DOI: https://doi.org/10.17921/1415-6938.2020v24n4p416-421

Genetic Pattern of Dental Caries in Families from a City in Southern Brazil

Padrão Genético da Cárie Dentária em Famílias de uma Cidade do sul do Brasil

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Abstract

Genetic factors may play an important role in the susceptibility to dental caries of the human population. The objective of this study was to investigate, by means of complex segregation analysis (CSA), the intergeneration pattern in the occurrence of caries in Brazilian families. This was a cross-sectional, observational genetic epidemiological study. The sample consisted of 21 families whose probands exhibited high levels of caries (DMFT>4.5). All participants underwent an oral examination. Dental caries was recorded according to the DMFT index (decayed, missing, and filled teeth), according to World Health Organization guidelines and the presence of gingivitis was assessed by using the gingival bleeding index. A questionnaire was applied to identify the sociodemographic profile and practices on oral health. Simple and multiple linear regression analysis were performed to test the association between dental caries and the independent variables. Statistical significance was considered at the 5% level. The S.A.G.E program drove the CSA. The prevalence of caries was 89.2%. In the multiple analysis only gingivitis remained associated (p = 0.005). The visual analysis of genograms identified a family pattern that suggests the predominance of the autosomal dominant model. The frequency of resistance allele “A” was estimated at 0.22. The mean decay value was 1.35 for AA and AB genotypes and 3.95 for BB. The results of the present study provide evidence as to the presence of a major gene with a dominant effect controlling the appearance of dental caries, within the same family.

Keywords: Dental Caries. Genetic Epidemiology. Oral Rehabilitation. Susceptibility.

Resumo

Fatores genéticos desempenham um importante papel na susceptibilidade à carie dentária na população. O objetivo deste estudo foi investigar, por meio da análise de segregação complexa (ASC), o padrão intergeracional da ocorrência da cárie dentária em famílias brasileiras. O estudo foi epidemiológico genético, observacional e transversal. A amostra foi constituída de 21 famílias que exibiam altos níveis de cárie (CPOD>4.5). Os participantes passaram por avaliação bucal, sendo que a cárie dentária foi registrada de acordo com o índice CPOD (dente cariado, perdido e obturado), seguindo as diretrizes da Organização Mundial de Saúde, bem como a presença de gengivite foi avaliada utilizando o índice de sangramento gengival. Foi aplicado um questionário para identificação dos fatores socioenconômicos e práticas de saúde bucal. Análises de regressão linear simples e múltipla foram realizadas para testar a associação entre cárie dentária e as variáveis independentes. A significância estatística foi considerada no nível de 5%, a ASC foi interpretada pelo programa S.A.G.E. A prevalência de cárie foi de 89,2%. Na análise múltipla, apenas a gengivite permaneceu associada (p = 0,005). A análise visual dos genogramas identificou um padrão familiar que sugere a predominância do modelo autossômico dominante. A frequência do alelo de resistência “A” foi estimada em 0,22. O valor médio de cárie foi de 1,35 para os genótipos AA e AB e de 3,95 para o BB. Os resultados do presente estudo fornecem evidências da presença de um gene importante com efeito dominante no controle do desenvolvimento de cárie dentária dentro da mesma família.

Palavras-chave: *Cárie Dentária. Epidemiologia Genética. Reabilitação Oral. Susceptibilidade.*

1 Introduction

Oral diseases, especially dental caries and periodontitis, are one of the most common public health issues worldwide with significant socio-economic impacts, and yet it is frequently neglected in public health policy (JIN *et al.*, 2016).

Pattern recognition of the risk factors that modulate dental caries will help the health care provider halt and overcome the destruction caused by dental caries. The factors are genetics, bacterial activity, diet, saliva, and pH (WONG; SUBAR; YOUNG, 2017).

In recent systematic review, it was found that 27 genes are associated with dental caries development. At the genetic level, 23 genes have at least one other gene with which they interact. The genes TUFT1, VDR, TFIP11, LTF, HLA-DRB1, MMP2, MMP3 and MUC5B were shown to be connected in interactive networks by at least 10 other genes (CAVALLARI *et al.*, 2019). However, no descriptions of the genetic model involved have been performed in respect of populations containing extreme phenotype (high DMFT index – decayed, missing or filled permanent teeth).

