Australian Dental Journal
The official journal of the Australian Dental Association
AUSTRALIAN DENTAL ASSOCIATION INC.
Australian Dental Journal 2015; 60: 2–11
doi: 10.1111/adj.12262

Genetic factors affecting dental caries risk

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ABSTRACT

This article reviews the literature on genetic aspects of dental caries and provides a framework for the rapidly changing disease model of caries. The scope is genetic aspects of various dental factors affecting dental caries. The PubMed database was searched for articles with keywords 'caries', 'genetics', 'taste', 'diet' and 'twins'. This was followed by extensive handsearching using reference lists from relevant articles. The post-genomic era will present many opportunities for improvement in oral health care but will also present a multitude of challenges. We can conclude from the literature that genes have a role to play in dental caries; however, both environmental and genetic factors have been implicated in the aetiology of caries. Additional studies will have to be conducted to replicate the findings in a different population. Identification of genetic risk factors will help screen and identify susceptible patients to better understand the contribution of genes in caries aetiopathogenesis. Information derived from these diverse studies will provide new tools to target individuals and/or populations for a more efficient and effective implementation of newer preventive measures and diagnostic and novel therapeutic approaches in the management of this disease.

Keywords: Cariology, genetics, heredity, immunity, saliva, twin.

Abbreviations and acronyms: AMBN = ameloblastin; CSA = complex segregation analysis; DMF = decayed, missing, filled teeth; DMFS = decayed, missing, filled tooth surface; HLA = human leukocyte antigen; GWAS = genome-wide association studies; LTF = lactotransferrin; MBL = mannose-binding lectin; MHC = major histocompatibility complex; SNPS = single nucleotide polymorphisms.

(Accepted for publication 25 August 2014.)

INTRODUCTION

Dental caries is a complex, chronic, multifactorial disease and one of the most prevalent diseases in industrialized and developing countries.[1] Caries appears to concentrate in specific groups of individuals. The phenomenon is termed as polarization and its cause remains obscure, representing one of the epidemiological disease aspects in which a portion of the population is in most need of treatment.[2] The Vipeholm study provided evidence of an individual's resistance to caries despite being on a highly cariogenic diet.[3] This suggests that susceptibility or resistance to caries could be a result of one or more genotypic, phenotypic and environmental influences. Heredity has been linked with dental caries incidence in scientific literature for many years. In 1899, GV Black[4] wrote that when the family remains in one locality, with the children living under conditions similar to those of their parents in their childhood, the susceptibility of caries will be very similar in the majority of cases. This will hold true even for particular teeth and localities first affected, the order of occurrence of cavities and the particular age at which they occur.

The purpose of this article is to review the literature on the genetic aspects of dental caries and provide a framework for the rapidly changing disease model of caries. We begin by establishing the role of genetics from the twin model of analysis, followed by linkage/association studies and conclude by analysing the various factors directly influencing the host, i.e. the tooth in question (Table 1).

Twin studies

Even with advances in human genetics and molecular biology, twin studies still have a role to play in shedding light on the influence of genes in development. The role of twins in the analysis of human behavioural and physical development was first described by

