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內文：

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. 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.

Introduction：

Polarization

In 1899, GV Black wrote that when the family remains in one locality, with the children living under conditions similar to those of their parents in their childhood：

1) particular teeth
2) localities first affected
3) the order of occurrence of cavities
4) the particular age at which they occur

We begin by establishing the role of genetics from the twin model of analysis, followed by linkage/ association studies and conclude by analyzing the various factors directly influencing the host, i.e. the tooth in question.

1. Twins studies

1) Mansbridge：greater similarity between monozygotic twins than dizygotic twins, while unrelated pairs of children showed less similarity
2) Goodman et al.：significant heritability for oral microorganisms, including Streptococci, salivary flow rate, salivary pH and salivary amylase activity
3) Lovelina et al.：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)
4) Rintakoski K et al.：suggesting genetic influence on oral health with possible gender differences(male 49%,female 68%).
5) Corby et al.：genetic or familial factors significantly contribute to the colonization of oral beneficial species in twins, and in turn the oral health of an individual.
6) Bretz et al.：genetic influence for caries incidence is at its highest when dentitions are emerging.

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.

【小結】遺傳對蛀牙有相當程度的影響，可能還牽涉到口腔的菌種表現。其

他伴隨的因子還包含性別、年齡等。

2. Linkage/association studies

1) Klien：It was found that a high DMF(齲齒指數) 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.
2) Klien：siblings of caries-free children had lower average caries scores than the siblings of susceptible children
3) Book and Grahnen：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.
4) Vieira et al.：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.
5) Shimuzu et al.：certain allele in some chromosomes associated with high caries experience while others with lower caries experience
6) Shaffer et al.：Except maxillary anterior teeth, the others are significantly heritable.

【小結】父母與子女、手足之間對個體有相當程度的關聯性。齲齒和其發生的性別、牙齒位置，背後都有基因的影響。

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.

接下來對基因如何調控牙齒構造、飲食偏好、宿主免疫反應、唾液成分來影響蛀牙發生做進一步的討論。

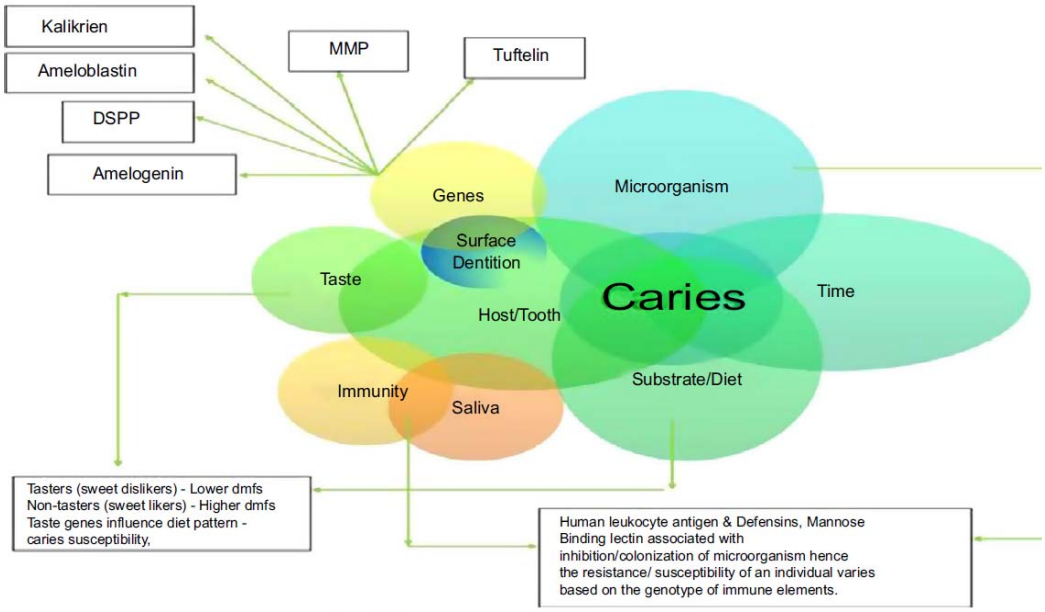

Fig. 1 Venn diagram showing interplay of genetic factors.

3. Tooth genes：

1) Zhang X et al.：Mutation of the dentine sialophosphoprotein gene causes dentinogenesis imperfecta type II.
2) Rajpar et al.：mutation in gene encoding enamel specific protein enamelin

caused autosomal dominant amelogenesis imperfecta.