In order to determine the presence of one or more major genes within families that might explain all or part of the family aggregation of the trait observed, the complex segregation analysis (CSA) may be used. The goal of CSA is to detect and discriminate between and amongst the different factors causing familial resemblance, ultimately aiming to demonstrate a major gene effect (OPAL *et al.*, 2015)

It should be emphasized that, despite advances in molecular genetics and genome-wide association studies, the exact nature of the genetic component that controls susceptibility to dental caries is still unclear (CAVALLARI *et al.*, 2019). Understanding the genetic aspects involved in the pathogenesis of caries could give rise to preventive strategies for this disease, which is one of the most prevalent in the world (OPAL *et al.*, 2015). One of the oral health targets established for 2020 is to lower the DMFT at 12 years of age, particularly amongst the high-risk groups (HOBDELL *et al.*, 2003).

Thus, the aim of the present study was to investigate the genetic inheritance model which best explains the family segregation pattern for dental caries, in a sample of 12 year-old schoolchildren with high and very high DMFT indices, living in a small municipality of southern Brazil.

2 Material and Methods

2.1 Outline of study

This is an epidemiological study that is genetic, cross-sectional and observational in nature, the population of which is made up of students aged 12 years old who, in 2012, took part in the oral health epidemiological study undertaken by the Municipal Health Department in Ibiporã, a small city in the state of Paraná, Brazil.

The study was approved by the Research Ethics Committee at the Northern Paraná University (#811.740/2014).

2.2 Definition of sample

Eligibility criteria: of the 288 twelve-year-old students, who, in 2012, took part in the epidemiological survey, 25 had a DMFT index classified as high or very high and, therefore, these children and their families were included in the sample of the present study, with at least three accessible generations. For the selection of these individuals, the classification criteria for caries attacks were employed based on the high DMFT (≥ 4.5) following the WHO criteria.(WHO, 1997) All other students, along with their respective families, were excluded from the study.

2.3 Data collection

Data collection was divided into clinical examination and interview, both performed by a single examiner. Prior to the collection, all subjects received information regarding the research study and were invited to sign the free and informed consent form, agreeing to take part in the study. The parents/legal guardians signed the document for minors under the age of 18.

The clinical examinations were conducted at home, in ambient conditions, under indirect natural light, with both examiner and examinee seated, using a wooden tooth pick, flat oral mirror and a WHO probe (CPI probe), after the removal of food debris with gauze, where required. Oral evaluations were made after the process of intra-examiner calibration. To test intra-examiner agreement, 2 families were reassessed observing the same conditions as in the original examination. The data sets were compared using the Kappa test. The Kappa value for the intra-observer repeatability statistical test was 0.8, indicating "very good agreement" between data sets.

For information on demographic and socioeconomic profile, previous and present medical history, oral health behaviour (hygiene habits, dietary habits and frequency of consumption of confections, number and frequency of visits to the dentist during the year, use of fluoride, amongst others), and oral health, a semi-structured questionnaire was employed. In order to evaluate experience and severity of dental caries, the DMFT index was used, following the diagnostic criteria established by the WHO(WHO, 1999)The presence or absence of gingivitis was evaluated through the gingival bleeding index, after a gentle probing of the gingival sulcus applied to all teeth. The severity of the gingivitis was analysed according to the Coutinho and Tostes classification (COUTINHO; AMARAL, 1997) which takes into account the number of gum surfaces that are bleeding in order to determine the severity of gum disease. When there are no bleeding surfaces, gingivitis was considered absent. For all other situations where bleeding surfaces were evident (mild, moderate or severe), it was assumed that gingivitis was present.

To minimize potential errors due to the lack of information with regard to third and fourth generations, some authors use only two generations to calculate penetrance values(DE VRIES *et al.*, 2004). For the present study, three generations were considered so as to make the genograms more informative.

2.4 Statistical analysis

The data collected during the epidemiological survey of the schoolchildren, as well as the data on their family members, were input to the application Statistical Package for Social Science – version 17.0 (SPSS Inc., Illinois, USA). The genograms were drawn using tools available in Microsoft Word 2007.

Initially to test the association between the independent variables and the number of decayed teeth (DT), simple linear analysis was conducted. Next, the multiple linear analysis was performed with the significance level set at 5%.

