Inherited Risks for Susceptibility to Dental Caries

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Abstract:

Dental caries incidence is affected by host factors that may be related to either the structure of dental enamel, immunologic response to cariogenic bacteria or the composition of saliva. Genetic variation of the host factors may contribute to increased risks for dental caries. This systematic review examined the literature to address the question, "Is the risk for dental decay related to patterns of genetic inheritance?"

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

Inherited disorders of tooth development with altered enamel structure increase the incidence of dental caries. Specific genetic linkage has not been determined for all of the syndromes of altered tooth development. Consequently genetic screens of large populations for genes or mutations associated with increased caries susceptibility have not been done.

Altered immune response to the cariogenic bacteria may also increase the incidence of caries. Association between specific patterns of HLA genetic inheritance and dental caries risk is weak and does not provide a predictable basis for predicting future decay rates.

The evidence supporting an inherited susceptibility to dental caries is limited. Genetic linkage approaches on well-characterized populations with clearly defined dental caries incidence will be required to further analyze the relationship of inheritance and dental caries.

Keywords: dental caries, inheritance, genetics, enamel, immunology

The Human Genome Project has achieved the intended goal and recently published the initial complete sequence of the human genome.[1,2] This information represents a magnificent resource to further characterize the genetic contribution to both the etiology of and susceptibility to disease and to develop new strategies for diagnosis, management and risk assessment. There have been reports that 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 using the information in the human genome to improve our understanding of the complexity of dental caries pathogenesis.

This review will focus on inherited traits that alter the susceptibility to dental caries in humans. The significant environmental and behavioral contributions to the incidence of dental caries complicate analyses of the role of genetics in dental caries. The genetic contribution is particularly difficult to isolate since there may be primary manifestations directly linked to the disease process and secondary outcomes due to an underlying genetically linked disease.

The literature was searched for evidence of a genetic contribution to caries based on four questions on examining inheritance that altered either the dental hard tissues, the immune response, the dietary consumption of sugar or the saliva. The first question examined the role of the dental hard tissues, the target for acid dissolution by cariogenic bacteria, and the genetic contribution of altered enamel biomineralization. The second question searched alterations in the immune response reducing the clearance of the bacteria. The third question evaluated the impact of inherited deficiencies in sugar metabolism that could alter the substrate availability. The fourth question examined the inheritance of parameters related either to salivary flow or saliva constituents. These four searches provided a broadly based analysis of several inherited

properties that have different roles in the multifactorial pathogenesis of dental caries and identified several thousand references containing potentially linked research results.

The literature existing on the genetic contribution to dental diseases has been reviewed several times in the past 40 years.[3-12] Genetically regulated processes that were identified to have a contribution to the caries incidence included tooth eruption and development, salivary flow and saliva components and tooth morphology. The most convincing data on the role of genetics in the pathogenesis of dental caries has been developed by analyzing the caries incidence in monozygotic and dyzogtic twins. The conclusions made by Niswander, "the accumulated data suggest that there are significant genetic factors in caries susceptibility," and "the relative magnitude of genetic effects compared to environmental effects is uncertain," remain as the field enters the 21st century.[6]

The objectives of this systematic review included; 1) To examine the literature on studies done in humans to identify genetic characteristics linked to either increased or decreased risk for the dental caries; 2) To exclude animal studies from the evidence-based reviews; 3) To review the literature for reports linking increased/decreased dental caries incidence with genetic syndromes; 4) To identify areas of future analysis that might provide greater insight into the genetic contribution to the risks for dental caries .

EVIDENCE FOR A GENETIC CONTRIBUTION TO DENTAL CARIES THROUGH TWIN STUDIES

Prior to the advent of molecular biology and analysis of the genomic DNA sequence the study of traits and susceptibilities in twins represented one of the most direct measures of analyzing the contribution of inheritance to disease incidence. Dental caries has been examined in twin populations since early in the 20th century (Evidence Table 1). One of the first studies

evaluating twins examined 301 pairs of twins, 130 monozygotic and 171 dizygotic.[13] The evaluation compared the caries incidence of monozygotic twins with same-sex dizygotic (93 pairs) and different-sex dizygotic (78 pairs) twins. The results demonstrated that monozygotic twins had a more similar caries incidence than dizygotic twins and that different-sex dizygotic twins had the greatest variance. The investigators concluded that the results "suggest that heredity plays a subsidiary part in the incidence of caries." Goldberg found that identical twins showed decay in corresponding teeth however a detailed statistical analysis was not completed.[14] These investigators reached the conclusion that, "Heredity affects dental decay only in as much as it controls the shape of a tooth and its pits and fissures and its position in the dental arch." The early twin studies provided some indication that inheritance played a role in caries, however the conclusions were that inheritance was only a contributor to the process.

