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Review On "Influence Of Host Genes On Dental Caries"

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Abstract: *The current paper reviews the influence of genetics on susceptibility of dental caries. It is clear from many dietary studies that, variation in susceptibility to dental caries exists even under the identical, controlled conditions. This implicates that, because of genetic differences, certain environmental factors are potentially more cariogenic for some people than for others. Although there is clear evidence that dental caries is a multifactorial, infectious disease, with many contributory environmental factors, there is also strong evidence for a genetic component in the etiology of this disease. Studies of twins, families, and animal models have all indicated that caries has a genetic component. Evidence of a genetic contribution to caries is based on four questions examining inheritance that altered the dental hard tissues; the immune response; sugar metabolism & consumption; salivary flow, salivary constituents; & salivary defense systems. Caries phenotypes in the primary dentition were highly heritable, with genes accounting for 54–70% of variation in caries scores. The heritability of caries scores in the permanent dentition was found to be 35–55%. The current paradigm of disease treatment is not designed to account for the multitude of genetic information known to impact our oral health. It may be time for another adjustment in our view of paradigm of oral health & disease treatment.*
Key words: *Dental caries, Genetics, Genetic traits, Host-genes, Inheritance,*

I. Introduction

Caries is a major public health concern worldwide, affecting more than 80% of the population in the world([1]). The etiology of dental caries has been studied for many years. Multiple factors contribute to a person's risk for caries, including: Environmental factors, such as diet, oral hygiene, fluoride exposure, and the level of colonization of cariogenic bacteria; and Host factors, such as salivary flow, salivary buffering capacity, position of teeth relative to each other, surface characteristics of tooth enamel, and depth of occlusal fissures on posterior teeth([2]). It is caused by the bacterial fermentation of sugars & other dietary carbohydrates which leads to the decay of tooth mineral. Dental caries can be defined as *"a carbohydrate-modified transmissible local infection with saliva as a critical regulator"* ([3]).

In spite of all that is known about this disease, there are still individuals who appear to be more susceptible to caries and those who are extremely resistant, regardless of the environmental risk factors to which they are exposed. Like many medical and dental diseases, it depends on a complex interaction between the genetic structure of an individual and the superimposed environmental factors, a combination of nature and nurture. Although there is clear evidence that dental caries is a multifactorial, infectious disease, with many contributory environmental factors, there is also strong evidence for a genetic component in the etiology of this disease. This has been supported by studies in both humans and animals ([4-8]).

Currently, dental caries is seen as multifactorial disease based upon host, microbial & environmental factors. It is clear from many dietary studies that variation in susceptibility to dental caries exists even under the identical, controlled conditions. This implicates that, because of genetic differences, certain environmental factors are potentially more cariogenic for some people than for others. This is not to say that dental caries is an inherited disease; rather, genetic influences may modify the over expression of this disease in the individuals [(9]).

The factors related to the host are under strong genetic control, but external factors - such as fluoride exposure, quality of dental hygiene, micro-biota, and type of diet - may overcome an individual's *a priori* genetic susceptibility ([1]). Although dental caries is a multifactorial infectious disease with many contributory environmental factors, there is also strong evidence for a genetic component in the etiology of this disease. Studies of twins, families, and animal models have all indicated that caries has a genetic component. Recent studies of twins reared together estimated the heritability for caries, adjusted for age and gender, as ranging from 45 to 64% ([1]).

The pattern of host inheritance contributes to either increased susceptibility or resistance to dental caries. Establishing a basis for the genetic contribution to dental caries will provide a foundation for future

studies in which the information in the human genome will improve our understanding of the complexity of dental caries pathogenesis ([4]).

II. Genetic Contribution To Dental Caries:

Evidence of a genetic contribution to caries is based on four questions examining inheritance that altered:

1. The dental hard tissues
2. The immune response
3. Sugar Metabolism & consumption
4. Salivary flow, salivary constituents & Salivary defense systems

2.1: The dental hard tissues

Amelogenesis is under genetic control, hence the size, shape, shade and even caries susceptibility can be affected by genetic variation. The proteins found in the enamel during amelogenesis are of two main groups; Amelogenins and Nonamelogenins (enamelin, ameloblastin & tuftelin). Variation in *amelogenin, ameloblastin* and *tuftelin* contribute to caries susceptibility. In addition, variation in *enamelin* may interact with the presence of S. *mutans* infection ([11]).

