




Role of Genetic Markers in Dental Caries: A Literature Review

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Abstract

Introduction This article reviews the literature on the role of genetic markers in the initiation and progression of dental caries and provides a modern understanding of the disease etiology. Dental caries is a complex, chronic, multifactorial disease which is influenced by genetic, environmental, and social factors. Identification of genetic risk factors will help screen and identify susceptible patients to better understand the contribution of genes in caries etiopathogenesis to formulate various diagnostic and novel therapeutic approaches in the management of the disease.

Materials and Methods Innovations and ideas were retrieved based on the literature in journals and textbooks indexed in PubMed, Google Scholar, Scopus, and Web of Science database. The theories obtained are then summarized into a continuous series; thus, readers can more easily understand the ideas and innovations offered.

Results Through interactions of the involved gene products, genetic markers have been constructed and provide us with insights into the molecular mechanisms underlying caries. There can also be gene–gene interactions or gene–environment interactions that create epigenetic effects that all possibly contribute to caries risk and resistance. A variety of caries markers have been identified, including genes affecting salivary flow rates and composition, tooth formation genes, as well as immune genes.

Conclusion Information derived from various diverse studies will provide new tools to target individuals and/or populations for a more efficient and effective implementation of new preventive measures and diagnostic and novel therapeutic approaches in the management of dental caries.

Keywords

- ▶ genetics
- ▶ dental caries
- ▶ salivary flow
- ▶ extracellular matrix

Introduction

The most common chronic illness that equally affects adults and children is dental caries. It is characterized by the demineralization of the tooth's inorganic component and the loss of its organic material, which frequently results in cavitation. Because it is a complex illness, the function of molecular-genetic markers and environmental factors in the development of caries can be taken into consideration. It

typifies the way that the pathogenesis of caries is understood nowadays.¹

Genetic Markers and their Significance in Dental Caries

The crucial role of genetic markers in tooth decay has been shown in twin research on the heritability of childhood tooth decay.² Additionally, the age-related development of dental

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caries is influenced by genetic markers linked to early childhood caries (ECC).³

Utilizing population association studies, familial analysis based on triads (father, mother, and child), genome-wide association studies (GWAS), and meta-analysis, the genetic loci linked to dental caries have been explored. 14q11.2, 14q24.3, Xq27, 5q13.3, and 13q31.1 are the five genomic sequences⁴⁻⁶ which may include loci linked to this illness. Several markers were also identified on region 4p21.⁷ For children with permanent teeth, new important caries markers have been revealed. Transforming growth factor beta family genes, the matrix metalloproteinase family genes, and genes associated with cytokine networks are three key gene clusters that have been discovered via functional analysis.⁸ In order to categorize different groups at risk during the early stages of caries development, it is therefore important to determine a wide variety of genetic loci coupled to the infection as well as the specific interactions between the encoded proteins during the early stages of disease development.

Although different genes are impacted, it is crucial to comprehend the network of diverse pathways and linked genes that underlie similar dental abnormalities. Networks representing this complicated scenario will help us understand the disease since protein networks contain many types of interaction and function.⁹

Dental caries is a multifactorial illness that develops as a result of the intricate interplay between environmental and genetic risk factors. Sugar-rich diets, poor oral hygiene, dental plaque, high levels of cariogenic bacteria, inadequate salivary flow, and other environmental factors have been reported as risk factors for caries (Selwitz et al, 2007). It has been estimated that 49.1 to 62.7% of the variation in caries risk scores is genetic in nature (Haworth et al, 2020). Caries risk is a complicated genetic trait that may be impacted by numerous loci, each of which may have only modest effects. Variations in the loci for enamel production, immunological response, saliva, taste, and dietary habits may be among these genetic risk factors for caries.¹⁰

Material and Methods

To strengthen the sensitivity and scope of the review, a well-defined and well-thought-out search strategy approach was used in this paper to present an idea and a novel concept on genetic markers of dental caries. This document extraction was done by utilizing PubMed, Embase, Scopus, Web of Science databases, Cumulative Index to Nursing and Allied Health Literature, and Google Scholar libraries and different Medical Subject Headings were used to update journal material, ideas, and developments based on literature reviews in journals and textbooks that were included in the study. In order to describe theories and connect them into a frame of mind that becomes an idea and invention, the literature review incorporates research findings and article reviews. To establish the validity of the hypothesis, additional research can be built upon this review paper. This article's literature review employs the method of comparing infor-

mation from several libraries using the same keywords in order to draw comparisons and conclusions. To make it simpler for readers to understand the concepts and innovations presented, the theories that have been obtained are then condensed into a continuous series.