Table 1. Studies supporting genetic association with caries

Study	Study population	Type of study	Factor	Finding	Increased suseptibility	Increased resistance	Ethnicity
Patir *et al.*[28]	91 caries 82 caries-free Age: 3–6	Case control	Tooth genes: AMELX, AMBN, TUFT1, ENAM, TFIP11	T allele of tuftelin rs3790506 and C allele of amelogenin rs17878486	Y	–	Turkish
Shimuzu *et al.*[38]	1831 Age: 1–82 years	Case control	Tooth genes: AMELX, AMBN, TUFT1, ENAM, TFIP11	T allele of AMELX rs946252 and C allele of AMBN rs4694075 Tuftelin interacting protein11	Y	– Y	Brazilian, Turkish, Argentinian, Filipino
Kang *et al.*[39]	120 patients (86 male and 34 female) Age: 22.7 ± 7.8 years	Case control	Tooth genes: AMELX	Single nucleotide polymorphisms (SNPS) in AMELX of rs5933871 and rs5934997	Y	–	Korean
Slayton *et al.*[40]	dmfs >4 (n = 92); dmfs = 0 (n = 343) Age: 3–5 years	Case control	Tooth genes: AMELX, AMBN, TUFT1, ENAM, TFIP11, KLK4	Tuftelin combined with high level of *S. mutans* Caucasians had higher dmfs compared to other populations	Y	–	Caucasian, Others
Deeley *et al.*[41]	7–14 years very low caries (n = 44) higher caries experience; n = 66	Case control	Tooth genes: AMBN, AMELX, Enamelin, TUFT1, TFIP11	Amelogenin	Y	–	Guatemalan-Mayan
Wang[46]	n = 333 Age: 4–7 years	Cross-sectional cohort	Tooth genes: DSPP KLK4 AQP5	DSPP, Aquaporin5 Minor allele G of Kalikrein4	Y	Y	Caucasian
Fushan[47]	n = 144	Case control	Taste genes: TAS1R2 TAS1R3	T alleles of TAS1R3 SNPS C alleles of TAS1R3 SNPS	Y	Y	Caucasian, African-American, and Asian
Kulkarni *et al.*[49]	n = 80 Age: 21–32 years	Case control	Taste genes	Polymorphisms in TAS1R2 and glucose transporter (GLUT2) genes	Y	–	Caucasian
Wendell[52]	n = 2449 Age: 1–42 years	Case control	Taste genes: TAS2R38 TAS1R2	Alleles of TAS2R38 (bitter taste receptor family) Alleles of TAS1R2 (sweet taste receptor family)	Y (mixed dentition)	Y (primary dentition) Y (mixed dentition)	Caucasian
Bagherian *et al.*[57]	Age: 12–71 months 44 ECC 35 caries-free	Cross-sectional	Immunity: HLA	Positive for the HLA DR 4 allele	Y	–	Not mentioned
Acton *et al.*[58]	186 women Age: 20.8 ± 3.7 years	Case control	Immunity: HLA	Presence of HLA DR3 and DR4	Y	–	African–American
McCarlie *et al.*[61]	n = 32	Case control	Immunity: HLA	HLA-DR4 positive	Y	–	Not mentioned
Valarini[63]	n = 164 Age: 15–19 years	Cross-sectional	Immunity: HLA	HLA allele DQ2 positive	–	Y	Brazilian
Ozturk *et al.*[64]	n = 296 age = 17–84 years	Cross-sectional cohort	Immunity: Defensins	Allele of beta defensin1: G20A Allele of beta defensin1: G52A	Y	Y	Caucasian, African–American
Olszowski[68]	105 girls; 74 boys 5 years (n = 71) 13 years (n = 108)	Case control	Immunity: AMELX, ENAM, MBL2, MASP2	MBL2 mutant genotype (GGC/GAC and GAC/GAC)	Y (5 years old)	Y (13 years old)	Polish

(continued)

Zakhary[75]	n = 208	Case control	Saliva: Acidic proline rich proteins Db allele	Caucasian Db gene frequency 14% African American Db gene frequency 37% Caucasian had greater *S. mutans* colonization Db- Caucasians more caries	Db–	Db+	Caucasian, African–American
Jonnason *et al.*[76]	12-year-old Swedish children with high (n = 19) or low (n = 19) caries experiences	Case referrent	Saliva: Glycoproteins	Glycoprotein 340 I polymorphism	Y	–	Swedish
Yu[77]	140 boys and 166 girls Age: 5–15 years	Case control	Saliva: Parotid proline rich protiens	Presence of proline rich proteins phenotypes Pa+ and Pr22	Y	–	Not specified
Ayad *et al.*[78]	DMFS = 0 (n = 9); mean age = 59.2 Mean DMFS = 38.4 (n = 9); Mean age = 51.2	Case control	Saliva: basic proline rich peptides	Phenotypes of basic proline rich proteins such as ps1 and con1	–	Y	Population of Rochester, NY, USA
Azevedo *et al.*[83]	110 (DMFT = 0 n = 48) (DMFT ≥1 n = 62) Age: 12 years	Case control	Saliva: Lactotransferrin	Allele A polymorphism in the second exon	–	Y	Caucasian

Galton.[5] These studies calculated the heritability (the proportion of the phenotypic variability due to genetic variance) between monozygotic and dizygotic twin pairs (Fig. 1).