Twin studies advanced later in the century as techniques to identify monozygotic twins and dizygotic twins were developed. Four studies detected a statistically significant genetic component in the susceptibility to caries and demonstrated that the caries experience of monozygotic twins had a greater concordance than either dizygotic twins or unrelated controls.[15-18] Mansbridge examined 224 pairs of twins and concluded that "Environmental factors clearly have greater influence but the genetic factors also contribute to the causation of dental caries."[16] These studies also had sufficient numbers of individuals and tooth surfaces to begin to compare pit and fissure versus smooth surface caries. This led to the conclusion of Finn and Caldwell that, "Equal genetic weight should not be ascribed to both types of lesions."[18] The findings were that the DMF difference between monozygotic and dizygotic twins was most dramatic for smooth surface caries on anterior teeth.

Additional twin studies were completed in the 1970s which further developed the previous line of research.[19,20] Bordoni concluded that there is a "strong genetic component in primary teeth which affects the incidence of caries."[19] This association was not further developed and the genetic contribution to tooth morphology and eruption timing was the major factor. Fairpo similarly concluded that his study "indicates that there is some genetic influence on the susceptibility to caries attack of both deciduous and permanent teeth."[20] In all of the studies the twins were reared together and the similar environmental aspects represented a confounding variable in the separation of the full contribution of the inheritance to the incidence of dental caries.

A major advance in the understanding of the role of inheritance and the incidence of dental caries was achieved by analyzing twins reared apart who were enrolled in the Minnesota Study of Twins Reared Apart.[21,22] These two studies had a major advantage in that the patients had an average age greater than 40 and did not share similar environments from shortly after birth until the time of analysis. The analysis demonstrated a highly significant ($p<0.001$) relationship between the numbers of teeth present and the percentage of teeth/surfaces restored when comparing monozygotic and dizygotic twins reared apart. Boraas concluded that the study provided "New evidence for a marked genetic component to dentate status and dental caries experience."[21] Boraas also speculated on the particular inherited traits that could contribute to the results by stating "Several genetically variable factors which may be involved in the development of dental caries and could contribute to the greater MZ [monozygotic] similarity in dental caries experience, 1) Salivary factors and oral flora, 2) tooth eruption time and sequence, 3) tooth morphology, 4) arch shape, 5) dental spacing, 6) propensity for diet."[21] Conry extended the same study to a greater number of twins and reached the same conclusions however he was

also unable to determine the specific genetic factor that contributed to the similarity of caries incidence between the monozygotic twin.[22] The analysis of twins raised apart provides the strongest evidence of a genetic contribution to the incidence of dental caries. The similarity in dental caries experience between monozygotic twins reared apart may be either a higher or a lower caries incidence. The analysis of dental caries incidence in monozygotic and dizygotic twins indicates that a large number of different genes contribute to the observed outcomes. Although the twin studies provided strong evidence of a genetic contribution to dental caries risk, none of the studies provided any evidence of linkage to specific genes.

GENETIC MODIFICATION OF DENTAL ENAMEL ALTERING SUSCEPTIBILITY TO DENTAL CARIES

The understanding of the genes that produce the enamel matrix has greatly expanded in the past few years as genome information has been developed. Several investigators have contributed to the cloning of enamel matrix genes, chromosomal localization of the genes and linkage of genes to human syndromes of altered tooth development.[23-30] In each of these analyses a highly defined clinical phenotype is available to identify the altered biomineralization matrix protein and to begin to search the genome for linkage to a precise change in DNA sequence. These types of studies provide a model for the approach to genetic linkage that can be used when the clinical phenotype is highly defined.

Numerous reports exist that mention dental caries as a component of a well defined inherited genetic syndrome with craniofacial phenotypes.[31-44] These case reports and small sample surveys often document alterations in the morphology of teeth and formation of the enamel as well as the caries experience of the patient. Although this information is available a correlation with genotype is precluded. These few sample references demonstrate the problems

in linking the genetic syndrome, often resulting from a single gene mutation, to the incidence of dental caries. It may be possible in the future to better analyze the genetic contribution to the dental caries incidence when the specific genes responsible for the syndrome are more well characterized.

