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Evidence of a contribution of genetic factors to dental caries risk

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Summary

Dental practitioners would find value in understanding the genetic contribution to caries risk for at least 2 reasons. First, they would be able to explain to patients that some forms of decay are more strongly associated with inherited risk. This would help explain for both the patient and dentist why persons with similar behavioral risks (eg, tooth brushing frequency or dietary habits) have different caries rates, thus avoiding the “blaming the victim” that sometimes accompanies preventive health messages in dentistry. In addition, future technological developments may make it possible to some day identify patients who are genetically at higher risk for caries. These patients then could be monitored more closely and provided with more aggressive prevention programs.

SUBJECTS

The literature was searched for evidence of a contribution of genetic factors to increased or decreased risk for dental caries. A search for global evidence of caries heritability was carried out using twin studies. Next, separate searches were carried out for evidence of heritability for 3 potential mechanisms associated with caries risk that included variation in the quality of the dental hard tissues, variation in host immune response, and variation in sugar metabolism. Each of the 4 searches is treated separately below. Inclusion criteria for the selected studies were not provided. No meta-analysis was attempted, since the selected studies, particularly twin studies, employed different statistical models to assess heritability (correlation coefficients, concordance rates, heritability estimates and intra-pair twin co-variation).

1. Twin Studies of Global Evidence of Dental Caries Heritability

- 10 articles employing the twin model study design (a total of 609 pairs of monozygotic (MZ) twins and 569 pairs of dizygotic (DZ) twins)
- 50% of studies with children and adolescents of an age range of 3 to 17 years
- 40% of studies in young adults and adults

2. Studies of Inherited Variations in Dental Enamel

- 4 reports employing cohort and case-control study designs in participants with epidermolysis bullosa

3. Studies of Inherited Variations in Immune Response
 - 7 reports of MHC analysis (immune complex genes) utilizing cohort and case-control study designs
 - At least 60% of the studies were in adults
4. Studies of Inherited Variations in Dietary Patterns and Sugar Metabolism
 - Literature too scarce to permit evidence-based review

EXPOSURE

Genetic factors that lead to variation in hard tissue quality, immune response, and sugar metabolism.

MAIN OUTCOME MEASURE

1. The primary outcome measure was dental caries phenotypic expression measured as Delayed, Missing, Filled (DMF) or def.
2. Secondary outcome measures included enamel content and cariogenic bacteria (the mutans streptococci and lactobacilli).

MAIN RESULTS

1. Twin studies provided evidence that a genetic contribution to dental caries phenotypic variation exists (Table 1).
2. The epidermolysis bullosa syndrome provides evidence for a gene defect directly altering the tooth structure and rendering it more susceptible to dental caries.
3. Genes in the Human Leucocyte Antigen complex are associated with altered enamel development, increased risk for dental caries and increased predisposition to cariogenic infections.
4. Evidence-based review did not reveal or made it possible to identify any links between inherited alterations in sugar consumption.

Commentary

CONCLUSIONS

Twin studies provide the opportunity to dissect the relative contribution of genetics and environment on dental caries variation. Accordingly, these studies can often suggest, but not prove, biological inheritance. Current evidence supports the notion that there is an inherited variation in enamel development that is associated with increased occurrence of dental caries. At present, these results are limited to specific populations with overt recognizable syndromes.

Evidence is presented that immune complex genes may modulate the presence of enamel defects and colonization of cariogenic bacteria.

ANALYSIS

Twin studies of dental caries have shown that genetic and environmental factors play significant roles. However, estimates of heritability from the reports reviewed (Table 1) display considerable variability, no doubt, caused by differences in statistical analysis models, age, gender, sample size, origin of cohorts and measurement of dental caries phenotype. In addition, cohort and case-control studies linking a particular gene to dental

caries are too few and these studies often neglect the role of environmental factors on dental caries development that could interact with genetic factors to induce disease. Consequently, a rigorous meta-analysis of the literature is problematic. The author, however, has conducted a thorough evidence-based review with the limited existing literature, and some level of evidence has emerged suggesting that inheritance contributes in important ways to dental caries susceptibility.

WEEKNESSES AND STRENGTHS

A major concern with this review article is that no criteria for study selection are provided.

The approach provided by the twin study model is driven by the fact that identical (MZ) twins share all their genes, whereas fraternal (DZ) twins, like siblings, share on average half their genes. If a particular trait is highly correlated between MZ twins and less correlated between DZ twins, one could infer that a genetic contribution to variation in that particular trait exists. In this review, the statistical approaches of data analysis to studies of dental caries in twins included the use of correlation coefficients, concordance/discordance rates, heritability estimates, and analysis of intra-pair covariances. This heterogeneity in statistical methodology prevented results from being evaluated by meta-analysis. More importantly, little attention was given to the measurement of dental caries traits *per se* and to methodological issues in dental caries research on the relative contribution of gene-environment interactions. Some of the studies reviewed suggested a stronger environmental contribution to caries experience, because MZ and DZ twins did not differ in these traits. Others found that resemblance in caries experience was stronger in MZ twins when compared to DZ twins, leading the researchers to conclude that this similarity was a result of a genetic contribution. The reasons for contradictory findings may lie in the different methodological techniques employed by the investigators, as well natural variation in dental caries, age effects, lengths of the studies, cultural backgrounds, variables analyzed, the measurement and clinical assessment of dental caries, and restorative treatment philosophies, among others.

Only one study (Bachrach & Young, 1927) enrolled children who had not received dental treatment. This is an important consideration when studying dental caries, because it eliminates potential effect modifiers such as treatment effects, dental attendance, and fluoride exposure, if genetic modulation of the phenotype is being evaluated. Moreover, it is also important to study surfaces of teeth as they transition from sub-clinical disease to clinical disease. This requires longitudinal investigations that are of an adequate length to study the onset and progression of the caries process and that employ contemporary objective methods to measure dental caries such as quantitative light fluorescence and digital imaging fiber-optic trans-illumination.

