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Review Article

Polygenic Architecture of Dental Caries: Single Nucleotide Polymorphisms in Genetic Epidemiology

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Abstract

This review presents the latest evidence on the link between genetic single nucleotide polymorphisms and dental caries, highlighting key genes and pathways involved, introducing foundational concepts, and discussing essential methodological considerations for future research. Several genes have been identified as significantly associated with caries experience, including those related to tooth mineral tissues, taste perception, salivary composition and flow, and immune response. Epistatic interactions appear to be crucial in explaining genetic influence. Inconsistencies in the literature are attributed to variations in caries classification, age groups, ethnic backgrounds, limited statistical power, and linkage disequilibrium. Population stratification often confounds results, and few studies adequately control for genetic ancestry. Ensuring Hardy-Weinberg equilibrium and accounting for linkage disequilibrium are essential to avoid bias. Bonferroni corrections for multiple comparisons are fundamental but rarely applied, contributing to inconsistent findings. In conclusion, genetic epidemiology studies suggest that dental caries has a genetic component, accounting for significant individual differences in disease risk.

Introduction

Dental caries is a multifactorial disease characterized by the localized demineralization of dental tissues due to acidic by-products resulting from bacterial fermentation of free sugars.[1,2] Dental caries is a widespread chronic condition affecting a significant portion of the global population.[3] Untreated dental caries impacts approximately two billion permanent teeth and 0.5 billion primary teeth, frequently resulting in dental pain,[4] failure of dental restorations,[5] and negatively affecting individuals' oral health-related quality of life.[6] While dental caries can be prevented through good oral hygiene, reduced intake of fermentable carbohydrates, and the use of fluoride—whether in water or in other vehicles such as toothpaste or mouthwash—controlling it at a population level remains challenging.[2] This is due to the strong influence of contextual, socioeconomic, and behavioral factors, making dental caries a persistent global public health issue.[2] Poor oral hygiene habits and high consumption of fermentable carbohydrates are closely related to unfavorable socioeconomic status and are the main factors that explain the development and progression of caries.[2,5]

However, differences in caries prevalence are noticeable among individuals with similar protective and risk factors and comparable oral health behaviors.[7,8] In these cases, genetic factors may play a role, influencing either increased resistance or susceptibility to dental caries.[9,10] A recent set of meta-analyses indicated that genetic factors could contribute to the observed differences in caries prevalence (Table 1).[11–22] Twin studies support this association, as monozygotic twins show higher concordance in caries experience than dizygotic twins.[23] Several genes have been identified as significant in the development and progression of dental caries.[9,17] These genes are categorized based on their functions: a) those related to tooth mineral tissues, b) taste perception, c) salivary composition and flow, and d) immune response. Research into genetic contributions to the occurrence of dental caries has been ongoing since the late 1980s, initially based on twin studies,[24–27] evolving into candidate gene association studies and, more recently, into genome-wide association studies (GWAS).

Keywords: Polymorphisms; Dental caries; Genetics; Single nucleotide polymorphism; Genome-wide association studies; GWAS; Polygenic architecture.

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Table 1. Systematic reviews of literature investigating the influence of single nucleotide polymorphisms on dental caries in candidate gene studies

Author	Study type	N studies	Population	Gene(s)	Main findings
Genes involved in tooth mineral tissues					
Li *et al*.[15]	Meta-analysis	4	Adults and children	*KLK4*	No overall associations with *KLK4*; subgroup analysis showed increased risk under dominant model (OR = 1.74, 95%CI [1.02–2.96])
Sharma *et al.*[16]	Meta-analysis	12	Children	*AMBN*, *KLK4*, *MMPs*, *AMELX*	Gene-based analysis found significant associations: AMBN (six variants), KLK4 (4), MMP20 (2), MMP9, and MMP13 (one each)
Hemati *et al*.[19]	Meta-analysis	17	Adults and children	*DEFB1*, *MBL2*	*DEFB1 was* associated with caries risk (OR = 1.22, 95% CI [1.02–1.47])
Chisini *et al*.[14]	Meta-analysis	18	Adults and children	*AMBN*, *AMELX*, *TFIP11*, *BMP*, *ENAM*, *MMPs*	Pooled SNPs in *AMBN* (OR = 0.45, 95%CI [0.29–0.72]), *AMELX* (OR = 1.78, 95%CI [1.23–2.56]), and *TFIP11* (OR = 1.64, 95%CI [1.08–2.50]) showed consistent associations with caries
Genes involved in taste					
Chisini *et al*.[13]	Meta-analysis	2	Adults and children	*TAS1R2*, *TAS1R3*, *TAS2R38*, *GLUT2*	Protective association found for *TAS2R38* (OR = 0.35, 95%CI [0.17–0.75])
Genes involved in saliva formation and composition					
Chisini *et al*.[11]	Meta-analysis	10	Adults and children	*CA6*, *AQP5*, *MUC5B*	*CA6 was* associated with higher risk (OR = 3.23, 95%CI [1.39–7.49]); *AQP5* variants linked to decreased risk (OR=0.75, 95%CI [0.59–0.95]); pooled salivary SNPs associated with increased caries risk (OR = 1.75, 95%CI [1.06–2.89])
Lips *et al*.[20]	Systematic review	16	Adults and children	*DEFB1*, *LTF*	Reported associations with *DEFB1* and *LTF* polymorphisms, though not all findings reached statistical significance
Genes involved in immune response					
Qin *et al*.[18]	Meta-analysis	10	Children	*VDR* (multiple SNPs)	VDR shows significant allele differences (OR = 1.33, 95%CI [1.30 – 2.30]); genotypes were associated with higher risk (OR = 1.33, 95%CI [1.06 – 1.67])
Aruna *et al*.[21]	Meta-analysis	15 (review), 2 (meta)	Children	*DEFB1*, *LTF*, *LPO*, *ALOX15*, *MBL2*, *TRAV4*, *MASP2*, *TNF-α*	No significant associations found in meta-analysis
Chisini *et al*.[12]	Meta-analysis	18	Adults and children	*MBL2*, *LTF*, *MASP2*, *DEFB1*, *FCN2*, *MUC5B*	Pooled *MBL2* SNPs associated with caries: homozygote (OR = 2.12, 95%CI [1.12 – 3.99])), heterozygote (OR = 2.22, 95%CI [1.44 – 3.44])); *MUC5B* SNPs associated in heterozygotes (OR = 1.83, 95%CI [1.08 – 3.09]))
Different polymorphism's groups investigated					
Gonzalez-Casamada *et al*.[22]	Systematic review	25	Children	Multiple genes incl. *VDR*, *AMELX*, *TUFT1*, *KLK4*, *MBL2*, *ENAM*, *DEFB1*, *TAS1R1*, *MMP13*	Risk genes: *VDR*, *AMELX*, *TUFT1*, *KLK4*, *MBL2*, *DEFB1*; protective SNPs in *MMP20*, *MMP9*, *TIMP2*, *ENAM*
Piekoszewska-Ziętek *et al*.[72]	Systematic review	30	Adults and children	*AMELX*, *AQP5*, *ESRRB*, *ENAM*, *TUFT1*, *MMPs*, *DSPP*, *BMP7*	*AMELX*, *AQP5*, and *ESRRB* had the strongest evidence with replication across studies and datasets
Chisini *et al*.[17]	Meta-analysis	13	Adults and children	*VDR*	Statistical significance was only observed when VDR results were stratified by population. East Asian population was associated with higher risk