One syndrome with alterations to the dental hard tissues and increased caries susceptibility, epidermolysis bullosa (EB), has been characterized. This syndrome has been shown to have both an alteration in the enamel and an increased caries incidence.[45-48] The analysis of the EB reports is presented in Evidence Table 2. The mutations in EB result in four different forms of the disease: recessive dystrophic; dominant dystrophic; junctionalis, and simplex. Wright examined 252 patients and characterized the caries disease incidence with the specific type of EB.[46] Analysis of the four forms has shown that two of the variants, EB-junctionalis and EB-recessive dystrophic, are associated with increased incidence of dental caries. The enamel from patients with these two variants has been analyzed for features that might result in the predisposition to dental caries.[47-48] The junctionalis form has been shown to have altered chemical composition of the enamel while the recessive dystrophic form does not exhibit altered enamel. Patients affected by EB have multiple associated oral mucosal complications associated with the separation of the mucosa and attendant complications. The evidence is strongest for EB-junctionalis that a primary defect in the enamel secondary to the disease has resulted in the increased dental caries risk. 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; β4-integrin, 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. The precise mechanism has not been determined however EB provides the best evidence for a syndrome related gene defect directly altering the tooth hard tissue and rendering the tooth more susceptible to dental caries.

GENETIC MODIFICATION OF IMMUNE RESPONSE ALTERING SUSCEPTIBILITY TO DENTAL CARIES

Individuals with either an inherited or acquired immune deficiency are subject to increased risks for and incidence of dental caries.[49] Animal models of differential caries susceptibility have also been linked to immune complex loci.[50] These observations have led to analyses of specific immune complex molecules for association with increased risks for caries. The analysis of the reports on the linkage of immune complex types with altered enamel development are included in Evidence Table 3. The earliest study was conducted by Lehner et al who analyzed the distribution of HLA DR antigens in a group of 24 individuals with either high or low DMFS indices.[51] In this study it was shown that HLA DRw6-1,2,3 had a significant relationship to the DMFS index and to low dose response to Streptococci mutans antigens. HLA-DR4 did not demonstrate the same relationship to caries incidence. A similar study was conducted by de Vries on military recruits matched for all criteria other than caries-free and caries-active.[52] The de Vries study did not detect a relationship between the HLA DR types and caries incidence. Recent studies by Senpuku and Acton have correlated specific HLA DR types with binding *S. mutans* antigens and *S. mutans* colonization.[53-54] Acton concluded that "genes within MHC modulate the level of oral cariogenic organisms," however their study of 186 African-American women did not demonstrate a positive correlation between HLA type and

DMFS. Analysis of celiac disease patients has also demonstrated a significant positive correlation between the HLA typing and the presence of enamel defects that predispose 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.[55-57] Mariani had a similar result with HLA-DR3 associated with increased enamel defects and HLA-DR5,7 were associated with a reduced frequency of enamel defects.[58] Celiac disease patients have an increased incidence of dental caries and the enamel defects correlated with the disease process may play a specific role.[55] The enamel defects in celiac disease, although correlated with the HLA-DR type, have not been attributed to a specific enamel-altering mechanism associated with the disease. Two different lines of investigation have provided evidence that the genes in the HLA complex are associated with altered enamel development and increased susceptibility to dental caries. The role of these genes in the immune response to cariogenic bacteria represents a mechanism that is based on inherited genetic complements and thus provides the opportunity in the future to future example specific allelic variants of these genes as a potential marker for increased dental caries risk.

INHERITED ALTERATIONS IN SUGAR METABOLISM ALTERING SUSCEPTIBILITY TO DENTAL CARIES

There were a very limited number of reports in this area and the literature was not sufficiently detailed to permit an evidence-based review. Early reports examined the relationship of sugar tasting and dental caries and identified a paradoxical relationship between the sensitivity to taste sugar and the incidence of dental caries.[59] Hereditary fructose intolerance is a genetic condition that has a direct relationship to the rationale for the stated question, however only a

limited number of small series studies exist.[60,61] In these series there is a statistically significant difference in the caries experience of individuals with hereditary fructose intolerance and non-affected controls, however this is directly related to the absence of cariogenic sugars in the diet. 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.