Prior studies in twins and families support heredity as an important, although minor, component in the aetiology of dental caries.[6] Mansbridge[7] studied the caries incidence in 224 pairs of like-sex twins (96 monozygotic; 128 dizygotic), revealing that dental caries experience had a greater similarity between monozygotic twins than dizygotic twins, while unrelated pairs of children showed less similarity. Surprisingly, he concluded that environmental factors have greater influence, although genetic factors also contribute to the causation of dental caries. However, it was Goodman *et al.*[8] who established the role of hereditary factors influencing caries aetiology while studying 38 like-sex monozygotic and dizygotic twin pairs and reported significant heritability for oral microorganisms, including Streptococci, salivary flow rate, salivary pH and salivary amylase activity.

Similarly, Conry *et al.*[9] observed in 46 monozygotic and 22 dizygotic twin pairs reared apart significant genetic variance (45–67%) for the number of teeth as well as tooth surfaces restored.

Oral health as an entity with a genetic basis was observed by Lovelina *et al.*[10] in 30 pairs of twins (9 monozygotic; 21 dizygotic). They found that monozygotic twin pairs had higher correlation rates for dental caries, periodontal disease and malocclusion (88.9%, 77.8% and 100% respectively) than dizygotic twin pairs (9.5%, 23.8% and 9.5% respectively). Another study observed a strong genetic component behind caries experience in twins (average age = 24.6 years) differing between males (49%) and females (68%), and a weaker genetic component affecting gingival health being similar for males and females (32%), suggesting genetic influence on oral health with possible gender differences.[11] Oral microbes that colonize in human mouths contribute to disease susceptibility, but it is unclear if host genetic factors mediate colonization. Corby *et al.*[12] observed moderate to high heritability estimates for microbial species (h^2 = 56–80%) in 118 caries-free twin and 86 caries-active twins. The similarity of the overall oral microbial flora was even evident in caries-free twins. Therefore, genetic or familial factors significantly contribute to the colonization of oral beneficial species in twins, and in turn the oral health of an individual.

Bretz *et al.*[13] observed a high heritability component (h^2) for surface based caries prevalence (h^2 = 64.6), lesion severity (h^2 = 61.7) and sucrose sweetness preference (h^2 = 55.2) in 115 pairs of twins aged 4–7 years old. Similarly in another study, Bretz *et al.*[14] reported significant heritability for surface based caries prevalence (76.3%) and lesion severity

