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GENETIC ASPECTS OF DENTAL CARIES - PART I

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INTRODUCTION: Dental caries is essentially a progressive loss by acid dissolution of the apatite (mineral) components of the enamel, then the dentin or of the cementum then dentin. Dental caries is a multifactorial disease, which is the result of interaction between the tooth (host) and the environment around it including the bacteria, saliva and diet of an individual. Interaction between three factors namely host, microflora and substrate was introduced by Keyes¹ (1960) – called 'Keyes cycle'. A fourth factor – time – was included by Newbrun² (1982).

The late 21st century has seen remarkable developments in understanding the caries process. Dental caries is now considered as an infectious communicable disease resulting in destruction of tooth structure by acid-forming bacteria in dental plaque (an intraoral biofilm), in the presence of sugar. This infection results in loss of tooth minerals that begins on the outer surface of the tooth and can progress through the dentin to the pulp; ultimately compromising the vitality of the tooth.

Caries is the most prevalent disease with a multifactorial etiology affecting the human race. Although the prevalence of dental caries in different communities around the world is decreasing, it is not yet extinct (Bowen et al 1991)³; and it has been found to be higher in certain high-risk groups (Winter 1998).

Increased risk for susceptibility to dental Caries: Incidence of dental caries is influenced by host factors like the structure of enamel, immunologic response to cariogenic bacteria, the composition of saliva, tooth eruption and development, salivary flow and tooth morphology.

The specificity of these factors is dependent on the genetic make-up of each individual and the expression of specific genes. It is possible that allelic variation related to a host factor may contribute to increased risks for the development of carious lesions. Genetic variation of various host factors may contribute to increased risk of Dental caries.

Numerous reports have described a potential contribution to the risk for Dental caries. Studies on twins have provided strong evidence for the role of inheritance. Thus establishing a basis for a genetic contribution to dental caries will provide a foundation of future studies utilizing the human genome sequence to improve to understanding of the disease process.

Inherited disorders of tooth development with altered enamel structure increase the incidence of dental caries. Altered immune response to cariogenic bacteria may also increase the incidence of caries.

Recently, Human Genome project published the initial complete sequence of the human genome. This information represented a magnificent resource to further characterize the genetic contribution to both the etiology of and susceptibility to the disease and to develop new

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strategies for diagnosis, management and risk assessment. Literature reports that the pattern of host inheritance contributes to either increased susceptibility or resistance to dental caries.

HOST FACTOR FOR DENTAL CARIES:

Structure of Enamel: Genetic modification of dental enamel alters susceptibility to dental caries. It has been reported that inherited disorders of tooth development that result in altered enamel structure increased the incidence of dental caries. Dental enamel that is insufficiently mineralized retains organic components and is more susceptible to decay.

Genes that produce enamel matrix have been identified. Cloning of enamel matrix genes, chromosomal localization of the genes and linkage of genes to human syndromes of altered tooth development has been accomplished. In all these conditions the basic defect is the altered bio-mineralization of the matrix protein and a change in DNA sequence.

Various studies mention dental caries as the component of well-defined inherited genetic syndromes with craniofacial phenotypes. One syndrome with alteration to the dental hard tissue (Enamel) and increased caries susceptibility is epidermolysis bullosa (EB). The mutation in EB results in four different forms of the disease:

- a. Recessive dystrophic.
- b. Dominant dystrophic.
- c. Junctionalis.
- d. Simplex.

Wright et al (1993, 1994)^{4,5} has reported that, EB-junctionalis and EB recessive dystrophic are associated with increased incidence of dental caries. He also found that the EB-junctionalis form has altered chemical composition of the enamel. Apart from these, EB patients have other oral complications leading to an increased susceptibility to caries (eg: separation of mucosa and attendant complication). Thus, primary defect in the enamel and secondary to the disease has resulted in the increased caries risk.

In EB-junctionalis, the enamel has greater porosity and thus increased surface area for the effects of acids generated by cariogenic bacteria. In addition, the enamel contains large amounts of serum albumin that inhibit crystal formation and thus re mineralization of altered sites. The genes responsible for EB-junctionalis are laminin 5, β_4 -integrin and type XVII collagen. All these genes have the potential to alter the relationship of the ameloblasts to the developing enamel extracellular matrix and thus leading to a primary defect in the enamel hard tissue.

Thus, the genetic mutations that are associated with the syndromes provide a link between inheritance and increased susceptibility to dental caries. The specific link for all of these syndromes of altered tooth development has not yet been determined. Consequently, it has not been possible to complete genetic screening of large populations to determine whether the same genes / mutations are also associated with increased susceptibility to dental caries in non-syndromic patients.

