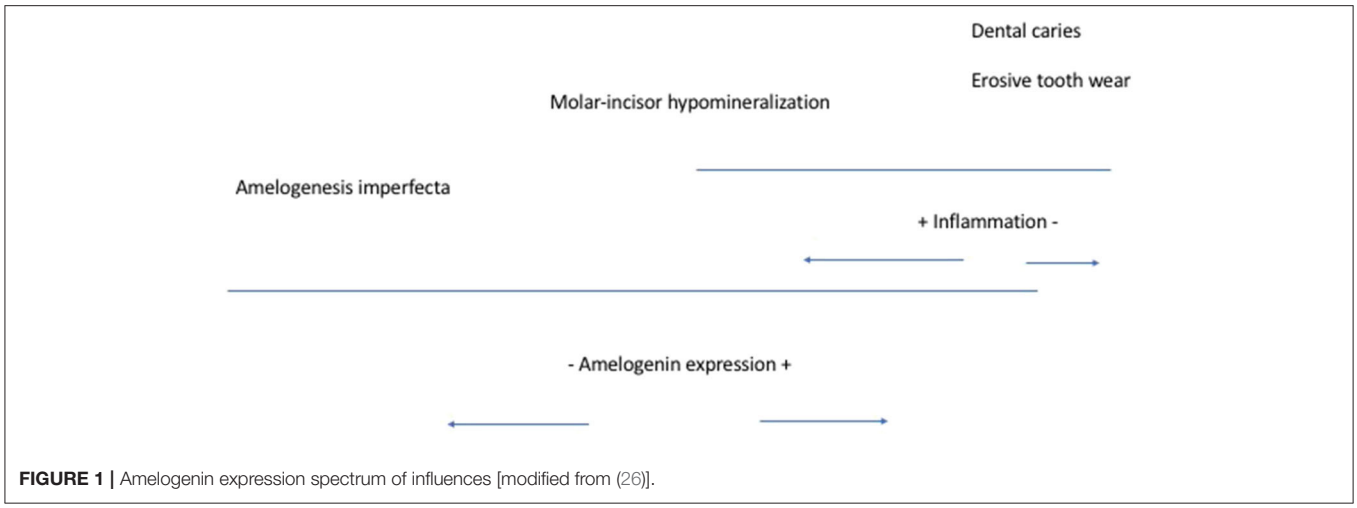

FIGURE 1 | Amelogenin expression spectrum of influences [modified from (26)].

variability in the clinical presentation of amelogenesis imperfecta. It has been suggested for specific subpopulations that the most prevalent in the amelogenesis imperfecta group are autosomal recessive hypomature amelogenesis imperfecta and autosomal dominant hypoplastic amelogenesis imperfecta (17). Amelogenesis imperfecta is typically classified into four phenotypes: hypoplastic type I, hypomatured type II, hypocalcified type III, and hypoplastic-hypomaturation type IV (18). This broad spectrum of conditions associates to different mutations and it is possible that some of them may increase individual susceptibility to dental caries whereas others may have a protective effect against the disease.

Patients with hypoplastic amelogenesis imperfecta appear to have lower levels of caries experience because of an alkaline pH of saliva enriched with *Bacillus* spp., *Enterococcus faecalis*, and *Enterococcus faecium* (19). An analysis of the enamel of individuals born with amelogenesis imperfecta submitted in laboratory to high cariogenic conditions may provide insight on the higher susceptibility of dental caries that some in the population have.

The dental enamel of a tooth affected by amelogenesis imperfecta shows under the scanning electron microscope extensive irregular, disorganized rough superficial enamel layer. The enamel appears parallel or irregularly decussate with filamentous prisms accompanied by small, irregularly rounded formations (20, 21). The challenge of these findings continues to be that the histopathology does not appear to clearly correlate to a specific type of amelogenesis imperfecta (hypoplastic, hypocalcified, or hypomature) or a particular mutation. However, calcium levels in enamel of amelogenesis imperfecta, as well as in unaffected teeth, differed significantly between anterior and posterior teeth, indicating that the factors that influence normal mineralization in different regions of the arch are not altered due to amelogenesis imperfecta (20). The susceptibility to dental caries due to amelogenin genetic variation may therefore come from small differences in chemical content and/or physical structure of the enamel. Differences in physical structure of the enamel have been hypothesized as a mechanism underlying MIH (22).

DISCUSSION

Variation in amelogenin that impacts enamel development that ultimately increases an individual susceptibility to dental caries may be through inflammation. Amelogenin contributes to early resolution of inflammation. It suppresses major histocompatibility class II (MHC II) gene expression. Apparently, it downmodulates the interferon gamma–induced cell surface expression of MHC II molecules in macrophages (23). Although these experiments were done using murine macrophages, this mechanism is apparently conserved between species (24, 25). This ability to enhance initial macrophage response and to reduce the duration of inflammation allows for providing the hydrophobic environment necessary for the initiation and growth of calcium hydroxyapatite crystals during enamel development (23). This hydrophobic environment allows for amelogenin to self-assemble into nanospheres and nanosphere ribbons to form the scaffold that will guide the growth of the crystals in the maturation stage of enamel development. These apparent different processes may be executed by the amelogenin alternative splice variants such as leucine-rich and tyrosine-rich amelogenin peptides, which are suggested to induce distinct cellular functions. We believe the consequences of amelogenin genetic variation in enamel development fall in a spectrum that ranges from amelogenesis imperfecta to dental caries [(26); **Figure 1**] and may explain a subset of cases of dental caries higher susceptibility. More localized enamel defects in comparison with amelogenesis imperfecta are seen in MIH. Proteins exclusively found in saliva of individuals with MIH include pathways for neutrophil-mediated adaptive immunity, the activation of the classical pathway of complement activation, extracellular matrix degradation, heme scavenging as well as glutathione and drug metabolism. In comparison, individuals without MIH had

proteins that belong to adaptive immunity related to platelet degranulation and the lysosome (27).

We believe enamel development happens under a catabolic environment that can be changed by inflammation and that leads to increased individual susceptibility later in life to dental caries. To test this hypothesis, longitudinal studies enrolling subjects at birth and recording all infections and allergic reactions are necessary to demonstrate that these events in the presence of certain molecular markers associate with higher caries experience for individuals who are exposed to cariogenic challenges.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

AV and AM conceived the idea, wrote first draft, and critically revised the final submitted version. Both authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.