ALOX15, arachidonate 15-lipoxygenase; *AMBN*, ameloblastin; *AMELX*, amelogenin; *AQP5*, aquaporin 5; *BMP*, bone morphogenetic protein; *BMP7*, bone morphogenetic protein 7; *CA12*, carbonic anhydrase XII; *CA6,* carbonic anhydrase VI; CI, confidence interval; *DEFB1*, defensin beta 1; *DSPP*, dentin sialophosphoprotein; *ENAM,* enamelin; *ESRRB,* estrogen related receptor beta; *FCN2,* ficolin 2; *GLUT2*, glucose transporter type 2 (SLC2A2); *KLK4*, kallikrein related peptidase 4; *LPO,* lactoperoxidase; *LTF*, lactoferrin; *MASP2*, mannan-binding lectin serine peptidase 2; *MBL2*, mannose-binding lectin 2; *MMP13*, matrix metalloproteinase 13; *MMP20,* matrix metalloproteinase 20; *MMP9*, matrix metalloproteinase 9; *MMPs,* matrix metalloproteinases; *MUC5B,* mucin 5B; OR, odds ratio; SNP, single nucleotide polymorphism; *TAS1R1*, taste receptor type 1 member 1; *TAS1R2*, taste receptor type 1 member 2; *TAS1R3,* taste receptor type 1 member 3; *TAS2R38,* taste receptor type 2 member 38; *TFIP11,* tuftelin interacting protein 11; *TIMP2*, tissue inhibitor of metalloproteinase 2; *TNF-α*, tumor necrosis factor alpha; *TRAV4,* T cell receptor alpha variable 4; *TUFT1*, tuftelin 1; *VDR*, vitamin D receptor.