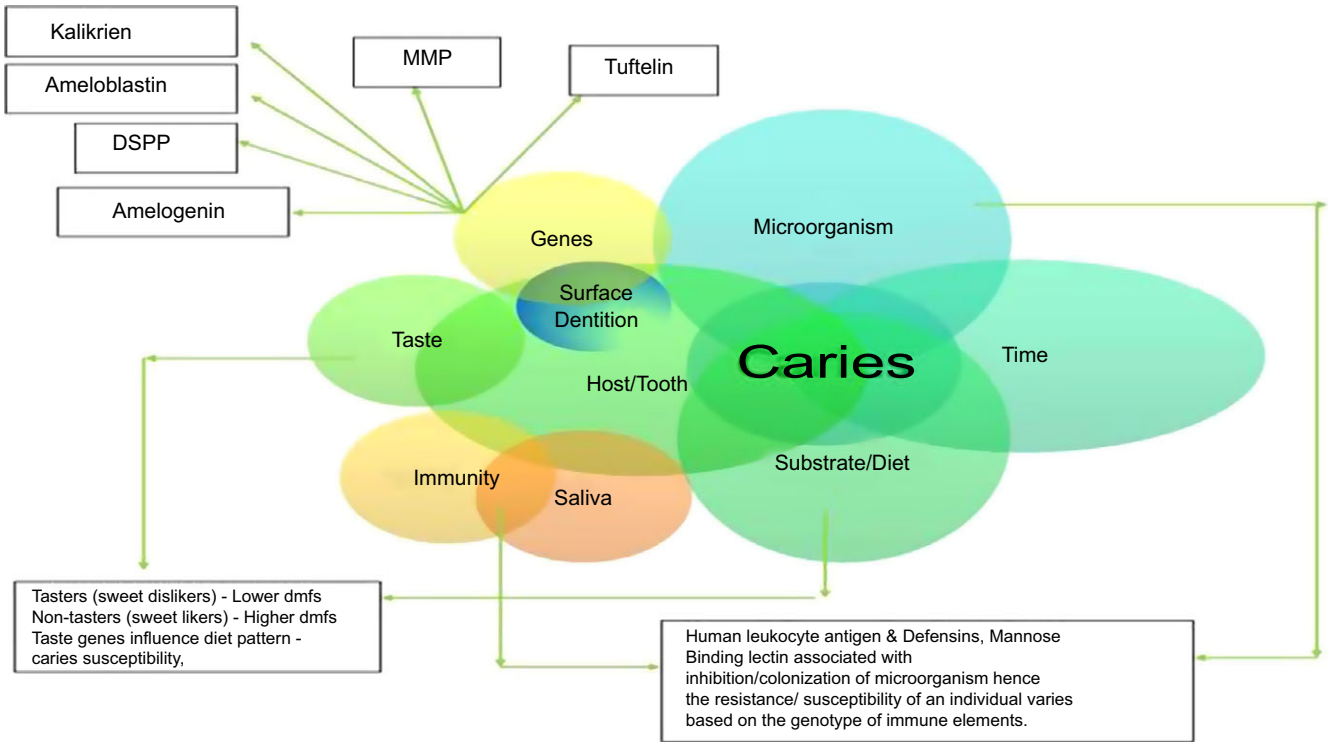

Fig. 1 Venn diagram showing interplay of genetic factors.

(70.6%) in 388 pairs of twins. Studying the emerging dentitions in 314 pairs of twins, Bretz *et al.*[15] noted a significant heritability for surface based caries prevalence of 30% in a younger age group (1.5–4 years) and 46.3% for an older age group(>6 years), whereas for an intermediate age group it was 13.3%. Even lesion severity had a high heritability (about 50%) for younger and older age groups. However, for the intermediate group it was 12.2%, indicating that genetic influence for caries incidence is at its highest when dentitions are emerging.

The higher concordance and heritability between twins in these studies demonstrates that dental caries occurrence and severity are influenced genetically by various factors. However, the influence of environmental factors cannot be dismissed and intervention strategies of fluorides and sealants will remain vital into the future. Gao[16] reported the heritability index of dental caries to be 8.7% in 280 pairs of like-sex twins (186 monozygotic, 94 dizygotic), suggesting that environmental influence is dominant in caries initiation whereas heredity is of little influence.

Linkage/association studies

One of the earliest studies was in 1946 when Klien[17] reported on 5400 people in 1150 families of Japanese ancestry, demonstrating that the decayed, missing, filled teeth (DMF) that occurred in offspring was quantitatively related to that which had been experienced by their parents. DMF was established for each individual and 30% of fathers with the lowest DMF rate were designated as low DMF; 30% with highest DMF were designated as high DMF and the rest as middle DMF. A similar grouping was done for mothers and children. It was found that a high DMF father and a high DMF mother produced offspring, both sons and daughters, with a high DMF rate. The authors concluded that dental caries is strongly familial based with probable genetic and sex-linked associations. In another study by Klien[18] of 488 siblings and 301 unrelated children, siblings of caries-free children had lower average caries scores than the siblings of susceptible children. Similarly, Book and Grahnen[19] selected the parents and siblings of subjects from the Vipeholm study who were highly resistant to dental caries and found they also had significantly lower caries experience than the parents and siblings of the remaining subjects. The authors could not detect any environmental factor that could explain the same and concluded that genetic factors play an appreciable part in determining individual resistance against dental caries; however, they did note these results were of minor consideration. The strong influence of the role of genes/heredity was observed in these historical landmark studies which laid the foundation for further research.