Inclusion and Exclusion Criteria

The authors skimmed through the reference list of all the studies that met the criteria developed by the research team. Systematic and well defined criteria for article selection was developed. Only original research articles were included in our final review. Articles published between 1990 and 2022 and also articles from a few journals in 1936, 1944, 1958, and 1973 were also included. For the final review, articles published in peer-reviewed and indexed journals were also included.

Pilot studies, correspondences, case reports, case series, and editorials and non- English papers were excluded from the final review. Finally, the articles without in range of keyword searches were also excluded.

Results

Genetic Studies and Various Genes Responsible for Etiology of Dental Caries

It has been extensively studied how various genotypes affect people's susceptibility to dental decay. Both an increase in biofilm pathogenicity and a risk of dental caries have been associated with genetic polymorphisms. In Afro-American women, the relationship between oral bacterial levels and innate host genes including human leukocyte antigen (HLA) class II and TNFA alleles as well as the decayed, missing, and filled tooth surface index was examined (Acton et al 1999). They discovered a connection between the colonization of *Streptococcus mutans*, *Lactobacillus casei*, and lactic acid-generating bacteria and the host HLA class II and TNF- α genetic profiles.¹¹

Animal Studies

Animal experiments have also suggested that genetic factors may contribute to higher susceptibility to caries (Steggerda and Hill, 1936).

Hunt et al (1944) discovered a significant influence of genetic variations across mouse strains in influencing the course of caries in their experiments. By contrast, in four inbred male mice strains when fed with a cariogenic diet and *S. mutans* inoculations, genetic factors have been shown to affect the caries scores of molar teeth (Kanamoto et al 1994).

Familial Aggregation Studies

Klein and Palmer studied the association between siblings' dental decay in 1930 and discovered that siblings of children who did not have caries had lesser caries scores than siblings of children who did. High concordance rates have been seen between monozygotic twins (Mz) in a number of dental phenotypes, including occlusal traits, tooth size, dental arch dimensions, and dental degeneration.¹²

According to Horowitz et al (1958), monozygotic twins exhibited higher caries concordance. In 82 sets of female-female twins between the ages of 6 and 12, Liu et al (1998) revealed significant facts of genetic effects affecting tooth and arch size, presence of third molars, and upper lateral incisor deformity, but little heritability in tooth eruption and caries. Therefore, in these twin investigations, there was no discernible difference in the incidence of caries between MZ and dizygotic (DZ) spouses. A hereditary component is more relevant than caries in tooth morphology and eruption timing, according to Bordoni et al. (1973), who evaluated tooth morphology and timing in 17 unrelated controls and 17 MZ twins.

Additionally, a study including 280 sets of twins discovered that MZ twins had a greater incidence of correlation rate for dental caries; however, the results lacked statistical significance (Gao, 1990).

Five gene loci were found in human genome-wide scan (392 markers) studies: Xq27.1, 14q11.2, and 5q13.3 for mild caries, whereas 114q24.3 and 3q31.1 for high caries susceptibility (Vieira et al, 2008). Dental caries has been linked to the genes enamelin (ENAM), tuftelin (TUFT1), amelogenin (AMELX), ameloblastin (AMBN), kallikrein 4 (KLK4), TUFT1-interacting protein (TFIP11), and (Slayton et al, 2005). HLA-DQB1 and HLA-DRB1 are major histocompatibility complex (class II genes) that were linked to ECC, according to Yu et al.

Bacterial ligand CD14 polymorphism induced by a specific CD14 genotype has indeed been linked to at least four carious lesions (De Soet et al, 2008).