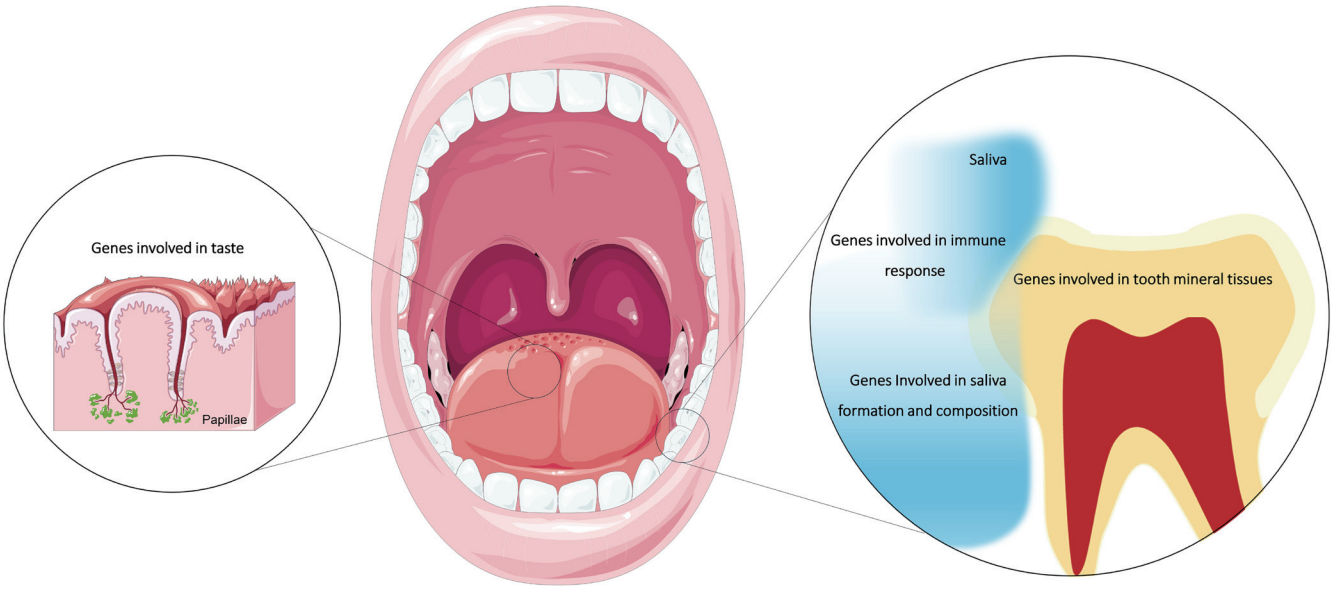

Fig. 1. Main genetic groups with potential association with dental caries according to genetic pathways. The figure illustrates the major categories of genes that may influence susceptibility to dental caries, organized by their biological functions and pathways. These groups include: (1) Enamel formation genes, which play roles in the development and mineralization of the tooth enamel and dentin; (2) Immune response genes, involved in innate and adaptive immune mechanisms that modulate the host response to cariogenic bacteria; (3) Saliva-related genes, which influence the composition, flow, and buffering capacity of saliva, impacting oral microbiota and caries risk; (4) Taste perception genes, which may affect dietary preferences and sugar intake, indirectly influencing caries development; Each group contributes to different aspects of caries pathophysiology, highlighting the multifactorial and polygenic nature of the disease.

Only a few studies have used GWAS to explore genetic factors in dental caries and identify potential new genes, revealing limited overlap among the studies' findings.[28–32] Most studies have focused on the association between genetic components and dental caries using the candidate gene approach to examine single nucleotide polymorphisms (SNPs). SNPs are variations of a single nucleotide and are among the most frequent types of DNA sequence variation. They affect only one nitrogenous base and are considered a major source of variation in the human genome.[33,34]

Therefore, understanding the genes and pathways that influence susceptibility to dental caries can provide better insights into the underlying complex mechanisms. This review aimed to comprehensively report the most up-to-date evidence on the link between genetic single nucleotide polymorphisms and dental caries, exploring the main results of genes and pathways that may affect dental caries and discussing the main methodological aspects that can contribute to developing new studies.

A comprehensive search was conducted across three databases (PubMed/Medline, Scopus, and Scielo) through February 2025. The search strategy combined MeSH terms and free-text keywords: ((Dental Decay) OR (Dental White Spot) OR (Susceptibility, Dental Caries) OR (Dental Caries Resistance)) AND ((Genetic Polymorphisms) OR (Genetic Polymorphism) OR (Polymorphism) OR (Polymorphisms) OR (Single Nucleotide Polymorphisms) OR (SNPs) OR (GWAS) OR (Genome Wide Association Studies)). The outcome was dental caries, measured via Decayed, Missing, and Filled Teeth (DMF-T) or the International Caries Detection and Assessment System (ICDAS). Observational studies (cross-sectional, cohort, and case-control) and reviews assessing SNPs and caries experience were included. No restrictions on age, language, or publication date were imposed. We excluded case reports, conference abstracts, letters, and qualitative studies. Data extraction focused on gene function, SNP associations, and methodological rigor.

Human genetic studies of dental caries

Most genetic studies focusing on the caries phenotype aimed to detect associations of genetic variants (mainly SNPs), based on previous hypotheses developed from the known etiopathogenesis of the disease.[9] These studies exhibited a pattern of selection and suggested that they could be grouped according to the mechanisms and characteristics of the genetic pathways in which they are involved (Fig. 1).

Genes involved in tooth mineral tissues

Most candidate gene studies investigated polymorphisms linked to genes involved in the development of tooth mineral tissues.[9,35] These genes are related to the processes of mineralization and formation of dental enamel, dentin, or cementum. They are frequently studied due to their known biological plausibility: genetic variants may alter the chemical properties of the tooth surface, making the mineral tissues more susceptible to demineralization by bacterial acids from biofilm.[35,36] A recent evolutionary study suggested that mammals' dietary habits may be influenced by genetic factors related to tooth development.[37] The protein encoded by *ENAM* is involved in the mineralization and organization of tooth enamel, and gene variations may result in changes in enamel mineralization.[38] Similarly, matrix metalloproteinase (*MMP*) genes are crucial in the formation of dentin and enamel[39]; specifically, the *MMP2* gene encodes gelatinase A (type IV collagenase). MMP2, expressed by ameloblasts and odontoblasts,[40] is overexpressed in decayed dentin compared to healthy dentin.[41] This protein may play a significant role in the progression of dental caries due to its ability to cleave

amelogenin, a key structural protein in the enamel matrix.[40] Thus, SNPs with functional impacts on MMP2 could alter its ability to cleave amelogenin, potentially influencing tooth demineralization.

Although GWAS have not consistently identified the same variants observed in candidate gene studies, several loci related to the formation of dental mineralized tissues have been associated with increased susceptibility to dental caries. In primary dentition, a GWAS identified an association with the *AJAP1* locus, which interacts with basigin, a modulator of MMP activity during odontogenesis.[30] For permanent teeth, loci in *DLX3* and *DLX4*—genes involved in tooth mineralization—were also associated in another GWAS.[10] Thus, these genes showed a potential association with dental caries through tooth mineralization. Additionally, *ADAMTS3* and *ISL1*, which may play roles in tooth development, were associated with caries susceptibility.[42]

In candidate gene studies, SNPs linked to mineral tissue genes were associated with different patterns of dental caries experience.[43] A systematic review and meta-analysis including 25 candidate gene studies identified several SNPs linked to the development of dental mineral tissues and the caries phenotype.[14] High heterogeneity was found among studies, although no publication bias was detected. Despite limited overlap of results among the included studies, the main association identified in the meta-analysis was with SNP rs134136 (*TFIP11)*. The T allele of rs134136 (*TFIP11*) was associated with a 51% higher risk in the high caries experience group, with no associations observed regarding the genotypes. Moreover, pooled SNPs from *AMBN* were associated with the low caries experience group, and pooled analysis of SNPs in *AMELX* showed an association with the high caries experience group.