GENETIC REGULATION OF SALIVARY GLAND FUNCTION ALTERING SUSCEPTIBILITY TO DENTAL CARIES

The fourth search question was based on the observation that xerostomia is associated with dramatically increased rates of dental caries. The topic of saliva and salivary function has been reviewed in detail in another systematic review in the conference and further discussion of those results have not been included in this paper.[62]

SUMMARY

The year 2001 has seen the publication of the initial complete human genome sequence from two competing international collaborations.[1,2] This resource will permit genetic evaluations that were impossible previously and dramatically extend the understanding of the genetic contribution to disease etiology and progression. As recently as two decades ago twin studies provided critical information linking genetics and disease susceptibility. The human genome will provide an unprecedented opportunity to extend the findings. Already the results developed from the human genome sequence have provided evidence that humans have far fewer genes than previously predicted and consequently individual genes may provide multiple proteins, each with

a different set of properties. The variation in proteins can contribute to the susceptibility for dental caries if a specific protein or a set of different proteins result in altering the host target, host immune response or salivary interacting factors. Future examinations will continue to examine the different genes critical to the development of craniofacial structures and the maintenance of intraoral homeostasis. Current evidence supports the linkage of altered dental enamel development with increased susceptibility to dental caries. Increased enamel porosity, decreased mineral content and the presence of enamel crystal inhibitory proteins all are directly linked to dental caries risk. At the present time these results are limited to defined populations with a recognizable genotype-phenotype relationship. In the future these studies may be extended to individuals without the syndromic phenotype but exhibiting altered susceptibility to dental caries, and allelic variants and protein isoforms will be correlated with genetic susceptibility to dental caries. Current evidence also supports the relationship of immune complex genes and different levels of cariogenic bacteria and enamel defects. The role of these genes and the functionality of the multiple protein isoforms should provide further information linking specific allelic inheritance and caries susceptibility. The multifactorial nature of dental caries has limited the opportunity to link patterns of inheritance with susceptibility to dental caries. The 21st century has brought a new resource, the human genome sequence, that will provide new avenues to investigate the different components contributing to the risk for dental caries.

REFERENCES

1. Venter C, et al. The sequence of the human genome. Science 2001;291:1304-51.

2. International Human Genome Sequencing Consortium. Initial sequence and analysis of the human genome. Nature 2001;409:860-921.

3. Hunt HR, Goodman HO. The inheritance of resistance and susceptibiltiy to dental caries, Int Dent J 1962;12:306-21.

4. Horowitz SL. Clinical aspects of genetic research in dentistry. J Dent Res 1963;42:1330-43.

5. Niswander JD. Effects of heredity and environment on development of dentition. J Dent Res 1963;42:1288-98.

6. Niswander JD. Genetics of common dental disorders. Dent Clin North Amer 1 1975;9:197-206.

7. Mandel ID. Relation of saliva and plaque to caries. J Dent Res 1974;53:246-66.

8. Mandel ID. Nature vs. nurture in dental caries. J Amer Dent Assoc 1994;125:1345-51.

9. Sofaer JA. Host genes and dental caries. Br Dent J 1993;175:403-9.

10. Hassell TM, Harris EL. Genetic influences in caries and periodontal diseases. Crit Rev Oral Biol Med 1995;6:319-42.

11. Townsend GC, Aldred MJ, Bartold PM. Genetic aspects of dental disorders. Aust Dent J 1998;43:269-86.

12. Chung CS, Runck DW, Niswander JD, Bilben SE, Kau MCW. Genetic and epidemiologic studies of oral characteristics in Hawaii's school children: I. Caries and Periodontal diseases. J Dent Res 1970;49:1374-85.

13. Bachrach FH, Young M. A comparison of the degree of resemblance in dental characters shown in pairs of twins of identical and fraternal types. Br Dent J 1927;48:1293-1304.

14. Goldberg S. The dental arches of identical twins. Dental Cosmos 1930;72:869-81.

15. Horowitz SL, Osborne, RH, DeGeorge FV. Caries Experience in Twins. Science 1958;128:300-1.

16. Mansbridge JN. Heredity and dental caries. J Dent Res 1959;38:337-47.

17. 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.