Genetic Markers in Tooth Maldevelopment

The qualities of a tooth's morphology influence how dental caries develops.¹³ The chewing surfaces and hard-to-reach tooth surfaces show higher susceptibility to caries. Caries-protective alleles of genes were also found to be regulating tooth formation with marked protection effects.¹⁴

The genes regulating tooth formation have shown that there was some evidence of genetic contribution to caries development, for instance, the dentin-sialophosphoprotein gene encodes two principal proteins of the dentin extracellular matrix of the tooth: the preproprotein secreted by odontoblasts and cleaved into dentin sialoprotein and dentin phosphoprotein. A whole range of mutations affecting dentin structure has been identified. Individual and interspecies variation in the DSP domain length and the variation was found to be between 770 and 902 amino acids.¹⁵ Due to a deficiency in the phosphoprotein required for the dentin's biomineralization process, which has traditionally been connected to an increased risk of caries lesions, mutations in the DSSP gene are linked to dentin that is softer and malformed.¹⁶

Features of Enamel Formation

Amelogenesis imperfecta is caused by several genes, including ENAM, AMELX, enamelysin or matrix metalloproteinase-20 (MMP-20), and KLK-4. Distal-less homeobox 3 (DLX3), family with sequence similarity 83 member H (FAM83H),

and solute carrier family 4 member 4 (SLC4A4) are the genes that have recently been discovered.¹⁷⁻¹⁹

The AMELX gene encodes a protein of the AMELX family of extracellular matrix proteins and plays an important role in biomineralization during dental enamel development. It is located on the X chromosome at region Xp22.31-p22.1. This gene was previously known under designations AMG, AI1E, AIH1, ALGN, AMGL, and AMGX.¹⁷

At first, mutations in the genes encoding enamel matrix were analyzed to detect mutations for the AMELX, ENAM,²⁰ KLK4,²¹ and MMP20 genes,²² as well as for the TUFT1 gene or the gene encoding protein interacting with TUFT1.^{23,24} These genes showed associations with caries.

The X and Y chromosomes of humans contain the AMELX genes. Ninety percent of the AMELX transcripts in males are coded by the gene AMELX (Salido et al., 1992).

The two AMELX mutations in exon 2 that result in X-linked amelogenesis imperfecta (AI) are the initiation codon for translation and AMELX secretion p.M1T is disrupted by the first mutation, while the second mutation alters the fourth amino acid in the signal peptide p.W4S. The p.M1T mutation would prevent the expression of AMELX from the faulty mRNA transcripts from being translated (null mutation).²⁵ Hypomaturation form of AI is brought on by defective AMELX protein release, and this type of AI results in a further pronounced lyonization pattern (Collier et al., 1997; Li et al., 2003). Women who have X-linked AI often have thinner (hypoplastic) white opaque enamel that alternates with normal, translucent enamel in vertical bands. The enamel layer is created by the KLK4 gene's protease, which is responsible for the systematic substitution of the mineral matrix for organic matrix.

The KLK4 gene is one of 15 genes of the kallikrein family of serine proteases located on the kallikrein cluster on chromosome 19. The function of protease is the orderly replacement of organic matrix with mineral matrix thereby generating an enamel layer.²⁶ KLK4 is mostly expressed in the secretory and basal cells of prostate glands as well as in a number of tissues, including the thyroid gland, reproductive glands, and developing teeth. The KLK4 gene's A Rs 2235091 (G/A) allele is associated with tooth decay resistance.²⁷

ENAM is involved in the formation of enamel and is incorporated in the formed crystalline of enamel prisms and between them. The physical properties depend on the expression of the ENAM gene along with the AMELX and AMBN genes. Enamel crystals run perpendicularly to the external tooth surface, indicating a contribution of the ENAM protein to thicker enamel.^{28,29}

The ENAM gene, which is situated on chromosome 4 and is located at locations 71859495-71877517 of the ENAM (NM) 031889 sequence, produces a matrix protein involved in the production of enamel. The C14625T (rs7671281) SNP in the ENAM gene is thought to affect the primary dentition's enamel thickness, which causes a substantial exchange (isoleucine replaces threonine) at position 648. Genes that make enamel are subject to genetic variation, which mostly affects caries susceptibility. Therefore, changes in the

expression of TUFT1, AMBN, and AMELX affect a person's vulnerability to caries.²⁹