Another systematic review assessing genetic and protein interactions included 51 studies and 27 genes and found that at least 23 of these genes interacted with others and influenced dental caries.[35] Although results showed limited overlap in different populations, some genes (*TUFT1*, *VDR*, *TFIP11*, *VDR,* and *TFIP11)* were consistently identified and shown to be connected in interaction networks involving at least 10 other genes.[35] This study highlighted two interaction networks among proteins encoded by these genes (Network 1: *MMP20*, *AMBN*, *ENAM*, *DSPP*, *TUFT1*, *TFIP11*, *AMELX*, *KLK4*; and Network 2: *MMP13*, *MMP3*, *MMP2*). These networks were found to influence dental caries. Therefore, the importance of considering dental caries as a polygenic trait in future studies becomes evident.[28]

The first longitudinal study evaluating the effect of tooth mineral tissue genes on dental caries was recently published. It assessed gene-gene interactions (*i.e.*, epistatic interaction).[44] Although no overlap with results from the previous meta-analysis was found in the initial analysis,[14] a highly significant overlap was identified during the epistatic analysis. Specifically, three-locus interaction models involving rs4970957 (*TUFT1*), rs243847 (*MMP2*), and rs5997096 (*TFIP11*), and a two-locus model involving rs243847 (*MMP2*) and rs388286 (*BMP7*), were associated with caries trajectory over the life course in a Brazilian population. These epistatic interactions appear to be an important mechanism to explain the genetic influence on dental caries—one that may not be detected through simple association analyses. Typically, the simple association between a polymorphism and a disease is insufficient to explain a complex genetic structure with multiple interaction pathways, especially in multifactorial phenotypes such as dental caries.[28] These findings underscore the importance of conducting robust analyses that consider gene-environment and epistatic interactions. Such approaches are essential to fully understand the polygenic nature underlying dental caries.

Genes involved in taste

The sense of taste allows a quick assessment of the nutritional value and potential presence of harmful substances.[45] The taste receptor gene played a key evolutionary role in deterring individuals from consuming toxic substances and enabling vertebrates to adapt to distinct environments and diets.[46,47] Among the five basic taste qualities (salty, sour, bitter, umami, and sweet), sweetness is generally associated with the presence of highly energetic food. Sweet taste perception is mediated by G-protein-coupled receptors in mammals, primarily expressed in the epithelial cells of the tongue and palate.[47] This family of receptors includes taste receptor type 1, member 1, member 2, and member 3, with the *TAS1R3* and *TAS1R2* genes encoding the taste receptor type 1, member 3 and taste receptor type 1, member 2 proteins, respectively.[48] Thus, SNPs in taste-related genes can modify taste sensitivity and lead to different dietary preferences,[45] resulting in higher sweet food consumption among certain individuals.[49] As a consequence, these individuals may face an increased risk of various diseases,[50] including dental caries.[49,50] Indeed, the pathway linked to taste perception genes is one of the most promising for explaining dental caries experience, since it has shown considerable associations in both candidate gene studies and GWAS results.[10,13,51]

A systematic review and meta-analysis identified twelve SNPs in four groups of genes (*TAS1R2, TAS2R38, TAS1R3,* and *GLUT2*) related to caries experience in candidate gene studies.[13] Although results varied by population ethnicity for some SNPs, two studies included in the meta-analysis showed that the CG genotype of the SNP rs713598 (*TAS2R38*) was associated with a reduction in caries experience.[13] The *TAS2R38* gene is located in a cluster in the taste receptor region (locus 12p13) and is responsible for sensitivity to bitter taste. Specifically, the SNP rs713598 results in a change from the amino acid alanine to proline at position 49. A recent GWAS involving five cohorts of children identified significant associations between early childhood caries and several genes, with a particular focus on the *TAS2R* gene family.[51] *TAS2R38, TAS2R3, TAS2R4,* and *TASR25* were also associated in an additional GWAS study,[10] highlighting strong concordance in results between different genetic study designs. The *TAS1R3* gene is a strong candidate because it encodes one of the three main taste receptor proteins: taste receptor type 1, member 3.[52] It is well established that human taste perception of sweets is mediated by the *TAS1R2* and *TAS1R3* genes.[52] The *TAS1R3* SNP (rs307355) has been extensively investigated, and studies consistently show its role in regulating the TAS1R3 protein.[53] Changes in this SNP have been shown to alter sweet taste perception.[53,54] One study found a strong association between the CT genotype at this SNP and increased experience of dental caries.[55] More recently, this finding was replicated in a longitudinal study that considered the trajectory of dental caries across the life course.[56] After applying robust statistical controls and corrections for multiple testing, the associations remained consistent at all follow-up points (ages 15, 24, and 31), with a dose-dependent effect related to the number of risk alleles, reinforcing the strength of the evidence. Furthermore, a significant epistatic interaction between rs307355 (*TAS1R3*) and rs35874116 (*TAS1R2*) was observed, affecting dental caries experience.[56] This interaction highlights the complex genetic architecture of dental caries and supports the hypothesis of epistasis underlying earlier findings related to *TAS1R2*.

Genes involved in saliva formation and composition

Considering that saliva plays an important role in the etiopathogenesis of dental caries, genetic epidemiology studies have inves-

tigated genes and polymorphisms that could impact salivary flow or composition. Saliva contains constituents that inhibit cariogenic bacteria in biofilms and includes calcium and phosphate ions, which are fundamental in remineralization processes.[57] Salivary flow also helps dilute microorganisms and ingested carbohydrates, preventing their accumulation on dental surfaces and consequently reducing caries risk.[57]

Carbonic anhydrase (*CA*) 12 was associated with dental caries in two GWAS studies.[10,31] Moreover, some SNPs linked to the *CA6* gene were associated with reduced salivary buffering capacity in Brazilian children and influenced the composition of the biofilm microbiota on the teeth of Swedish adolescents.[58,59] This can be explained by the role of CA6 in neutralizing bacterial acids such as lactic acid by converting salivary's $HCO3^-$ into water and carbon dioxide, thereby maintaining pH balance through buffering.[60] This mechanism accounts for the increased colonization of *Streptococcus mutans* in individuals with *CA6* SNPs, which in turn influences caries risk in Swedish adolescents.[59]