Vieira *et al.*[20] detected a link between low caries experience and loci 5q13.3, 14q11.2 and Xq27.1 in 46 Filipino families, which included a significant

gender difference in mean DMFT between fathers (10.96) and mothers (14.45). A protective locus for caries was identified on the X chromosome (Xq27.1) which may have implications for gender differences. High caries experience was linked to loci 13q31.1 and 14q24.3, and the presence of genes related to saliva flow control and diet preferences in these regions was also highlighted. The authors reported that 14q24.3 encodes a protein similar to the oestrogen receptor, which could also contribute to observed gender differences. Kuchler *et al.*[21] also suggested genetic factors contributing to high caries experience may exist in the gene loci 13q31.1. Shimuzu *et al.*[22] made a similar finding in a study of 471 Filipino families. They reported that T allele of rs6862039 in BTF3 was associated with high caries experience on chromosome 5q12.1–q13.3, whereas T allele of rs27565 located in intron 3 of PART1 gene, G allele of rs4700418 in ZSWIM6 gene and G allele of rs875459 in CCNB1 gene were associated with low caries experience. A genome-wide association study (GWAS) by Shaffer *et al.*[23] revealed a few loci (ACTN2, MTR and EDAR-ADD, MPPED and LPO) with a possible biological role in caries susceptibility, although not genome-wide significant.

Global measures of caries experience ignore the fact that tooth surfaces exhibit differences in susceptibility to decay and are differentially affected by risk factors. Shaffer *et al.*[24] performed GWAS in 920 participants aged 18–75 years, identifying a significant association between caries in the anterior mandibular teeth and LYZL2 gene, which codes a bacteriolytic agent involved in host defence. Another significant association between caries of the mid-dentition teeth and AJAP1, a gene involved in tooth development, was also observed in this study. By cluster analysis, Shaffer *et al.*[25] studied 1068 participants aged 18–75 years based on trait similarity among biological relatives, estimating DMFS of anterior mandibular surfaces had lowest prevalence of caries with 54% heritability while DMFS in posterior non-pit fissure surfaces (h^2 = 43%) and mid-dentition surfaces (h^2 = 40%) were significantly heritable. Another notable observation was DMFS of the maxillary incisors was not heritable, corresponding to surfaces with a fairly high prevalence of caries. The high heritability of some surfaces from this study suggests a higher genetic predilection to caries. Similarly, decay patterns as novel phenotypes in understanding the nature of dental caries was studied by Shaffer *et al.*[26] by principal component and factor analysis. They observed certain decay patterns were heritable (h^2 = 30–65%), whereas others were not, indicating both genetic and non-genetic aetiologies of decay patterns.

The goal of complex segregation analysis (CSA) is to detect and discriminate between and amongst the different factors causing familial resemblance, ultimately aiming to demonstrate a major gene effect. Wereneck *et al.*[27] observed in a sample of homogenous, isolated families in the Brazilian Amazon strong evidence of the presence of a major gene controlling decayed teeth following a dominant model with an estimated frequency of the resistance allele 'A' of 0.63.

The results of these studies further add to the evidence of a genetic component controlling the development of caries at various aspects such as gender, salivary, immunological and surface heritability. However, it is a wide perspective to know there is a genetic influence but to explore deeper we need to understand the genetic influence of factors directly influencing the tooth (host), substrate/diet (taste genes), microbial colonization (immunity, saliva) and which in turn are also interspersed.

Tooth genes

The calcium phosphate hydroxyapatite crystals forming the bulk of enamel are controlled through the interaction of a number of organic matrix molecules that include amelogenin, enamelin, ameloblastin, tuftelin and dentine sialophosphoprotein. The amelogenin (AMELX) gene resides on the p arm of the X chromosome and its locus is Xp22.31-p22.1.[28] It forms a scaffold for enamel crystallites and controls their growth.[29] The ameloblastin (AMBN) gene is located in chromosome 4;[30] a key adhesion molecule for enamel formation and plays an important role by binding and maintaining the differentiated phenotypes of secretory ameloblasts.[31] The dentine sialophosphoprotein gene encodes two principal proteins of the dentine extracellular matrix of the tooth: the preproprotein is secreted by odontoblasts and cleaved into dentine sialoprotein and dentine phosphoprotein. Dentine phosphoprotein is thought to be involved in the biomineralization process of dentine.[32] Tuftelin plays a role in the initial stages of mineralization and overexpression may lead to imperfections in both enamel prisms and crystallite structure.[33] The principal function of matrix metalloproteinase's 20 and kalikrien 4 in dental enamel formation are to facilitate the orderly replacement of the organic matrix with mineral, generating an enamel layer that is harder, less porous and unstained by retained enamel proteins.[34]