The Complex Segregation Analysis was performed using the Statistical Analysis for Genetic Epidemiology program (S.A.G.E.) version 6.3, through the segregation analysis program known as SEGREG. The data extracted from the genograms and the SPSS were compiled in Microsoft Excel spreadsheets, which were required for handing off the data to the S.A.G.E. program.

3 Results and Discussion

Of the 25 families selected for the sample, 21 authorized the evaluation. Four did not agree to take part in the research study, even after clarification about the importance of the project. The parents/guardians alleged that they had completed the dental treatment and that when they needed to, they would call back or find a public dental service. These 21 families comprised 197 individuals making up the genograms. The DMFT index was available for 154 individuals who were evaluated by the examiner. Data for 43 subjects were obtained via information from relatives.

Ten families were regarded as complete and with three accessible generations, so only these were included in the analysis. The other families were excluded due to the lack of information (premature death of the proband's grandparents, making it impossible to obtain any information related to oral condition, loss of contact of the biological father, adoptions cases, there for without genetic involvement among family members and family members hospitalized in a rehabilitation clinic, amongst others).

The sociodemographic profile of the schoolchildren and their families is shown in Table 1. Of a total of 157 individuals, the majority (57.3%) were female and of white ethnic (77.9%). Amongst the family members, the mean age was 37.45 ± 23.85 years. Only 39.7% of those interviewed had more than 8 years of schooling. The mean years of schooling was 7.2 ± 3.5 and the average family income was R$ 1,040.97 ± 526.44.

Regarding oral health behavior (Table 1), 42.9% indulged in the habit of eating confections between meals (nibbling) more than 3 times a day; 82.7% brushed their teeth more than once a day; only 34.6% used dental floss, and; 64.2% reported having visited the dentist during the year. It should be emphasized that 89% confirmed having received information about oral health care.

Table 1 - Number of decayed teeth according to characteristics of the studied Brazilian families

Characteristics	N	%	Decayed Component	
			Mean	SD
Sociodemographics				
Gender				
Female	90	57.3	0.90	1.77
Male	67	42.7	1.01	2.37
Skin colour/race				
Not-white	27	22.1	2.04	2.73
White	95	77.9	0.97	2.04
Schooling in years				
≤ 8	47	60.3	2.04	2.62
≥ 9	31	39.7	1.06	2.14
Mean age in years	37,4 ± 23,8			
Mean Family income*	1040,97±526,44			
Oral health behaviors/ information				
Daily between meal frequency				
None	26	31.0	1.73	1.86
≤ 3 times	22	26.2	1.18	2.42
4 times or +	36	42.9	1.72	2.75
Daily tooth brushing frequency				
Once	14	17.3	2.43	3.91
Twice or +	67	82.7	1.43	2.01
Dental floss use				
No	53	65.4	1.96	2.75
Yes	28	34.6	0.93	1.51
Fluoride use				
No	52	64.2	2.00	2.56
Yes	29	35.8	0,90	2.05
Already visited the dentist				
No	29	35.8	2.90	3.14
Yes	52	64.2	0.92	1.57
Number of visits to dentist/last year				
None	34	42.0	2.62	3.07
Once	17	21.0	1.29	1.64
Twice or +	30	37.0	0.63	1.40
Access to oral health information				
No	9	11.0	4.22	3.49
Yes	73	89.0	1.29	2.07
Oral health clinical conditions				
Presence of gingivitis				
No	52	54.2	0.62	1.14
Yes	44	45.8	2.64	3.05

Source: Research data.

Considering the whole sample, the prevalence of caries was 89.2% and the DMFT index ranged from 0 to 28, with a mean score of 15.17±0.97. The analysis of the index by component showed a mean decayed component value of 0.95±2.04. Amongst the schoolchildren, the DMFT index varied between 4 and 16, with a mean value of 8.05±3.11. The analysis of the index by component showed a mean decayed value of 2.42±3.58.

The results of the simple linear regression (Table 2) showed that the following variables were associated with higher scores of the decayed component: having gingivitis ($p < 0.0001$), not using fluoride ($p = 0.050$); not having visited the dentist yet ($p< 0.0001$); not having visited the dentist last year ($p = 0.001$), and not having received information on oral health care ($p < 0.0001$). When all the variables were included in the model, only the presence of gingivitis remained statistically significant when associated with the untreated decayed scores ($p = 0.005$). There was a higher mean decayed component value among individuals with gingivitis (2.64±3.05) when compared to individuals without gingivitis (0.65±1.16).