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.

3) Shimuzu et al.：Two alleles was significantly higher in a high caries 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.
4) Kang et al.：SNPS in AMELX of rs5933871 and rs5934997 were significantly associated with caries susceptibility.
5) Shaffer et al.：heritability for pit-and-fissure and smooth-surface caries in the primary dentition was greater than the permanent dentition. Genetic factors exert different effects on caries risk in pit-and-fissure versus smooth-surface in the primary dentition.(Zeng et al.：BCOR gene－pit-and-fissure, BCORL1－smooth-surface)

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.

【小結】組成牙齒的蛋白基因發生變異，會造成礦化程度不全而容易蛀牙。而基因對乳恆齒列齲齒及發生位置也有不同的影響。

4. Taste genes：

1) Wendell et al：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
2) Fushan AA et al.：SNP located at rs307355 and rs35744813 of the TAS1R3 coding sequence strongly correlate with human taste sensitivity to sucrose.
3) Kulkarni et al.：SNP in the sweet taste receptor (TAS1R2) and glucose transporter (GLUT2) genes individually and in combination are associated with caries risk.
4) Pidmale et al.：tasters (sweet dislikers) had lower dmfs values compared to non-tasters (sweet likers).

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.

【小結】基因會影響飲食偏好，而嗜吃甜食的人容易蛀牙。

5. Immunity：

1) Bagherian et al.：Being positive for the HLA DR 4 allele increases the risk for early childhood caries 10 times more compared to the caries-free group.
2) Acton et al.：

－High levels of Streptococcus mutans were positively associated with the presence of DR3 and DR4 alleles

－TNFa allele103 was negatively and TNFa 117 was positively associated with high levels of Lactobacillus acidophilus.

3) Lehner T et al.：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.
4) McCarlie et al.：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.
5) Defensins：Ozturk et al. 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
6) Mannose-binding lectin (MBL)：Olszowski 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.

【小結】人體的免疫蛋白基因表現可能影響蛀牙發生，人種間的差異有待進一步的研究。

6. Saliva：

1) Zakhary et al.：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.
2) Jonasson et al.：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.
3) Yu PL et al.：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).
4) Azevedo et al.：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.

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.

【小結】基因會影響唾液成分，改變 biofilm 的組成而影響蛀牙的發生。

Conclusion：

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.

問題討論

1.	Risk factors for dental caries?	
	(A)	Bacteria
	(B)	Tooth / Host
	(C)	Diet

	(D)	Time
	(E)	All of above
答案 (E)	出處：Prevention in Clinical Oral Health Care P.45 作者：David P. Cappelli，Connie C. Mobley	
2.	dentinogenesis imperfecta 的特徵不包括：	
	(A)	Gray to yellowish-brown color
	(B)	Broad crown with constriction of cervical area (tulip shape)
	(C)	Radiographically, the teeth appear solid, lacking of pulp chamber and root canal
	(D)	Enamel is very strong
答案 (D)	出處 Shafer'S Textbook Of Oral Pathology (6Th Edition) P.54-55 作者：R. Rajendran	

1	基因可以藉由下列哪些方式影響蛀牙的機率? Genetic factors can not affect dental caries risk by: (A) 口水的組成 the component of saliva (B) 口水的流量 the level of saliva flow (C) 牙齒的結構 the structure of tooth (D) 飲食的偏好 Determine his or her food preferences (E) 以上皆是 All of the above
答 案 (E)	出處：Genetic factors affecting dental caries risk. Aust Dent J 2015;60:2-11
2	在基因影響蛀牙機率的相關研究當中，我們不能發現 According from this article, we can ‘t figure out: (A) 蛀牙相關基因跟性別無關 dental caries risk have nothing to do with gender differences (B) 蛀牙相關的基因對於乳齒列跟恆齒列的影響是一樣大的 heritability for caries in the primary dentition s is the same in the permanent dentition (C) 喜歡吃甜食與否會影響蛀牙機率 tasters (sweet dislikers) have lower caries rate when compared to non-tasters (sweet likers). (D) 同卵雙胞胎在口腔疾病表現的相似度比異卵雙胞胎高 monozygotic twin pairs had higher correlation rates for oral dieases than dizygotic twin pairs
答 案 (A)	出處：Genetic factors affecting dental caries risk. Aust Dent J 2015;60:2-11