The Mucin 5B (*MUC5B*) gene encodes a protein responsible for mucus secretions in saliva, which reduces the adhesion of *Streptococcus mutans* and inhibits biofilm formation.[61] A decrease in MUC5B in the dental pellicle can make teeth more susceptible to *Streptococcus mutans* attachment, increasing the risk of dental demineralization.[61] In this context, SNPs in *MUC5B* were associated with higher biofilm presence and increased dental caries in a sample of Brazilian children.[62]

Aquaporins (AQPs) are a family of small integral membrane proteins that appear to play a role in saliva production through the genes encoding *AQP2*, *AQP5,* and *AQP6,* which are clustered in the 12q13 region.[63] Two polymorphic variants (rs10875989 [*AQP2*] and rs3759129 [*AQP5*]) were associated with dental caries in candidate gene studies.[64] These proteins are crucial for the secretion and composition of saliva and contribute to the physiological protection of the teeth and oral cavity. AQP5 facilitates water transport and is essential for producing tears, pulmonary secretions, and saliva. It is located in the apical membranes of serous acinar cells in both the salivary and lacrimal glands. It is hypothesized that SNPs in AQP genes may affect natural salivary composition or flow, disrupting homeostasis.[9] Mouse models with targeted deletion of the *AQP5* gene showed reduced saliva flow and increased dental caries,[65] supporting *AQP5*'s involvement in caries pathogenesis and its interaction with fluoride in humans.[64]

A recent systematic review and meta-analysis included 16 studies totaling 6,207 individuals and assessed 44 candidate genes, covering four genes related to saliva (*CA6, AQP2, AQP5,* and *MUC5B*).[11] Although most SNP associations were lost in the meta-analysis, the TT genotype of rs17032907 (*CA6*) showed an odds ratio 3.23 times higher in individuals with dental caries. When SNPs in *AQP5* were pooled, a 25% reduction in caries likelihood was observed. Similarly, pooling all SNPs related to salivary composition and flow showed that the effect allele was associated with a 75% increase in caries experience in homozygous individuals.[11] Importantly, none of the SNPs assessed in this meta-analysis overlapped with variants identified in GWAS studies available in the literature.[30–32,42,66–71] This discrepancy between candidate gene studies and GWAS findings can be explained by several methodological and conceptual differences. First, phenotyping inconsistencies across studies, such as variability in caries definitions, diagnostic criteria, population ethnic backgrounds, or inclusion of primary versus permanent dentition, can lead to divergent genetic associations. Second, GWAS apply stringent genome-wide significance thresholds to minimize false positives, often requiring very large sample sizes to detect modest effect sizes. In contrast, candidate gene studies typically examine fewer loci with less rigorous statistical correction, increasing the risk of false positives. Many candidate gene studies are underpowered, limiting their ability to detect true associations, especially if effect sizes are small. These factors, combined with the complex and multifactorial nature of dental caries, help explain the limited overlap between findings and highlight the need for harmonized phenotyping and larger, collaborative studies to clarify the genetic architecture of this condition.

Furthermore, GWAS can detect variants beyond the traditional scope of candidate gene approaches, often identifying intergenic regions or genes involved in less obvious biological pathways. This broader discovery potential reflects the hypothesis-free nature of GWAS, allowing identification of previously unanticipated mechanisms contributing to caries susceptibility, as summarized in Table 2.[10,28-32,42,51,68]

Genes involved in immune response

Some proteins present in saliva are related to individual immune responses because they possess antimicrobial, antiviral, antifungal, and anti-inflammatory properties.[9,72] Lactoferrin (*LTF*), defensin beta 1, and mannose-binding lectin 2 (*MBL2*) are genes encoding proteins that have been linked to the immune function.[9] Studies suggest that these proteins act as host defense factors, influencing the nonspecific immune system as well as adaptive immunity.[9,72] Consequently, they may affect bacterial colonization on tooth surfaces and thus influence caries experience.[72]

A systematic review including 6,947 individuals from diverse ethnic backgrounds identified 22 SNPs linked to six different immune response genes (*MBL2, LTF, MASP2,* defensin beta 1, *FCN2*, and *MUC5B*), assessing the influence of host immune response-related polymorphisms.[12] Eighty-two percent of these SNPs were related to the possible functional impact on protein coding. Although there was limited overlap of results across studies, SNPs in *MBL2* were consistently associated with higher caries experience in both homozygote and heterozygote analyses.

MBL2 encodes a soluble mannose-binding protein present in serum. This protein is part of the innate immune system, recognizing mannose and N-acetylglucosamine on the surfaces of various microorganisms and activating the complement cascade via an antibody-independent pathway.[73] Therefore, it was proposed that *MBL2* variants could influence microbial colonization and, consequently, dental caries susceptibility.[74] Specifically, the CG and GG genotypes of SNP rs11003125 in *MBL2* were associated with increased odds of dental caries.[74] Similarly, the *LTF* gene, located at 3p21.31, encodes lactoferrin, a protein mainly expressed in the salivary glands.[75] Lactoferrin is present in neutrophil granules and has strong antimicrobial activity, making it an important component of the nonspecific immune system.[75,76] Evidence suggests that LTF plays a crucial role in host defense against a broad spectrum of microorganisms,[76] which could explain its association with caries experience observed in some studies.[77,78]

GWAS and candidate gene evidence

GWAS have identified novel loci associated with dental caries that were not previously explored in candidate gene studies, while also reinforcing some previously hypothesized pathways. For instance, GWAS implicated genes such as *AJAP1*, which modulates MMP activity during tooth development,[30] that had not been investigated in candidate gene studies. Conversely, genes like *DLX3/DLX4* (linked to tooth mineralization),[10] *CA12* (linked to salivary buffering