Table 2 - Linear regression analysis of explanatory variables on decayed component among Brazilian families

Explanatory variables	Unadjusted Regression Coefficient (SE)	*P* value	Adjusted[1] Regression Coefficient (SE)	*P* value
Gender	0.11 (0.33)	0.729	0.06 (0.65)	0.930
Skin colour/race	0.55 (0.24)	0.025	0.16 (0.38)	0.678
Schooling in years	-0.98 (0.56)	0.088	-1.07 (0.55)	0.055
Mean age in years	-0.01 (0.01)	0.110	0.03 (0.02)	0.255
Mean Family income*	0.00 (0.00)	0.299	0.00 (0.00)	0.125
Daily between meal frequency	0.02 (0.31)	0.951	0.44 (0.40)	0.284
Daily tooth brushing frequency	0.99 (0.71)	0.167	-0.49 (0.78)	0.531
Dental floss use	1.03 (0.56)	0.070	-0.20 (0.76)	0.780
Fluoride use	1.10 (0.55)	0.051	-0.32 (0.76)	0.673
Already visited the dentist	1.97 (0.52)	0.000	0.33 (1.38)	0.809
Number of visits to dentist/last year	0.99 (0.28)	0.001	0.23 (0.73)	0.754
Access to oral health information	2.93 (0.79)	0.000	0.97 (0.90)	0.286
Presence of gingivitis	2.02 (0.45)	0.000	1.58 (0.53)	0.005

* Brazilian currency – Reais

Source: Research data.

Table 3 shows that of the 21 families checked, 18 (85.72%) exhibited an autosomal dominant pattern. In two families (9.52%), caries disease was sporadic, suggesting an autosomal recessive model. Only one of the genograms (4.76%) exhibited both the dominant and recessive inheritance patterns.

Amongst the 197 individuals comprising the genograms, 102 (51.78%) were female and 95 (48.22%) were male. The male/female ratio was 1:1.07. Eleven probands (52.38%) were male and 10 (47.61%) were female (Table 3).

Table 3. Distribution of affected individuals and unaffected by gender in 21 families evaluated probands affected by tooth decay

Family	Model	Proband	Affected relatives		Relatives not Affected		Phenotype unknown		Total
			M	F	M	F	M	F	
1	AD	M	3	3	1	2	0	0	10
2	AD	F	3	4	0	1	0	0	9
3	AR	M	4	3	0	0	0	1	9
4	AD	F	2	2	0	0	1	0	6
5	AD	F	3	4	0	1	0	0	9
6	AD	M	5	3	0	0	0	0	9
7	AD	M	5	3	0	0	1	0	10
8	AR	M	3	6	0	0	0	0	10
9	AD	M	2	4	1	0	1	0	9
10	AD	M	3	4	0	1	0	0	9
11	AD	F	1	3	0	0	2	1	8
12	AD	F	6	6	0	0	0	0	13
13	AD/AR	F	6	3	0	0	0	0	10
14	AD	M	3	3	0	0	1	0	8
15	AD	F	4	4	0	0	0	0	9
16	AD	F	3	3	1	1	0	0	9
17	AD	F	3	3	0	0	1	0	8
18	AD	M	3	4	0	0	0	0	8
19	AD	M	4	3	0	0	1	1	10
20	AD	F	3	5	0	0	0	0	9
21	AD	M	4	10	0	0	0	0	15
Total		**11 (M) 10(F)**	**73**	**83**	**3**	**6**	**8**	**3**	**197**

M: male; F: female; AD: Autosomal dominant with complete penetrance; AR: Autosomal Recessive or new mutation. Autosomal only with the affected proband.

Source: Research data.

No correlation was identified between father-mother, father-child or mother-child pairs, so these parameters were not included in this table.

Model I (sporadic model) only included non-genetic covariables with a significant impact on susceptibility to the disease. The variable gingivitis was significantly associated with the decayed component in the multiple regression analysis, therefore it was included in the CSA. In this sporadic model, it is assumed that the phenotype occurs randomly in the studied population, that is to say, in the absence of a major gene or multifactorial components, the values for d were set at [1] and Q at [0]. The sporadic model without family correlation was rejected, as opposed to the model that included the children-children correlation (model I vs. II, $\aleph^2$ (1 df) = 6.11, p = 0.013).