18. Finn SB, Caldwell RC. Dental caries in twins I. A comparison of caries experience of monozygotic twins, dizygotic twins and unrelated children. Arch Oral Biol 1963;8:571-85.

19. Bordoni N, Dono R, Manfredi C, Allegrotti I, Prevalence of dental caries in twins. J Dent Children 1973;40:440-3.

20. Fairpo CG. Total caries experience in monozygotic and like-sexed dizygotic twins of Caucasoid origin aged 5 to 15 years. Arch Oral Biol 1979;24:491-4.

21. Boraas JC, Messer LB, Till MJ. A genetic contribution to dental caries, occlusion and morphology as demonstrated by twins reared apart. J Dent Res 1988;67:1150-5.

22. Conry JP, Messer LB, Boraas JC, Aeppli DP, Bouchard TJ. Dental caries and treatment characteristics in human twins reared apart. Arch Oral Biol 1993;38:937-43.

23. Aldred MJ, Crawford PJM, Roberts E, Thomas NST. Identification of a nonsense mutation in the amelogenin gene (AMELX) in a family of X-linked amelogenesis imperfecta (AIH1). Hum Genet 1992;90:413-6.

24. George A, Gui J, Jenkins NA, Gilbert DJ, Copeland NG, Veis A. In situ localization and chromosomal mapping of the AG1 (Dmp1) gene. J Histochem Cytochem 1994;42:1527-31.

25. Lench NJ, Brook AH, Winter GB. SSCP detection of a nonsense mutation in exon 5 of the amelogenin gene (AMGX) causing X-linked amelogenesis imperfecta (AIH1). Hum Molec Genet 1994;3:827-8.

26. Deutsch D, Palmon A, Dafni L, Catalano-Sherman J, Young MF, Fisher LW. The enamelin (tuftelin) gene. Int J Dev Biol 1995;39:135-43.

27. Lagerstrom-Fermer M, Nilsson M, Backman B, Salido E, Shapiro L, Pettersson U, Landegren U. Amelogenin signal peptide mutation: Correlation between mutations in the amelogenin (AMGX) and manifestations of X-linked amelogenesis imperfecta. Genomics 1995;26:159-62.

28. MacDougall M, DuPont BR, Simmons D, et al. Ameloblastin gene (AMBN) maps within the critical region for autosomal dominant amelogenesis imperfecta at chromosome 4q21. Genomics 1997;41:115-8.

29. Wright JT, Kula K, Hall K, Simmons JH, Hart TC. Analysis of the tricho-dento-osseous syndrome genotype and phenotype. Am J Med Genet 1997;72:197-204.

30. Price JA, Bowden DW, Wright JT, Pettenati MJ, Hart TC. Identification of a mutation in DLX3 associated with tricho-dento-osseous (TCO) syndrome. Hum Molec Genet 1998;7:563-9.

31. Myllarniemi S, Holmerg PC. Caries resistance in children with congenital chloride diarrhoea. Arch Oral Biol 1975;20:239-40.

32. Takala I, Alvesalo L, Palin-Palokas T, Paunio K, Suoranta K. Caries prevalence in Turner's syndrome (45, X females). J Dent Res 1985;64:126-8.

33. Shellhart WC, Casamassimo PS, Hagerman RJ, Belanger GK. Oral findings in fragile X syndrome. Am J Med Genet 1986;23:179-87.

34. Schroeder HW, Sybert VP. Rapp-Hodgkin ectodermal dysplasia. J Pediatr 1987;110:72-5.

35. Wechsler MA, Papa CM, Haberman F, Marion RW. Variable expression in focal dermal hypoplasia. An example of differential X-chromosome inactivation. Am J Disease Child 1988;142:297-300.

36. Dahllot G, Ussisoo-Joandi R, Ideberg M, Modeer T. Caries, gingivits and dental abnormalities in preschool children with cleft lip and/or palate. Cleft Palate J 1989;26:233-7.

37. Anavi Y, Mintz SM. Prader-Labhart-Willi syndrome. Annals Dent 1990;49:26-9.

38. Nance MA, Berry SA. Cockayne syndrome: review of 140 cases. Am J Med Genet 1992;42:68-84.

39. Da Fonseca MA, Mueller WA. Hallerman-Streiff syndrome: case report and recommendations for dental care. J Dent Child 1994;61:334-7.