The age of the cohort of interest for studies of dental caries has to be defined. The age range of the majority of the studies reviewed was too large, which might explain the contradictory results reported. If dental caries susceptibility is indeed inherited, then its onset likely starts in infancy, affecting the primary dentition and, without intervention, it could extend to the permanent dentition. Accordingly, it is within this time frame that tooth surfaces are more susceptible to the mechanisms of de- and re-mineralization. Furthermore, variations in the magnitude or severity of lesions must be measured to determine variations along the continuum from an absolute state of dental health to rampant caries manifestation.

For most studies of dental caries using twin samples, the actual sample size was too small to derive definitive conclusions. For instance, a subsequent small change in sample size of an originally low sample size can alter heritability estimates (Boraas et al, 1988; Conry et al, 1993). In addition, some studies have employed a limited number of teeth in the analysis,

which makes it difficult to generalize to the overall state of resistance or susceptibility to dental caries for a particular person.

Serological assessment of zygosity was not performed in many of the studies reviewed. Because the basis of twin studies lies on comparisons of MZ and DZ twins, every twin requires a reliable method of identification. A visual criterion for ascertainment of twins has been found to be 90 to 95% accurate (Cavalli-Sforza and Bohmer, 1971).

DMFT/S or def/s scores are not true rates of caries attack but counts of tooth morbidity. Most studies of dental caries in twins employed this index for caries examination. Given the wide range of ages in most of these studies, a 58-year-old person with 3 teeth and 2 of them decayed is not comparable to a 15-year-old with 28 teeth and 2 of them decayed. In other words, no surface-specific rates were used in these studies that could provide an overall measure of liability for a subject. In addition, the statistical methods applied in most of the published twin studies were for the most part simplistic in the light of more sophisticated recent methods of twin analysis (Neale and Cardon, 1992). Caries assessment for most studies was performed under less than ideal conditions and sometimes not described at all in the methods of the study. The precise description of caries traits is of paramount importance if a genetic contribution to a particular trait is being determined clinically or if genotype-phenotype associations are being performed.

Increased enamel porosity, decreased mineral content, and enamel crystal inhibitory proteins are well characterized in syndromic phenotypes leading to increased caries development. These findings, as the author acknowledges, have to be extended to persons of the general population exhibiting altered susceptibility to dental caries. Genes that regulate the immune complex have been associated with increased colonization of cariogenic bacteria and enamel defects, which provides the possibility of linking specific allelic variation and caries susceptibility in the general population.

Lastly, the author recognizes that the multifactorial nature of dental caries has precluded direct correlations of inheritance with dental caries. Twin study designs can be developed that can accommodate important covariates (eg, sucrose taste preference, enamel porosity, pit and fissure anatomy, cariogenic organisms, salivary protein-rich peptides, behavioral markers, salivary gland function, among others) as to dissect the contributions of gene and environment to the phenotype. Moreover, information on the association of genetic markers spanning the whole genome with dental caries susceptibility and related phenotypes may actually become possible with the recent decoding of the human genome.

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TABLE 1

Evidence for genetic contribution to dental caries through analysis of twins

Year	Authors	Study design	Study population	Controls	Genetic analysis	Caries assessment	Data analysis	Conclusions
1927	Bachrach & Young	Matched pairs	MZ Twins (130) 3–14 yrs	DZ Twins (171)	Zygosity Testing	DMF, dmf	Correlation MZ and caries 0.67	Heridity a subsidiary part in caries incidence
1930	Goldberg	Comparative	MZ & DZ Twins 42 pairs		Zygosity Testing	Arch form	Comparison	Heridity affects caries through tooth form
1958	Horowitz et al.	Matched pairs	MZ Twins (30)	DZ Twins (9)	Zygosity Testing	Caries Experience Ratio	F-Test p<0.001	MZ Greater caries concordance
1959	Goodman et al.	Matched pairs	MZ Twins (19) 19 yrs	DZ Twins (19)	Zygosity Testing	Caries Experience Ratio	F-Test p<0.05	Intrapair variance of DZ greater than MZ
1959	Mansbridge	Matched pairs	MZ Twins (96) 5–17 yrs Age/Sex/Eruption	DZ (128) Unrelated (112)	Zygosity Testing	DMF, dmf p<0.001	Chi-square	Genetic contribution less than environment
1963	Finn and Caldwell	Matched pairs	MZ Twins (35) 7–15 yrs	DZ Twins (31) Unrelated (25)	Zygosity Testing	DMF, dmf	F-Test p<0.0005	Smooth surface caries greater genetic link
1973	Bordoni et al.	Matched pairs	MZ Twins (17) 4–8.5 yrs	Unrelated (17)	Zygosity Testing	dmf	F-Test p<0.001	Genetic contribution less than environment
1979	Faipor	Matched pairs	MZ Twins (100) 5–15 yrs	DZ Twins (120)	Zygosity Testing	DMF, dmf	F-Test p<0.001	Genetic contribution to caries for deciduous & permanent dentitions
1988	Boraas et al.	Matched pairs	MZ Twins (64) 40 yrs Reared apart	DZ Twins (33) 40yrs Reared apart	Zygosity Testing	DMFS	2-way ANOVA p<0.001	Marked genetic component to dental caries experience
1993	Conry et al.	Matched pairs	MZ Twins (46) 40 yrs Reared apart	DZ Twins (22) 40 yrs Reared apart	Zygosity Testing	DMFS	2-way ANOVA p<0.005	Teeth present, surfaces restored and caries attributable to genetic variance

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