Defects in these genes are associated with many diseases. Mutation of the dentine sialophosphoprotein gene causes dentinogenesis imperfecta type II.[35,36] Rajpar *et al.*[37]observed that splicing mutation in gene encoding enamel specific protein enamelin caused autosomal dominant amelogenesis imperfecta. Kim *et al.*[32] observed in families with dentine sialophosphoprotein mutation, the softer malformed dentine

was always associated with elevated risk of diseases in the oral cavity. Thus, mutations in these genes results in the production of abnormal proteins or reduces the amount of these proteins in developing teeth, resulting in defective mineralization that could influence both bacterial adherence or resistance of enamel to acid ph, thereby increasing the susceptibility of surfaces to dental caries.

Apart from defective mineralization, genotypic variations also make the enamel more susceptible. Shimuzu *et al.*[38] suggest that variation in enamel formation genes influence the dynamic interactions between the enamel surface and oral cavity. The frequency of T allele of AMELX rs946252 and C allele of *AMBN* rs4694075 was significantly higher in a high caries experience group. They also observed *Tuftelin interacting protein11* to be associated with the enamel surface's ability to uptake fluoride in very low concentrations, thus decreasing individual susceptibility to demineralization at subclinical levels. Similar findings were observed by Kang *et al.*[39] in a study of Korean subjects who lived in fluoridated areas during childhood, the single nucleotide polymorphisms (SNPS) in AMELX of rs5933871 and rs5934997 were significantly associated with caries susceptibility. Significant association of tuftelin, amelogenin with increased susceptibility to dental caries was reported by Patir *et al.*,[28] Slayton *et al.*[40] and Deeley *et al.*[41] Tannure *et al.*[42] observed that polymorphism in MMP13 (rs2252070) demonstrated a significantly decreased risk for caries.

Differential genetic factors in the enamel surface of the primary and permanent dentition, as well as pit-and-fissure and smooth-surface, also predispose individuals for development of carious lesions. Shaffer *et al.*[43] observed heritability for pit-and-fissure and smooth-surface caries in the primary dentition was greater than the permanent dentition. It was also highlighted that common genes are involved in caries risk for both surface types. However, genetic factors exert different effects on caries risk in pit-and-fissure versus smooth-surface in the primary dentition. Substantial heritability of caries in the primary dentition (54–70%) compared to the permanent dentition (35–55%) with covariation in these traits due to common genetic factors was also reported by Wang *et al.*[44] The notion that genes differentially affect cariogenesis across the surfaces was also supported by Zeng *et al.*[45] who identified several potential caries genes, i.e. BCOR gene in pit-and-fissure and BCORL1 in smooth-surface caries. One of the few studies of candidate genes observing single nucleotide polymorphisms in three genes (dentine sialophosphoprotein, Kallikrein4 and Aquaporin5) showed consistent association with protection against caries for pit-and-fissure and smooth-surface caries in 333 Caucasian parent-child trios. However, minor allele (G) of Kallikrein4, was associated with increased caries risk for smooth-surface.[46]

These studies report the role of specific genes in increasing the susceptibility to caries, as well as differential effects both on the dentitions and surfaces attributable to genes. However, the complexity is compounded by genetic phenotypes which manifest as differential effects on the population/races/dentition/surfaces being studied. Further research is required, not only on the same populations but also to replicate and identify new genes in different races, ultimately leading to improved understanding of the nature of disease.

Taste genes

Human sweet taste perception is mediated by the heterodimeric G-protein coupled receptor complex encoded by the *TAS1R2* and *TAS1R3* genes. Bitter taste perception appears to be largely mediated by the *TAS2R38* gene.[47,48] These genes act through their influence on taste and dietary habits, resulting in sensitivity or insensitivity to cariogenic foods. Genetic association analysis revealed that two single nucleotide polymorphisms located at rs307355 and rs35744813 of the *TAS1R3* coding sequence strongly correlate with human taste sensitivity to sucrose. Individuals who carry T alleles display reduced sensitivity to sucrose compared to those who carry C alleles.[47] Similar findings were observed by Kulkarni *et al.*,[49] that polymorphisms in the sweet taste receptor (TAS1R2) and glucose transporter (GLUT2) genes individually and in combination are associated with caries risk. Pidmale *et al.*[50] observed that tasters (sweet dislikers) had lower dmfs values compared to non-tasters (sweet likers) which was statistically significant in 119 children aged 36–71 months.