40. Lukinmaa P-L, Waltimo J, Pirinen S. Microanatomy of the dental enamel in autoimmune polyendocrinopathy-candidiasis-ectodermal dystropy (APECED): Report of three cases. J Craniofac Genet Dev Biol 1996;16:174-81.

41. Karlstedt E, Kaitila I, Pirinen S. Phenotypic features of dentition in diastrophic dysplasia. J Craniofac Genet Dev Biol 1996;16:164-73.

42. Bokhout B, Horman FX, van Limbeek J, Kramer GJ, Prahl-Andersen B. Incidence of dental caries in the primary dentition in children with a cleft lip and/or palate. Caries Res 1997;31:8-12.

43. Paul T, Brandt RS. Oral and dental health status of children with cleft lip and/or palate. Cleft Palate Craniofac J 1998;35:329-32.

44. Rolling I, Clausen N, Nyvad B, Sindet-Pedersen S. Dental findings in three siblings with Morquio's syndrome. Int J Pediat Dent 1999;9:219-24.

45. Wright JT, Fine JD, Johnson LB, Steinmetz TT. Oral involvement of recessive dystrophic epidermolysis bullosa inversa. Am J Med Genet 1993;47:1184-8.

46. Wright JT, Fine JD, Johnson L. Dental caries risk in hereditary epidermolysis bullosa. Pediat Dent 1994;16:427-32.

47. Kirkham J, Robinson C, Strafford SM, et al. The chemical composition of tooth enamel in recessive dystrophic epidermolysis bullosa: significance with respect to dental caries. J Dent Res 1996;75:1672-8.

48. Kirkham J, Robinson C, Strafford SM, Shore RC, Bonass WA, Brookes SJ, Wright JT. The chemical composition of tooth enamel in junctional epidermolysis bullosa. Arch Oral Biol 2000;45:377-86.

49. Madigan A, Murray PA, Houpt M, Catalanotto F, Feuerman M. Caries experience and cariogenic markers in HIV-positive children and their siblings. Pediat Dent 1996;18:129-136.

50. Suzuki N, Kurihara Y, Kurihara Y. Dental caries susceptibility in mice is closely linked to the H-2 region on chromosome 17. Caries Res 1998;32:262-265.

51. Lehner T, Lamb JR, Welsh KL, Batchelor RJ. Association between HLA-DR antigen and helper cell activity in the control of dental caries. Nature 1981;292:770-772.

52. De Vries RR, Zeylemaker P, van Palenstein-Helderman WH, Huis in't Veld JH. Lack of association between HLA-DR antigens and dental caries. Tissue Antigens 1985;25:173-174.

53. Senpuku H, Yanagi, K, Nisizawa T. Identification of Streptococcus mutans PAc peptide motif binding with human MHC class II molecules (DRB1-0802, 1101, 1401 and 1405). Immunology 1998;95:322-330.

54. Acton RT, Dasanyake AP, Harrison RA, et al. Association of MHC genes with levels of caries-inducing organisms and caries severity in African-American women. Human Immunol 1999;60:984-989.

55. Aine L, Maki M, Keyrilainen O, Collin P. Dental enamel defects in celiac disease. J Oral Path Med 1990;19:241-245.

56. Aine L. Coeliac-type permanent-tooth enamel defects. Annal Med 1996;28:9-12.

57. Aguirre JM, Rodriquez R, Oribe D, Vitoria JC. Dental enamel defects in celiac patients. Oral Surg 1997;84:646-650.

58. Mariani P, Mazzilli MC, Lionetti P, et al. Coeliac disease, enamel defects and HLA typing. Acta Paediatrica 1994;83:1272-1275.

59. Zengo AN, Mandel ID. Sucrose tasting and dental caries in man. Arch Oral Biol 1972;17:605-607.

60. Newbrun E, Hoover C, Mettraux G, Graf H. Comparison of dietary habits and dental health of subjects with hereditary fructose intolerance and control subjects. J Amer Dent Assoc 1980;101:619-626.

61. Saxen L, Jousimies-Somer H, Kaisla A, Kanervo A, Summanen P, Sipila I. Subgingival microflora, dental and periodontal conditions in patients with hereditary fructose intolerance. Scand J Dent Res 1989;97:150-158.

62. Leone CW, Oppenheim FG. Physical and chemical aspects of saliva as indicators of risk for dental caries in humans. J Dent Educ 2001;65:XX.