Table 2. Main findings for genome-wide association studies

Author	Main findings
Alotaibi *et al*.[10]	For deciduous caries, suggestive loci were identified in *TAS2R38*, *TAS2R3*, *TAS2R4*, and *TASR25*, all involved in taste perception. For permanent dentition, loci were found in *DLX3* and *DLX4*, which play roles in tooth mineralization. Additional genes such as *SPTSSA*, *ID4*, *MIR3660*, *MIR4643*, *CA9*, *TLN1*, and *CNTNAP2* were associated with gene regulation, sphingolipid metabolism, pH balance, cell migration, and neural function. *APTAX*, *NFX1*, *REL*, and *PAPOLG* may influence caries risk through immune and tissue repair mechanisms
Fries *et al*.[28]	Identified associations with *CA12*, a gene related to salivary flow, and with *PITX1-AS1*, *FUT2*, *ADCY9*, *C10ORF11*, *BAHCC1*, *HIST1H2BE*, *FAM118A*, and *CHRNA3*
Laajala *et al*.[29]	Reported loci in *RN7SKP246*, *NAMPTP2*, *CTTNA2*, *LRRTM1*, *PHYKPL*, *RMND5B*, *DET1*, *ISG20*, and *MFGE8*, though none are currently linked to known cariogenic pathways
Shaffer *et al*.[30]	Significant association with *AJAP1* (rs3896439, $p = 2 \times 10^{-8}$), which interacts with basigin, a modulator of MMP activity during odontogenesis. Additional findings include *ABCG2* (a stem cell marker in odontogenic tissues) and *LYZL2* (a host defense-related bacteriolytic factor). Suggestive loci were also identified in *PKD2*, *EDNRA*, *TGFBR1*, *NKX2-3*, *IFT88*, *TWSG1*, *IL17D*, *SMAD7*, and members of the SCPP gene family
Shungin *et al*.[31]	*Identified associations with CA12, a gene related to salivary flow;* Identified also loci include *KRTCAP2*, *WNT10A*, *C5orf66*, *FGF10*, *HLA*, *PBX3*, *FOXL1*, *MC4R*, and *MAMSTR*; no direct connection to cariogenic pathways was established
Wang *et al*.[42]	Reported associations with *RPS6KA2* and *PTK2B* (involved in MAPK signaling), and *RHOU* and *FZD1* (linked to Wnt signaling), both pathways previously implicated in caries. *ADAMTS3* and *ISL1* are involved in odontogenesis, while *TLR2* participates in immune responses against oral pathogens
Zeng *et al*.[32]	Suggestive associations were found with *BCOR* and *BCORL1*; mutations in *BCOR* are known to cause oculofaciocardiodental syndrome, a disorder characterized by dental anomalies. Additional loci include *INHBA*, *CXCR1*, and *CXCR2*, all potentially involved in cariogenesis
Haworth *et al*.[68]	*ALLC* was identified, though its role in caries or related pathways remains unclear.
Orlova *et al*.[51]	The study identified genes linked with early childhood caries: *CDH17*, *TAS2R43*, *SMIM10L1*, *TAS2R14*. *TAS2R43* and *TAS2R14* are linked to taste perception

ABCG2, ATP binding cassette subfamily G member 2; ADAMTS3, ADAM metallopeptidase with thrombospondin type 1 motif 3; ADCY9, adenylate cyclase 9; AJAP1, adherens junctions associated protein 1; ALLC, allantoicase; APTAX, aprataxin pseudogene; BAHCC1, BAH domain and coiled-coil containing 1; BCOR, BCL6 corepressor; BCORL1, BCL6 corepressor like 1; C10ORF11, chromosome 10 open reading frame 11; C5orf66, chromosome 5 open reading frame 66; CA9, carbonic anhydrase IX; CDH17, cadherin 17; CHRNA3, cholinergic receptor nicotinic alpha 3 subunit; CNTNAP2, contactin associated protein-like 2; CTNNA2, catenin alpha 2; CXCR1, C-X-C motif chemokine receptor 1; CXCR2, C-X-C motif chemokine receptor 2; DET1, De-Etiolated Homolog 1; DLX3, distal-less homeobox 3; DLX4, distal-less homeobox 4; EDNRA, endothelin receptor type A; FAM118A, family with sequence similarity 118 member A; FGF10, fibroblast growth factor 10; FOXL1, forkhead box L1; FUT2, fucosyltransferase 2; FZD1, frizzled class receptor 1; HIST1H2BE, histone cluster 1 H2B family member E; HLA, human leukocyte antigen; ID4, inhibitor of DNA binding 4; IFT88, intraflagellar transport 88; IL17D, interleukin 17D; INHBA, inhibin subunit beta A; ISG20, interferon stimulated exonuclease gene 20kDa; ISL1, ISL LIM homeobox 1; KRTCAP2, keratinocyte associated protein 2; LRRTM1, leucine rich repeat transmembrane neuronal 1; LYZL2, lysozyme like 2; MAMSTR, MEF2 activating motif and SAP domain containing transcriptional regulator; MC4R, melanocortin 4 receptor; MFGE8, milk fat globule-EGF factor 8 protein; MIR3660, microRNA 3660; MIR4643, microRNA 4643; NAMPTP2, nicotinamide phosphoribosyltransferase pseudogene 2; NFX1, nuclear transcription factor, X-box binding 1; NKX2-3, NK2 Homeobox 3; PAPOLG, poly(A) polymerase gamma; PBX3, Pre-B-cell leukemia homeobox 3; PHYKPL, 5-phosphohydroxy-l-lysine phospho-lyase-like; PITX1-AS1, PITX1 antisense RNA 1; PKD2, polycystin 2, transient receptor potential cation channel; PTK2B, protein tyrosine kinase 2 beta; REL, Rel proto-oncogene, NF-kB subunit; RHOU, Ras homolog family member U; RMND5B, required for meiotic nuclear division 5 homolog B; RN7SKP246, RN7SK pseudogene 246; RPS6KA2, ribosomal protein S6 kinase A2; SCPP, secretory calcium-binding phosphoprotein family; SMAD7, SMAD family member 7; SMIM10L1, small integral membrane protein 10 like 1; SPTSSA, small proteolipid transmembrane alpha subunit; TAS2R14, taste receptor type 2 member 14; TAS2R3, taste receptor type 2 member 3; TAS2R38, taste receptor type 2 member 38; TAS2R4, taste receptor type 2 member 4; TAS2R43, taste receptor type 2 member 43; TASR25, taste receptor type 2 member 25; TGFB1, transforming growth factor beta receptor 1; TLN1, talin 1; TLR2, Toll-like receptor 2; TWSG1, twisted gastrulation bmp signaling modulator 1; WNT10A, Wnt family member 10A.