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Genetic modification of immune response altering susceptibility to Dental Caries:

Individuals with either an inherited or an acquired immune deficiency are subject to increased risks for and incidence of dental caries. It is now believed that, there are some specific Immune complex molecules associated with increased risk of dental caries. According to Lehner et al⁶. HLA DRW 6-1, 2, 3 have a significant relationship to the DMFS index and a low dose response to *S. mutans* antigens. However, the de Vries et al⁷ study did not detect a relationship between HLA DR types and caries incidence. Recently studies by Senpuku et al and Acton et al have correlated specific HLADR types with binding *S. mutans* antigens and *S. mutans* colonization. Acton et al concluded that genes within MHC modulate the level of oral cariogenic organisms.

Another immunologic disorder – celiac disease also demonstrated a significant positive correlation between HLA typing and the presence of enamel defects that predispose to dental caries. According to Aine and Aguirre, HLA-DR 3 is highly associated with the frequency of dental enamel defects in patients with celiac disease.

Mariani et al⁸ has also reported with HLADR3 associated with increased enamel defects and HLA-DR^{9,10,11} were associated with a decreased frequency of enamel defects. In celiac disease, the genes in the HLA complex are associated with allied enamel development and increased susceptibility to dental caries.

Even though the association between specific patterns of HLA genetic inheritance is weak, additional research is required to examine the contribution of specific HLA type and the risk for dental caries.

Inherited alterations in sugar metabolism altering Susceptibility: Very limited studies have been conducted in this area. The relationship of sugar tasting and dental caries has been identified. A paradoxical relationship exists between the sensitivity to taste sugar and the incidence of dental caries. Hereditary fructose intolerance is also a genetic condition. In these correlations there is a statistically significant difference in the caries experience of individuals with hereditary fructose intolerance and controls and is directly relative to the absence of cariogenic sugars in the diet. However, ingestion of the cariogenic substrate is the most likely avenue for contribution of the multifunctional 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 genetically unique mechanisms.

Genetic regulation of salivary gland function altering susceptibility to dental Caries:

Salivary function is critical to maintain dental enamel mineralization and altering the pathogenicity of cariogenic bacteria. The evidence is strong that xerostomia increases the risk of dental caries. There is only weak evidence that xerostomia has a defined genetic basis rather than being the result of some acquired effect that reduces the result of some acquired effect that reduces the functioning of the salivary glands. Studies concerning the influence of salivary protein on dental plaque formation suggest as much for genetic control of this multifactorial trait.

A group of salivary proteins have been designated as "Proline-Rich-Proteins" (PRPs) because of their high content of amino acids. Proline has been linked to early plaque / pellicle formation. These proteins closely resemble the enamel matrix proteins in composition and

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structure and bond tightly to hydroxyapatite crystals. PRP's are inherited as autosomal dominant trait. At least eight different polymorphic proline-rich-proteins are known and all these proteins are coded for by a block of genes called "salivary protein complex" which is located on the short arm of human chromosome no: 12 (Goodman et al.¹⁰ 1959; Karn RC et al¹² 1985; Mamula et al.¹³ 1985); only a few studies have attempted to associate these salivary protein phenotypes with oral disease.

Dodds MW et al (1997)⁹ reported that there was an association between two specific proline rich protein phenotypes (Pa+ & Pr₂₂) and increase in dental caries score in the permanent teeth of children. (5-15 yrs of age). This suggests that persons with the genotype Pa + or Pr₂₂ may be at significant risk for increased susceptibility to dental caries, whereas the allelic genes, Pa- & Pr₁₁ may confer caries resistance. The mechanism of action could be related to the formation of caries susceptible plaque on the teeth at risk.

The participation of such polymorphic protein systems in oral disease is perfectly concordant with the concept of the multifactorial disease model, which is often invoked to explain dental caries.

Genetics and site attack in dental Caries: Several reports are available in the literature regarding the pattern of caries attack on the enamel surfaces of a tooth, i.e. Mesial, Distal, and Occlusal and on different teeth in the arch. For a maxillary incisor site of attack are paired into 3 types:

- a. Adjacent proximal surfaces (single / double attacks)
- b. Mesial / distal surfaces of the same tooth (unilateral / bilateral).
- c. Corresponding sites on the right and left sides of the mouth (asymmetrical or symmetrical attacks).

Studies also show that ratio of individuals with these types of attacks tend to fall to a limited value with age. Accordingly, theories of caries etiology have developed from these observations. Two widely talked theories are:

1. Jackson's theory: The fundamental principal is that, superimposed on a general susceptibility to caries is a pattern of relatively susceptible and resistant sites within each mouth that depends on the genotype of the individual.

The proposed developmental basis for different pattern of site attack:

Mechanism for the inheritance of different patterns of site attack:

1. Presence of multiple qualitatively distinct sets of odontoblasts within each tooth.
2. Distribution of these sets is under genetic control. Thus, a potential difference in pattern of distribution of these sets exists between all individuals except for identical twins.
3. The pattern of caries susceptibility at the enamel surface is related to the way in which these specialties have been distributed within the odontoblast layer during development.