2.1.1: Amelogenins:

Amelogenins are highly conserved proteins and constitute 90% of the enamel organic matrix. The Amelogenin (AMELX) gene resides on the p arm of the X chromosome. Its locus is Xp22.31 - p22.1. Amelogenin and its protein product contribute to enamel formation in the dentition. The amelogenin protein constitutes 90% of the enamel matrix ([12]). A mutation / deletion in the AMELX gene results in X-linked amelogenesis imperfecta. There is a possibility that a deficient amelogenin gene or a decreased amount of amelogenin protein leads to disruption of formation of enamel matrix and therefore increased caries susceptibility([12]).

Both the X and Y chromosomes have a version of the *amelogenin* gene. The Y - chromosome has an *amelogenin* - like gene *(AMELY)* that corresponds to the *amelogenin* gene in the X -chromosome *(AMELX).* Both *AMELX* and *AMELY* genes are transcriptionally active in male developing tooth buds. Therefore, it is possible that the presence of an *AMELX* caries susceptibility allele in males may be compensated by the homologous (and of course active) *AMELY* gene. Therefore females tend to show higher scores of caries experience than males ([11-13]).

- Presence of C allele of the *amelogenin* increases dmfs.
- Locus on chromosome Xq27.1 harbors a protective caries gene ([11]).

2.1.2: Ameloblastin:

Ameloblastin may contribute to caries susceptibility. *Ameloblastin* is expressed during the differentiation of inner enamel epithelium into ameloblasts, with intense localization in the Tomes processes of secretary ameloblasts. In contrast to *amelogenin,* only modest amounts of *ameloblastin* can be detected in enamel matrix ([11]).

Tuftelin:

The tuftelin protein is secreted into the enamel matrix and can be detected at the dentin - enamel junction. Its expression (just before the beginning of enamel mineralization) and its acidic nature make it a good candidate for involvement in the initial stages of enamel mineralization. It is involved in enamel development and mineralization, combined with high levels of *S. mutans* results in increased susceptibility to dental caries. The over-expression of tuftelin in the extracellular enamel matrix led to imperfections in both enamel prisms and crystallite structure (proved in a transgenic mouse model). Sequence changes in the tuftelin gene could also be indirectly affecting caries susceptibility by interfering with other gene or protein interactions ([2, 11]).

- T allele of the *tuftelin* increases dmfs ([11]).
- Variation in *tuftelin* in the presence of *S. mutans* and variation in *amelogenin* contributed to higher caries experience in humans ([11]).

2.1.3:Enamel development:

Genes in the HLA complex are associated with altered enamel development and increased susceptibility to dental caries. Aine and Aguirre have shown that HLA-DR3 is highly associated with the frequency of dental enamel defects in patients with celiac disease. Mariani had a similar result with HLA-DR3 associated with increased enamel defects and HLADR5 associated with a reduced frequency of enamel defects ([10]).

2.2: The immune response

One aspect of genetic effects is genetic modification in immune response. Since mutans streptococci are found in almost all individuals, the large differences in oral colonization levels between individuals can be explained by variations in the immune response. Individuals with either inherited or acquired immune deficiency are subject to increased risk for dental caries ([10]).

2.2.1: Beta defensins (DEFB):

It act as chemo attractants for T-cells and dendritic cells of the acquired immune system and monocytes, suggesting a major role for these peptides in host defense against infection.

- It is intriguing that variation in the promoter region of DEFB1 is associated with both higher and lower caries scores.
- Carrying a copy of the variant allele of the DEFB1 marker rs11362 (G-20A) increased the DMFT and DMFS scores more than five-fold. Also, carrying a copy of the variant allele of the DEFB1 marker rs179946 (G-52A) correlated with low DMFT scores ([15, 16]).

2.2.2: Human leukocyte antigen (HLA) or major histocompatibility complex (MHC): molecules have important roles in the immune responsiveness ([14]).

- Differences in MHC molecules may cause some variations in immune responses against microorganisms and may influence children's susceptibility to ECC. Positive HLA-DRB1*04 may increase the risk of ECC ten times.
- Studies by Senpuku and Acton have correlated specific HLA DR types with binding *S. mutans* antigens and *S. mutans* colonization. Acton concluded that "genes within MHC modulate the level of oral cariogenic organisms".
- Genes within the MHC, especially the DR4 group, can influence susceptibility to dental caries. Acton *et al*. demonstrated that high levels of *S. mutans* were positively associated with the presence of DR3 and DR4 alleles in African-American women ([14]).