capacity),[28] and taste-related genes (*TAS2R38*, *TAS2R3*, *TAS2R43, TAS2R14*) were confirmed by GWAS and align with established biological categories.[10,51] Moreover, GWAS revealed loci in less obvious pathways, such as *BCOR*,[31] known to cause oculofaciocardiodental syndrome, a disorder characterized by dental anomalies. These findings suggest broader biological mechanisms beyond traditional candidate pathways and confirm the roles of taste-related and tooth mineralization genes identified in candidate studies.

The limited overlap between GWAS and candidate gene results arises from methodological and conceptual differences, some of which also explain inconsistencies within candidate gene studies themselves. Candidate gene studies, often underpowered and focused on biologically plausible genes based on prior hypotheses, typically lacked rigorous correction for multiple testing, increasing the likelihood of false positives. In contrast, GWAS use a hypothesis-free approach that detects variants with modest effects across the genome, including those in intergenic regions or non-canonical pathways. Phenotypic heterogeneity—such as varying caries definitions (Decayed, Missing, and Filled Teeth index [DMFT] vs. ICDAS), age groups, or dentition types—further complicates replication. Additionally, population stratification and ancestral diversity contribute to discrepancies, as allele frequencies and linkage disequilibrium patterns differ among ethnic groups.

Methodological issues in genetic studies on dental caries

Genetic epidemiology studies have shown evidence that genetic components are involved in the etiopathogenesis of dental caries,

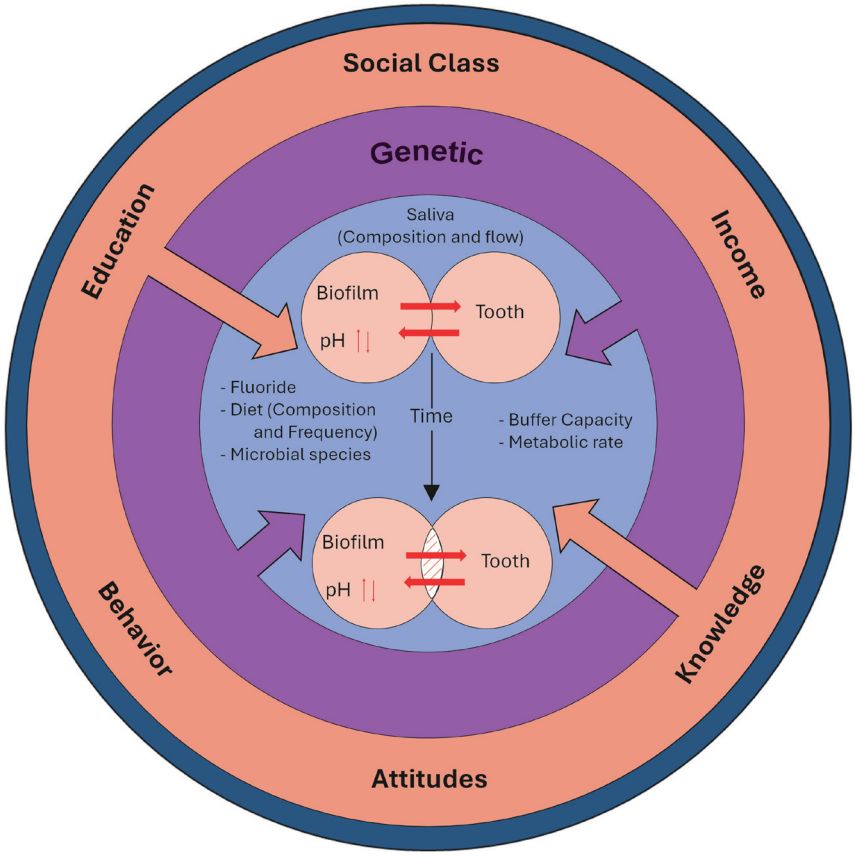

Fig. 2. Theoretical model of dental caries including genetic factors. The figure illustrates a multifactorial framework that integrates genetic, biological, behavioral, and environmental components involved in the development of dental caries. Genetic factors are positioned as upstream contributors that influence host susceptibility through multiple pathways—such as enamel formation, immune response, saliva composition, and taste perception—which, in turn, affect the individual's interaction with cariogenic bacteria and dietary habits. The model emphasizes that dental caries is not solely a result of external factors (e.g., sugar intake, oral hygiene, education level, or income), but also a consequence of complex gene–environment interactions that shape individual risk profiles.

although the actual pathways are not yet fully understood. Therefore, incorporating genetic aspects into theoretical models to explain dental caries may be proposed (Fig. 2). Thus, in addition to contextual factors, SNPs appear to influence individual susceptibility to dental caries.