Genetic Markers in Saliva

The amount of saliva produced and its composition are key factors in the development of caries.³⁰ Additionally, saliva contains calcium and phosphates that are crucial for remineralization, and increased salivary flow rates have been linked to a preventive impact against caries.³¹ Aquaporin-5 is encoded by the *AQP5* gene and contributes to the production of pulmonary secretions, tears, and saliva.³² Key participants in the hydration of the extracellular matrix during tooth development are aquaporins-4 and -5. The *AQP5* gene plays a function in the formation of caries and is linked to decreased salivation.³³ Lysine (Lys) is changed to arginine (Arg) at position³⁴ owing to the lactoferrin gene's second exon's polymorphism (A/G; rs1126478). It prevents *S. mutans* from adhering, preventing the subsequent development of biofilms. It modifies the host's immunological reaction against germs.³⁵

Oral Microbiota

S. mutans is the main bacterial pathogen in dental caries. It is a major cariogenic bacterium that causes caries initiation. This bacterium can be detected in saliva using real-time polymerase chain reaction.³⁶

Microbiological cultivation, molecular identification, gene expression patterns, and metabolomics analyses show the importance of the entire bacterial community in understanding the role of the microbiome in the pathology of dental caries.³⁷

Current research into oral microbiota, including dental biofilm and saliva, in representatives of different regions worldwide with and without caries revealed a wide range of microorganisms within oral microbiota—up to 700 species, with *Streptococcus* being the most prevalent (sometimes more than 50%).^{38–40} Moreover, a wide variation in the qualitative and quantitative microbial composition in healthy children and in children with caries was observed and the features of microbiota associated with its vertical transmission were considered. *Streptococcus* has been found to have a nearly ubiquitous prevalence,^{40–42} except for African populations.

In these populations, the proportion of *Streptococcus* constitutes only 20%; the *Enterobacter* species (up to 60%) dominate and a high proportion of the *Serratia* species (up to 25%) and many *Rothia* species were noted.³⁹ The proportion of *Streptococcus* was 40% and that of *Prevotella* was up to 25% in saliva in Chinese populations.⁴⁰

The study of microbiota-derived from twins is most advantageous because it relies on studying twins raised in the same environments and with the same vertical transmission of oral microbiota. Therefore, diverse factors influence the quantitative and qualitative composition of mouth microbiota: genetic, immune, behavioral, and environmental factors as well as the features of vertical transmission (or heritability) of microbiota. Environmental factors and dietary habits are the most significant factors.³⁸

Genetics, Environment, and Dental Caries

Peterson et al showed 14 of the 19 twin pairs were most similar to each other with respect to their gene expression patterns, suggesting that either genetic and/or environmental factors are significant determinants of dental plaque microbiota gene expression patterns. The linkage associations between dental caries based on plaque microbiota of Monozygotic (MZ) and Dizygotic (DZ) twin pairs. Among the six MZ twin pairs, four (66%) displayed linkage compared to 10 of the 13 DZ twin pairs (76%). These results suggest that genetic and/or environmental factors are dominant to caries status as determinants of gene expression patterns.³⁸

Molecular-Genetic Markers in Early Childhood Caries

A tissue with a high mineral content is the dental enamel, with hydroxyapatite crystals occupying 85% of its volume. AMELX, AMBN, ENAM, TFIP11, and TUFT1 are key molecules that contribute to the structure of ameloblasts. According to Pavlic et al (2007), ENAM, which makes up around 5% of the entire enamel matrix protein, is the principal protein in the enamel matrix while it is developing. The results of the multivariable evaluations showed that the GG in ENAM (rs1264848) is protective against ECC. When the T allele of rs3796704 was used to simulate the presence of *Streptococcus mutans*, Patir et al (2008) discovered the link between this gene and the prevalence of caries in Turkish youngsters. Another study established the mechanism by which ENAM may contribute to caries by increasing the susceptibility of the enamel surface to demineralization (Shimizu et al 2012). It has been discovered that the *KLK4* (rs198968) genotypes AG and GG are protective against ECC.⁴²

Lactotransferrin polymorphism is linked to ECC. One of the immune system's components, the glycoprotein, has antibacterial properties, especially in young children. Therefore, ECC susceptibility is a product of gene-environment interactions, and ECC may be influenced by genetic variation in the immune system response and enamel formation genes.⁴²