Genetic sensitivity to taste is an inherited trait in children.[51] Wendell *et al.*[52] said the changing genetic constitution of taste pathways as the child grows is related to his or her food preferences as certain alleles of taste genes TAS2R38 (bitter taste receptor family) were caries protective in the primary group, whereas certain alleles of taste genes TAS1R2 (sweet taste receptor family) were associated with caries risk and protection in the mixed dentition group.

Genetic variations contribute to differences in dietary habits which in turn influence dental caries as observed by Pados *et al.*,[53] Keskitalo[54] and Krondl *et al.*[55] Eating habits as well as sucrose sweetness recognition of monozygotic pairs were more alike than that of dizygotic twin pairs. However, Rupesh *et al.*[56] found a strong genetic component among sibling pairs within the same family with more than half of siblings (61%) in the same taste category.

Thus, we can conclude taste preference is significantly modulated by host genetics and genes involved in taste preference may play a role in the development of food habits. In addition, cultural forces may significantly influence taste perception and the few studies reporting heritability of sweet preference in children have studied culturally different populations.

Immunity

One aspect of genetic effects is modification in immune response. Human leukocyte antigen (HLA) or major histocompatibility complex (MHC) molecules have important roles in the immune responsiveness which is controlled by genes on the short arm of chromosome 6. Polymorphism in MHC molecules may cause some variations in immune responses against oral colonization levels between individuals and may influence an individual's susceptibility to caries.

Bagherian *et al.*[57] revealed that being positive for the HLA DR 4 allele increases the risk for early childhood caries 10 times more compared to the caries-free group. Acton *et al.*[58] demonstrated that high levels of *Streptococcus mutans* were positively associated with the presence of DR3 and DR4 alleles in 186 African-American women, whereas TNFa allele103 was negatively and TNFa 117 was positively associated with high levels of *Lactobacillus acidophilus*. A similar trend towards a relationship between HLA-DR4 and high levels of mutans streptococci though not statistically significant was observed by Wallengren.[59] In the 13 who expressed HLA-DR4, 8 were heavily colonized by mutans streptococci. In a Caucasian population, a higher dose of streptococcal antigen was required to release T-helper activity in DR4 positive individuals compared to cells carrying the HLA DR1,2,3,6 cross reactive groups.[60] McCarlie *et al.*[61] reported HLA-DR4 positive subjects exhibited reduced reactivity to *S. mutans* antigen I/II, lower specific secretory immunoglobulin A activity/total Immunoglobulin A and a lower specific reactivity to whole cell *S. mutans* UA159, suggesting a potential link between HLA-DR04 and caries. Absence of HLA-DR4 antigens with low, or undetectable, levels of mutans streptococci have also been studied.[62] Valarini *et al.*[63] found that individuals positive for HLA-DQ2 allele were less likely to have dental caries than those who were negative for this allele.

Defensins are key elements of the innate immunity system located at 8p23.1 and provide a first line of defence for oral tissues and other organs. Ozturk *et al.*[64] reported that variant allele of beta defensin1, i.e. G-20A are associated with either a five-fold increase in DMFT or with decreased caries experience (i.e. G-52A), thus differentially playing a role in bacterial colonization. Mannose-binding lectin (MBL) plays an important role in innate immunity and have been proved to affect susceptibility to some infectious diseases.[65–67] Olszowski[68] studied 5-year-old children and found the frequency of MBL2 mutant genotype (GGC/GAC and GAC/GAC) was higher in the high caries group compared with the low caries group, while the opposite was observed in 13-year-old children. Similarly, Pehlivan *et al.*[69] found the distribution of MBL genotypes did not significantly differ between carious and caries-free groups although the frequency was higher in the carious group due to the smaller sample.