2.3: Sugar Metabolism & consumption:

2.3.1: Fructose intolerance: In hereditary fructose intolerance, an autosomal recessive disorder caused by deficiency of the enzyme fructose-1-phosphatase aldolase, the blood glucose level may fall in response to fructose ingestion, causing pallor, vomiting, sweating & even coma. Affected individuals therefore develop a strong aversion to sweet & high proportions are caries free ([17]).

Since ingestion of the cariogenic substrate is the most likely avenue for contribution to the multifactorial process of dental caries, inherited defects in sugar metabolism would most likely alter substrate availability in a manner identical to any other dietary restriction and not by a genetically unique mechanism ([10]).

2.3.2: Genetic sensitivity to the bitter taste:

Sensitivity to taste is an inherited trait in children ([18, 19]). Inherited behavior and taste thresholds may play an important role in the frequency of carbohydrate intake ([18, 20]). Genetic sensitivity to taste may be associated with a preference for or rejection of some foods by children ([19]).

The importance of the ability to taste phenylthiocarbamide (P.T.C.) was realized long back in 1930 by Fox, when he failed to make any taste out of it, while his colleague found it to be bitter. Thereafter, Synder (1932) showed that the inheritance of the ability to taste P.T.C. was dependent on a single autosomal dominant gene ([21]).

Mennella et al classified children and their mothers into three groups based on their TAS2R38 genotype (gene that encodes a taste receptor responsive to bitter taste) ([18, 22]).

- Type AA had two bitter insensitive alleles (nontasters),
- Type PP had two bitter sensitive alleles (supertasters) and
- Type AP had one of each (medium tastes).

Children accordingly may be supertasters, medium tasters or nontasters as determined by the subject's taste threshold.

Taste worlds of humans vary because of taste blindness to phenylthiocarbamide (PTC) and its chemical relative 6-npropylthiouracil (PROP) ([23]). PROP paper is a useful tool in determining the genetic sensitivity to bitter and sweet tastes as well as the burn sensation.[24, 25] Sensitivity to the bitter taste of PROP is an inherited trait ([18, 19]). The subset of population identified as supertasters who rate PROP paper as intensely bitter. A supertaster child is able to perceive stronger bitter and sweet tastes as compared to medium and non-tasters ([18, 23, 26]). Anatomically, super-tasters also have a higher density of fungiform papillae and taste receptors on the anterior portion of the tongue than medium tasters and non-tasters ([18, 23-25, 27]). Supertasters are thus able to perceive taste in a lower concentration of bitter or sweet substance than non tasters. In contrast, non-tasters may not be able to perceive sweet or bitter taste in the same concentration as supertasters and hence, require a higher

concentration to perceive taste in the food products. Non-taster children may therefore have higher concentration and frequencies of sugar intake compared to children who are medium or super-tasters and are therefore more susceptible to dental caries ([18, 20]). Higher prevalence of dental diseases would be observed among non-taster children as compared to children who were medium and supertasters ([18, 28]).
Knowledge of an individual's taste threshold may facilitate the identification of children who are at high risk for developing dental caries. Women are more likely to be supertasters than men are. Anatomical data revealed that women have more fungiform papilla than men ([18, 23]).

2.4: Salivary flow, saliva constituents, & salivary defense systems:

2.4.1: Salivary flow:

Salivary flow rates and compositional analysis have been shown to be generally less protective in women than in men.[13] In all age groups, females were found to have a lower mean flow rate of whole saliva than males. A lower salivary flow rate in females puts them at a higher risk for caries because they lack saliva's mechanical washing, buffering, and re-mineralization benefits ([13, 29]).