There have also been reports linking dermatoglyphic patterns to early caries. Children without early childhood caries had a higher frequency of ulnar loops, but those with early childhood caries had a higher whorl frequency, fewer palmar ridges, and a smaller axial tri-radius and angular tri-radius angle. A multifactorial congenital abnormality of the lip and palate is another disorder of the dentoalveolar system for which dermatoglyphic patterns have previously been seen.⁴³ As a result, early caries can be predicted by dermatoglyphic patterns.⁴⁴

Additionally, groups of kids with congenital cognitive abnormalities and cleft lip and palate anomalies have been searched for caries-associated indicators; an extremely high severity and a rise in the prevalence of caries have been discovered.^{45,46}

The severity of caries is influenced by a combination of socioeconomic, genetic, and environmental variables.⁴⁷ It is interesting to notice that early caries-associated genes have different effects on youngsters depending on their gender.

The size of the genetic influence in primary dentition is higher in men than in women various genes can have analogous effects on both genders' permanent dentition.⁴⁸

Environmental and Social Factors

Many factors influence the risk of developing dental caries: external factors such as demographic characteristics (age, gender, ethnic origin, and educational level); anthropometric factors (height, body mass index, and waist line); endogenous factors such as saliva flow rate; and environmental factors such as diet, tooth-brushing frequency, quality of water, and fluoride exposure.⁴³ The composition of the oral microbiota of dental biofilm and saliva can also be regarded as an external factor.

Associations have been identified between separate decay patterns and sex, race, educational attainment, and tooth brushing frequency. These results are consistent with the premise that overall caries experience can be partitioned into patterns of decay with distinct (though not necessarily mutually exclusive) risk factors.

Demographic (age, sex, birth year, race/ ethnicity, and educational attainment), anthropometric (height, body mass index, waist circumference), endogenous (saliva flow), and environmental (tooth brushing frequency, home water source, and home water fluoride) risk factors have been tested and are found to be associated with the caries patterns. Females are known to be at higher risk for caries compared to men.⁴⁸ The fluoride content in tap water and oral cavity hygiene are the most crucial environmental factors.

One finding of the study—that water consumption appeared to be protective against caries—could have broad public health implications, particularly when considered in light of recent trends in water and soft drink consumption (Putnam and Allshouse, 2000). For example, as recently discussed by Sohn et al. (2001), plain water and milk consumption have declined, while carbonated beverage consumption has increased in recent years. The present study also found that less frequent toothbrushing and higher sugared beverage consumption were associated with caries experience, which is consistent with both earlier (Alanen et al, 1985) and more recent studies (Petti et al, 2000). Such changes in consumption patterns, particularly if they continue, and in light of the study's findings regarding water consumption, suggest that water fluoridation's impact on caries prevention could be declining. Thus, if there were less water consumption and if there is substitution of carbonated beverages (soft drinks) and other sugared beverages for water, it would be reasonable to expect that caries prevalence would increase. This would be primarily due to the detrimental effects of the sugar (and acid) in the drinks but could also be due in part to the nonfluoridated status of some of them

Socioeconomic factors are also important, such as the parents' education level associated with a better understanding of the importance of oral hygiene and daily routine of personal hygiene for preservation of teeth.^{49–51} Dietary

habits and taste preferences of an individual, in particular, sweet-tasting food intake, play a substantial role.⁵²

Conclusion

The knowledge of the genetic basis of caries will enable us to identify high-risk groups and provide them with targeted screening, preventive measures, and interventional strategies. As with diseases, genetics has an important effect on the etiology of dental caries. This is supported by animal studies, twin studies, and studies on salivary proteins, taste receptors, and bacterial genetics that cause variation in caries susceptibility. Today's caries etiology and treatment procedure are not designed to take into account the large amount of genetic information that affects oral health. Knowledge of genetic susceptibility and/or familial connection to the host and cariogenic bacteria associated with dental caries may provide preventive dental treatment options for patients and their families. Future studies with a larger number of subjects are needed to identify the effect of genetics on the etiology and treatment process of dental caries.

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Conflict of Interest

None declared.

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