Altun *et al.*[70] failed to establish an association between human leukocyte antigens, DRB1, DQB1, dental caries and colonization by mutans streptococci. Ozawa *et al.*[71] also reported a weak association of salivary numbers of mutans streptococci with HLA-DQB1. It is conceivable that the pattern of HLA polymorphisms varies somewhat between racial and ethnic groups. However, it would be wrong to deny the role of immunity to determine whether a direct or indirect effect coded by a single or group of genes underlies the development of caries.

Saliva

Saliva presents various innate or acquired defence factors capable of inhibiting bacterial invasion, growth and metabolism by different mechanisms, such as bacterial adherence and streptococci acid production.[72] Although the physical properties of saliva (pH, volume and viscosity) are known to modify the carious process,[73] the role of genes remains essentially unexplored. Differences in caries experience might be due to polymorphic acidic proline rich proteins in saliva encoded at two loci PRH1 and PRH2.[74]

Zakhary *et al.*[75] observed that the presence of Db allele of PRHI in 14% Caucasian showed greater *S. mutans* colonization than African-American. However, caries experience was less in magnitude suggesting that linkage disequilibrium with Db could enhance the mutalistic growth of actinomyces in biofilms promoting antibody production reducing the caries experience as only db negative Caucasians had significantly more caries. Jonasson *et al.*[76] also noted that salivary receptor gp-340, which mediates adhesion of *S. mutans*, showed more caries experience in subjects positive for both gp-340 I variant and Db positive allele. Another study found a significant increase in the decayed, missing, filled tooth surfaces (DMFS) of 306 children with proline rich proteins Pa+ and Pr22 than in those with the other phenotypes (Pa– or Prll and Pr12).[77] Ayad *et al.*[78] also reported that phenotypes of proline rich proteins such as ps1 encoded by PRB1 and con1

encoded by PRB2 expression to be significantly higher in caries-free subjects. These studies are consistent with earlier studies by Azen[79] and Anderson.[80] Azen found that Pa– phenotype to be significantly more prevalent than Pa+ among caries-free subjects (68%) when compared to caries active subjects (52%), similar to Anderson[80] (prevalence of Pa– 65% vs 45% respectively). However, this difference was not significant owing to a smaller sample size. Peres *et al.*[81] observed in 245 children a positive association between buffer capacity and the carbonic anhydrase VI gene rs2274327 (C/T) polymorphism. Although it seems logical that salivary buffer capacity is a contributing factor for enamel demineralization, its effect may be overshadowed by several other factors.

Lactotransferrin (LTF) is a multifunctional metalloprotein belonging to the transferrin family, secreted in saliva with antibacterial effects.[82] Azevedo *et al.*[83] found an association of Allele A polymorphism in the second exon of LTF gene with lower values of DMFT as well as with higher levels of salivary flow showing a protective effect against caries. Velliyagounder *et al.*[84] reported a similar polymorphism to be associated with antibacterial activity against *S. mutans*, a main cariogenic bacterium. However, Brancher *et al.*[85] observed no polymorphism in the putative promoter region of the LTF gene to be associated with caries experience.

Several salivary proteins influence biofilm cariogenicity but a single factor may not hold the key to our questions. Investigations capturing the genetic information of salivary proteins as a whole may provide a clearer view of the caries progress. The differentiating factors in various studies analysing salivary proteins could be due to functional overlapping and certain rare variations in the genes.

Future perspectives

The post-genomic era will present many opportunities for improvement in oral health care but will also present a multitude of challenges. The identification of genetic risk factors will help to screen and identify susceptible patients, and better understand the contribution of genes in caries aetiopathogenesis. If risks could be identified prior to the occurrence of cavitated lesions, minimalistic resources (time, cost) could be used to prevent dental caries as well as alleviate the patient's pain and suffering. Information derived from these diverse studies will provide new tools to target individuals and/or populations for a more efficient and effective implementation of newer preventive measures and diagnostic and novel therapeutic approaches in the management of this disease.

CONCLUSIONS

We can conclude from the literature that genes have a role to play in dental caries; however, both environmental and genetic factors have been implicated in the aetiology of caries. Additional genetic studies in different populations will have to be conducted to replicate these initial findings in order to diagnose and treat dental caries from a more molecular or genetic basis.

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