2.4.2: Acidic proline-rich proteins (PRPs):

PRPs in saliva influence the attachment of bacteria associated with caries. At least 8 different polymorphic PRPs are known, & all these proteins are coded by a block of genes called *the salivary protein complex,* located on the short arm of chromosome 12 ([9]). The acidic PRPs comprise 37% of the salivary proteins that adhere to freshly cleaned teeth. They attach to apatite by their acidic N-terminal domain, and this exposes their proline-rich C-terminal domain to bind to oral bacteria and initiate biofilm development. Caries severity and *S. mutans* colonization have strong genetic components. Much of these genetically determined differences in caries experience might be due to polymorphic, acidic proline-rich proteins (PRP) in saliva encoded at two loci, *PRH1* and *PRH2*. Three alleles (*Db, Pa*, and *Pif*) provide polymorphisms at the *PRH1* locus, and 3 alleles (*Pr1*, Pr1´, and *Pr2*) at the *PRH2* locus. Yu et al reported significant association between two specific PRPs phenotypes (Pa+ & Pr22) & increased in dental caries in permanent teeth. Allelic genes, Pa- & Pr11/Pr12, appear to confer caries resistance ([9, 30]).

2.4.3: Salivary defense systems:

Salivary defense systems play a significant role in maintaining the health of oral cavity and preventing caries. These defenses include factors which inhibit or reverse demineralization of exposed tooth surfaces, such as simple mechanical rinsing, buffering action, and calcium phosphate binding proteins as well as antimicrobial activities including microorganism aggregation and clearance from the oral cavity, immune surveillance, and the secretion of antimicrobial peptides (AMPs) ([31, 32]). *Antimicrobial peptides AMPs* are natural antibiotics that provide a first line of defense against a wide spectrum of pathogens ([31, 33-35]). These peptides may be particularly important in the oral cavity, where members of the microbial flora are present in high numbers at all times.
The three main AMP families are defined by amino acid composition and three-dimensional structure: ([31, 33, 36-38])

1. α -helical peptides without cysteine (the cathelicidins), ([36])
2. Peptides with three disulfide bonds (α - and β -defensins), ([33, 37]) and
3. Peptides with an unusually high proportion of specific amino acids, for example, the histatins ([38]).

Salivary AMP concentrations showed large variation between individuals, with a significantly higher level of salivary-defensins HNP1 to -3 in children with no caries. The α -defensins HNP1 to -3 are expressed in neutrophils and participate in nonoxidative microbial death and have been identified in gingival crevicular fluid ([31, 39,40]). The salivary levels of HNP1 to -3 antimicrobial peptides may represent a genetically determined factor that contributes to caries susceptibility. Low salivary levels of α-defensins (HNP1 to -3) could be a new and useful measure of the risk for caries in children ([31])

III. Genes And Their Effects On Dental Caries Of Primary And Permanent Dentitions:

Caries phenotypes in the primary dentition were highly heritable, with genes accounting for 54–70% of variation in caries scores ([41]). The heritability of caries scores in the permanent dentition were 35–55%, which was also substantial, although this was lower than analogous phenotypes in the primary dentition. Assessment of the genetic correlation between primary and permanent caries scores indicated that 18% of the co-variation in these traits was due to common genetic factors. Therefore, dental caries in primary and permanent teeth may be partly attributable to different suites of genes or genes with differential effects. Sex and age explained much of the phenotypic variation in permanent, but not primary dentition. Dental caries are heritable, and suggest that genes affecting susceptibility to caries in the primary dentition may differ from those in permanent teeth ([41]).

IV. Caries Experience In Inherited Disorders

4.1 Disorders with Reduced susceptibility: ([17])

4.1.1 Hereditary fructose intolerance

In hereditary fructose intolerance, an autosomal recessive disorder caused by deficiency of the enzyme fructose - 1- phosphatase aldolase, the blood glucose level may fall in response to fructose ingestion, causing pallor, vomiting, sweating & even coma. Affected individuals therefore develop a strong aversion to sweet & high proportions are caries free.

4.1.2 Primary immunodeficiency

Relatively low caries experience is also found in patients with primary immunodeficiency, probably a result of prolonged antibiotic therapy.

4.1.3 Chronic renal failure:

Chronic renal failure occurs in a number of inherited disorders. Appears to inhibit caries, probably through high salivary pH.

4.1.4 Congenital chloride diarrhea:

High pH may be implicated since metabolic alkalosis is a feature of this disease.

4.1.5 Growth hormone deficiency:

Has been associated with resistance to caries, the suggested explanation being retarded eruption with consequently increased time for enamel maturation before exposure to the oral environment.

4.1.6 Down syndrome: Possibly related to delayed eruption & inter-dental spacing.

4.1.7 Turner syndrome: Due to inter-dental spacing.

4.2 Disorders with Increased susceptibility: ([17])

4.2.1 Epidermolysis bullosa (EB):

has been shown to have both an alteration in the enamel and an increased caries incidence.