Distinct sets of odontoblasts are due to (1) differences in the type; site and orientation of antigenic determinants and the cell membrane; (2) This results in determination of tooth shape.

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Thus, difference between right and left homologous tooth morphology are due to multiple, distinctive sets of odontoblasts and the architecture of their associated protein fibers in dentine and enamel. In addition, odontoblasts within a given tooth comprise a vastly complicated mosaic of distinctive elements. The complex shapes of organs like teeth derive from the multiplicity of mosaic elements, the contact relation between them and the morphology of the individual cells and extracellular elements.

Cells with a particular TCF (tissue coding factor) are distributed at one or more anatomical sites and the distribution differs from one genotype to another. Thus, morphological differences between genotypically dissimilar individuals can be accounted to this concept.

Hence there is a greater concordance for pattern of site attack between identical twins as opposed to fraternal twins. This is due to a variety of inherited characteristics such as tooth morphology, tooth position and salivary constitution and environmental factors like diet and oral hygiene practices.

Many authors auction the histologic aspect of Jackson's theory. Current concept is that, a relatively small number of simple cellular for as can give rise to complex changes of form regional differentiation are control by quantitative gradients rather than by a mosaic of qualitatively distinct elements.

Burch's Auto-aggressive Hypothesis: According to Burch hormonally distributed mitotic control proteins (MCPs) control normal growth, synthesized by lymphoid system. Each antigenically specific cell type in the developing body carries a unique tissue coding factor (TCF) and the growth of each cell type is controlled by the corresponding specific MCP.

A somatic forbidden cell in a lymphoid stem cell can produce a forbidden clone which synthesizes a mutant form of MCP that is pathogenic towards the cell type bearing the complementary TCF, resulting in tissue distraction and the initiation of an auto aggressive disease.

Age prevalence of dental caries at a particular site, or set of genetically associated sites, depends on (1) the proportion of the population that is genetically predisposed, (2) different mutation rates (3) the number of pathogenic forbidden clones (4) the average interval or latent period between the initiation of the last forbidden clone and the emergence of dental caries.

In dental caries, the target cells are odontoblasts and once they have suffered an auto-aggressive attack, their associated hard tissue is rendered susceptible to the diffusion of exogenous cariogenic factors like acids, chelating agents etc. In one person, certain sets of odontoblasts may be at risk with respect to an auto-aggressive attack, but in another person of dissimilar genotype, different sets of cells may be at risk.

However, the drawback of this theory is that it does not give a clear explanation. Low resistance of surface enamel to caries can be influenced by the status of underlying odontoblasts. If so then it may be expected that teeth rendered non-vital by trauma should be more susceptible to caries than normal vital teeth.

Observations to support Jackson's Theory: Some of the additional points that support Jackson's theory are:

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1. Relationship between lingual pit caries and proximal caries of the maxillary incisors: According to this, an individual who has both decayed or filled lingual pits and proximal sites had an appreciably higher proportion of bilateral attack than incisors without of pits.

Caries prevalence for permanent second molars for Nigerian population is twice as high as for first molar when compared with Western population.

These differences in caries prevalence within the same population or in two different populations, according to Jackson are due to genetic difference between the individuals.

Comment: According to the opponents of this theory, these findings cannot be regarded as evidence for the genetic prevalence of dental caries. If this is true, then persons visiting the dentist regularly are likely to be genetically different from those who do not. Thus to demonstrate these differences, the only possible way is to study the distribution of individuals with particular patterns of site attack in families.

2. Stability of caries pattern prevalence with time and Place: In a study conducted in UK, the caries prevalence for maxillary incisors in the year 1959 to 1961 was 49%. This consistency of caries pattern prevalence has been taken as evidence supporting the proposed genetic control of specific site vulnerability.

Comments: Factors like lack of change in frequency of a particular attribute in a population with time or the uniformity of its frequency in population from different areas do not provide evidence for genetic control of the attribute.

3. Symmetry of site attack with in Individuals: A symmetrical caries attack for maxillary and mandibular incisors appears to occur more frequently due to genetically controlled site vulnerability.

Comments: Correlated attacks on the 2 sides of the mouth can be explained in terms of common constitutional and local environmental factors.

4. Prevalence of mirror image patterns of site Attack: According to this, a particular pattern of site attack is generally similar to that of the corresponding mirror image pattern. i.e., the pattern **(d)**-s occurs with the same order of frequency as does **s-(d)** etc. These patterns can be explained only with the genetic hypothesis.

The opponents to this hypothesis stated that the explanation to these patterns is more complex and as to how and why these similar frequencies are maintained cannot be clearly understood.