The observed inconsistencies in the literature can be attributed to various factors, such as differing categorizations of dental caries and the diverse age groups of the populations studied.[9] Additional factors include diverse ethnic backgrounds, limited statistical power, linkage disequilibrium, and potential epistatic interactions, all of which can affect results. An important source of bias in genetic association studies is the ancestry of the population. Population stratification can confound genetic association results and cannot be ignored, as it may lead to failure to detect true associations or to false positives. Indeed, only a few studies have accounted for population stratification or controlled for genetic ancestry.[9] Some studies controlled for population based on individuals' self-reported race; however, caution is warranted when using race as a proxy for ancestry because it may poorly correlate with genetic ancestry in some populations. Therefore, approaches that use a wide range of SNPs to characterize population ethnicity, considering resources such as the HapMap and Human Genome Diversity projects, represent a recent and promising strategy to address this issue.

Genetic association studies are more complex than genetic analyses based solely on recombination events during meiosis.[28] These complexities can introduce biases in associations between alleles/genotypes and phenotypes such as dental caries. SNPs deviating from Hardy-Weinberg equilibrium (HWE) can lead to false-positive associations, particularly if homozygotes are less frequent than expected. Significant deviations from HWE in a relatively homogeneous population may indicate genotyping errors or participant selection bias.[79] Therefore, it is crucial to ensure that target SNPs conform to HWE before performing association analyses.

When investigating the associations between different loci and a specific trait, especially when loci are closely located on the same chromosome, potential linkage disequilibrium must be considered.[79] Linkage disequilibrium refers to the nonrandom association of alleles at different loci.[79] This linkage disequilibrium among SNPs has led some researchers to exclude SNPs in linkage disequilibrium from epistatic analyses. However, investigations into linkage disequilibrium are inconsistent in the literature, with some studies presenting these analyses and others not reporting them.[80–84] Failure to assess linkage disequilibrium can introduce significant bias in study results.[79]

Bonferroni multiple test corrections must be applied to avoid type I errors (false positive associations). Type I errors occur when

a study incorrectly concludes that there is an association when none exists, often due to multiple comparisons inherent in genetic studies. The primary source of false positives is failure to control for multiple comparisons, such as through Bonferroni corrections in logistic regression analyses.[81] Bonferroni corrections remain the standard approach for avoiding false positives, where the significance level is adjusted by dividing α by the number of tests.[85] A recent systematic review found that few candidate gene studies investigating dental caries applied corrections for multiple comparisons.[14] These methodological shortcomings may contribute to the inconsistent results observed in the literature.

Therefore, future studies should address these issues, and past findings should be interpreted with these limitations in mind. For population stratification, reliance on self-reported race or ethnicity is insufficient, especially in admixed populations. Researchers should incorporate genomic control methods such as principal component analysis or mixed models using ancestry-informative markers, which robustly account for population structure. When interpreting prior studies lacking such controls, results should be viewed with caution, particularly in ethnically heterogeneous populations. Regarding HWE, deviations should not be treated as simple statistical anomalies but rather examined as potential indicators of genotyping errors, selection bias, or population substructure. Reports should explicitly describe how HWE was tested, the thresholds used, and whether any SNPs were excluded. In the context of linkage disequilibrium, detailed mapping of linkage disequilibrium blocks and transparent reporting of r^2 values or D' measures are essential, particularly when interpreting associations derived from candidate gene studies where nearby variants may confound results. For epistasis analyses, the traditional single-locus framework is inadequate to capture complex genetic architectures. Thus, robust approaches such as interaction models, polygenic risk scores, or network-based analyses should be employed. Findings from studies using only additive models or uncorrected bivariate interactions should be considered preliminary. Finally, concerning multiple testing, failure to apply corrections like Bonferroni or false discovery rate adjustments undermines the credibility of positive findings. Future studies must explicitly report the total number of comparisons and the adjusted significance thresholds used. Meta-research suggests that many inconsistencies in the literature could be resolved or better contextualized if such practices were adopted consistently. Therefore, when reviewing past literature, readers should weigh the strength of associations not only by p-values but also by methodological rigor, especially regarding statistical correction and population genetic validity.

Limitations

This review provides a narrative synthesis of the genetic epidemiology of dental caries; however, as a literature review rather than a systematic review, it has inherent limitations. The absence of a predefined protocol or explicit inclusion/exclusion criteria for study selection may introduce selection bias, as the synthesis relies on the authors' interpretation of relevant studies. Methodological heterogeneity across included studies—such as variations in caries definitions (e.g., DMFT vs. ICDAS), genetic analysis approaches (candidate gene studies vs. GWAS), and population demographics—limits direct comparability of findings. While efforts were made to include diverse perspectives, the narrative format may prioritize certain studies or pathways over others, potentially overlooking nuanced insights. These limitations highlight the need for future systematic reviews with meta-analyses to quantitatively integrate evidence and clarify the polygenic architecture of dental caries.

Conclusions

Dental caries is a complex, multifactorial disease mainly related to poor oral hygiene habits, high consumption of fermentable carbohydrates, and unfavorable socioeconomic status. Genetic epidemiology studies have demonstrated that dental caries also has a genetic component, which can explain significant differences in individual risk. Although replication studies in diverse populations are still necessary, numerous SNPs and genes have been studied across various populations, showing associations with dental caries. Future studies should consider diverse ethnic backgrounds in analyses, increase statistical power, evaluate linkage disequilibrium, and explore potential epistatic interactions among SNPs. To strengthen the field, it is essential to promote larger, multiethnic studies and meta-analytic collaborations to advance scientific knowledge and facilitate translational impact. Ultimately, genetic studies may lead to the development of gene expression panels capable of identifying individuals at high risk for dental caries, paving the way for more personalized prevention strategies.

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Conflict of interest

The authors declare no conflicts of interest.

Author contributions

Research conception and design (LAC, MBC), data analysis (LAC, LCS), writing of the manuscript (LAC, LCS, RVC, FSC, FFD). All authors critically reviewed and approved the final manuscript.

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