The mutations in EB result in four different forms of the disease:

1. Recessive dystrophic
2. Dominant dystrophic
3. Junctionalis and
4. Simplex.

In EB-junctionalis, the enamel has greater porosity and thus increased surface area for the effects of acids generated by cariogenic bacterial, and the enamel contains large amounts of serum albumin that inhibits crystal formation and thus remineralization of altered sites. The genetic origin for EB-junctionalis has been linked to one of three different genes: **laminin 5, 4integrin and Type XVII collagen**. All three of these genes have the potential to alter the relationship of the ameloblast to the developing enamel extracellular matrix and thus lead to a primary defect in the enamel hard tissue([10]).

4.2.2: Rapp-Hodgkin ectodermal dysplasia: Gross carious teeth are seen.

4.2.3: Focal dermal hypoplasia: A gross carious tooth is one of the clinical features.

4.2.4: Rubinstein-Taybi syndrome: The marked caries found in about one-third of patients is perhaps a result of poor dental care resulting from a small mouth opening, misalignment of the teeth & mental retardation.

4.2.5: Klinefelter syndrome: Increased susceptibility to caries has been found ([12]).

V. Genome-wide Scan

AR Vieira et al report the first genome-wide scan performed for caries. Forty-six families with similar cultural and behavioral habits, and living in the Philippines, were studied, and genome-wide genotype data and DMFT (Decayed, Missing due to caries, Filled Teeth) scores were evaluated. They found; ([1])

Three regions yielded suggestive positive results for **low caries susceptibility:**

- 5q13.3
- 14q11.2 and
- Xq27.1

Another two regions yielded suggestive positive results for **high caries susceptibility:**

- 13q31.1 and
- 14q24.3

5.1.1: 5q13.3: CARTPT (cocaine- and amphetamine-regulated transcript) is located in 5q13.3. This gene appears to have a role in reward, feeding, and stress, and it has the functional properties of an endogenous psycho-stimulant ([1, 42]). A behavior that includes decreased ingestion of sweet foods would contribute to a lower caries experience.

5.1.2: 14q11.2 **:** It is very close to OR4E2 (olfactory receptor, family 4, subfamily E, member 2), which interacts with odorant molecules in the nose, to initiate a neuronal response that triggers the perception of a smell. Taste and smell are subsumed under the term 'flavor'. Many flavors are recognized mainly through the

sense of smell (e.g., anyone will have trouble identifying the chocolate flavor if one holds one's nose while eating chocolate, even though one can distinguish the food's sweetness or bitterness). Genetic variation in genes regulating olfactory and taste sensations may predispose someone to be more or less inclined to eat certain foods, and therefore to have a less or more cariogenic diet.

5.2.1 13q31.1: It is near SPRY2 (Sprouty2). Sprouty2 has been shown to inhibit the Ras/MAP kinase pathway ([43]). The MAP kinase cascades constitute highly conserved signaling systems that have been deemed to play various roles in physiological responses, including immune responses. In addition, SPRY2 is an antagonist of FGF signaling, which is implicated in controlling the integrity of oral mucosa and as having mitogenic effects in the salivary glands as well ([1, 44]).

5.2.2 14q24.3: This locus is close to ESRRB (estrogen-related receptor beta). This gene encodes a protein with similarity to the estrogen receptor. Its function is unknown; however, this gene is likely to have diverse biological functions ([1, 45]). One can argue that a gene with estrogen related function could also contribute to the observed gender differences in caries frequency. Estrogens have been known to have a depressing effect on the secretion of growth hormone from the anterior pituitary. Growth hormone is known to be closely related to the development and maintenance of normal histologic structure of salivary glands, the function of which, in turn, might influence caries formation ([1, 46]).

VI. Conclusion:

Genetic plays a very important role in understanding the modern-day dental caries pathogenesis. This has been well supported by the studies where they have showed certain allelic genes of enamel protein, salivary proline rich proteins, taste & HLA complex causes variation in caries susceptibility. The current paradigm of disease treatment is not designed to account for the multitude of genetic information known to influence our oral health. It may be time for another adjustment in our view of paradigm of oral health & disease treatment. Knowledge of a genetic predisposition &/or a family correlation to host bacteria associated with dental caries could allow for prophylactic treatment option for patient & their families. Since the knowledge is supported by limited studies, it warrants for further research.

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