5. Cervical caries on maxillary Incisors: According to the acid theory, the symmetrical distribution of plaque, on the labial surface of maxillary incisors predisposes to cervical caries, and they are also distributed symmetrically. Despite the symmetrical distribution of caries plaque, the

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presence of caries only on one side is taken as evidence of genetically controlled site specific vulnerability to caries.

Comment: Even though there is some degree of symmetry of attack, it not consistent with independent genetic control of attack at corresponding site on the two sides of the mouth.

6. The proportion of caries free sites in the dentition as a Whole: Throughout the life span of certain individuals, a certain number of proximal sites remain caries free. And theory offers no convincing explanation for this, of is considered as intrinsic host factors specific to particular site on teeth responsible for this phenomena.

Comments: Many studies have indicated a graded increase of enamel resistance with increasing exposure to the oral environment. Thus longer a site remains sound the less likely it is to suffer a carious attack. Thus initial small quantitative difference of vulnerability or local environment between sites in the same mouth could therefore be amplified with age, resulting in the apparently qualitative all or none phenomenon of vulnerability as opposed to resistance.

An alternate Hypothesis: It is well known that, there is reduction to caries initiation as age increases. Jackson interpreted this as being due to saturation of intrinsically vulnerable sites by caries free sound sites that are intrinsically resistant.

There is a variety of compelling evidence to show that changes occur in the surface enamel with exposure to the oral environment. According to Jenkins, these changes are summarized as under:

1. Permeability of enamel decrease with age
2. Enamel surface concentration of fluoride increases after eruption and areas of fluoride uptake are more in those areas, which suffered an early demineralization.
3. Solubility of surface enamel to acid decreases with age.
4. If two comparable rats are fed with cariogenic diet one immediately after weaning and other some weeks later, first group develops mores caries over a given period than the other group. These finding suggest an overall gradual increase in resistance of enamel to caries with age. Thus, the observed change in prevalence of attack with age at a given site can be interpreted as a direct consequence of this graded increase in resistance.

REFERENCES:

1. Acton RT, et al. Association of MHC genes with levels of caries-inducing organisms and caries severity in African- American women. Human Immunol 1999; 60: 984-9.
2. Azen, E. A.; Goodman, P. A.; Lalley, P. A.: Human salivary proline-rich protein genes on chromosome 12. Am. J. Hum. Genet. 37: 418-424, 1985.
3. Bowen. W. H. K. Schilling, E. Giertsen, S. Pearson, S. F. Lee. A. S, Bleiweis, and D. Beeman: Role of a Cell Surf ace-Associated Protein in Adherence and Dental Caries. Infect. Immun. 59: 4606-4609 (1991).

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4. Wright JT, Fine JD, Johnson L. Dental caries risk in hereditary epidermolysis bullosa. *Pediatr Dent* 1994; 16: 427- 32.
5. Wright JT, Fine JD, Johnson LB, Steinmetz TT. Oral involvement of recessive dystrophic epidermolysis bullosa inversa. *Am J Med Genet* 1993; 47: 1184-8.
6. Lehner T, Lamb JR, Welsh KL, Batchelor RJ. Association between HLA-DR antigens and helper cell activity in the control of dental caries. *Nature* 1981; 292: 770- 772.
7. De Vries RR, Zeylemaker P, van Palenstein-Helderman WH, Huisin't Veld JH. Lack of association between HLADR antigens and dental caries. *Tissue Antigens* 1985; 25: 173-4.
8. Mariani P, et al. Coeliac disease, enamel defects and HLA typing. *Acta Paediatrica* 1994; 83: 1272-5.
9. Dodds MW, Johnson DA, Mobley CC, Hattaway KM (1997). Parotid saliva protein profiles in caries-free and caries-active adults. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 83: 244-251.
10. Goodman HO, Luke JE, Rosen S, Hackel E. Heritability in dental caries, certain oral microflora and salivary components. *Amer J Hum Genet* 1959; 11: 263-73.
11. H Senpuku, K Yanagi, and T Nisizawa Identification of *Streptococcus mutans* PAc peptide motif binding with human MHC class II molecules (DRB1*0802, *1101, *1401 and *1405). *Immunology*. 1998 November; 95(3): 322–330.
12. Karn, R. C.; Goodman, P. A.; Yu, P.-L.: Description of a genetic polymorphism of a human proline-rich salivary protein, Pc, and its relationship to other proteins in the salivary protein complex (SPC). *Biochem. Genet.* 23: 37-51, 1985.
13. Mamula, P. W.; Heerema, N. A.; Palmer, C. G.; Lyons, K. M.; Karn, R. C.: Localization of the human salivary protein complex (SPC) to chromosome band 12p13.2. *Cytogenet. Cell Genet.* 39: 279-284, 1985.

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