Then, in addition to the significant covariable, the dependency of the decayed phenotype was checked via model II (children-children family correlations). The inclusion of the major gene with a dominant effect maintained a statistically significantly association ($\aleph^2$ (3 df) = 7.89, p = 0.048).

In order to discard the possibility of significant family dependency due to shared environmental factors, a major gene effect was included in the models (models III and IV). With the removal of the residual children-children correlation (model III vs. IV) there was no significant impact ($\aleph^2$ (2 df) = 5.92, p = 0.052). So these results suggest the presence of a major gene controlling the decayed phenotype with an estimated frequency of allele A of 0.22. The mean number of decayed teeth was estimated at 1.35 for individuals with genotypes AA and AB, and 3.91 for BB

The CSA conducted in the present study evidenced the existence of a major gene effect transmitted following a dominant model, with frequency of resistant allele “A” estimated at 0.22. The mean number of decayed teeth value was estimated at 1.35 for individuals with genotypes AA and AB, and 3.91 for BB. After adjusting for age and gingivitis, only the presence of gingivitis maintained an association with a higher number of teeth with active caries in this study population.

These results are in agreement with those described by Werneck et al.(WERNECK *et al.*, 2011)who reported a greater number of teeth with active caries in individuals carrying the BB genotype than in those who carried the AA or AB genotypes. Besides the gingivitis, the authors observed that the age remained associated with the number of active caries, which only increased in the 20-29 age bracket and subsequently diminished. In their research, patients with gingivitis also exhibited a higher mean decayed component value.

Gingivitis and dental caries both have an important, common etiological component in the dental biofilm. Adequate oral hygiene, with the constant and effective disarrangement of this biofilm is necessary for the prevention of these oral pathologies that are common in the general population (45.8%). It should be stressed that gingivitis is an important predictor of a high number of caries lesions.(JULIHN *et al.*, 2006)

A limitation of this study to be considered is the use of the DMFT. The use of a more sensitive index that can measure the severity of the lesion, such as the International Caries Detection and Assessment System (ICDAS), should be considered in forthcoming studies, as well as an evaluation of individuals attending dental clinics, due to the difficulty and restrictions present when conducted in the home environment.

DNA-based molecular studies may, therefore, be able to confirm the genetic effect on susceptibility to caries and explain cases where environmental or behavioural factors would not explain the presence/absence of dental caries. Therefore, it has become essential that a partnership be established between the Public Health Service and Universities (Academia) so as to enable future DNA-based molecular studies.

Family oral health history is a valid representation of the existence of common genetic and environmental factors that may contribute to an individual’s oral health condition. It is also related to how these influences could contribute to health across all generations(CAVALLARI *et al.*, 2019). Very few studies, however, have been conducted into intergenerational associations of an oral health nature (SHEARER *et al.*, 2012).

The acquisition of basic information about oral disease in the family history may be regarded as a first step to identifying high-risk individuals and the families that could benefit from preventive and treatment efforts, such as in the Public Health Services, in addition to serving as a supplement to information obtained from the DMFT index. The goal of intergenerational studies is to explain the risk factors related to the families of children exposed to a greater risk than their peers, of diseases affecting the oral cavity. Practically, the oral health condition of parents cannot be changed without substantial effort, time and resources (SHEARER; THOMSON, 2010)

The results of the present study provide evidence as to the presence of a major gene with a dominant effect controlling the appearance of dental caries, within the same family. Family history of oral health would appear to be a valid representation of the complex interaction between genetic factors and shared environmental factors, exposures and behaviour that contribute to the oral health conditions of an individual and his family members.

Further studies are needed in an attempt to identify predisposing genetic factors and/or protective factors, which will contribute to the development of more effective public health policies and strategies aimed at promoting health and consequently reducing the prevalence of this disease.

4 Conclusion

From the results obtained in the present study, the following conclusions may be reached: among the sociodemographic, behavioral and clinical factors investigated, only gingivitis remained associated with a higher number of decayed teeth; the presence of an autosomal dominant inheritance pattern was detected in most families evaluated.

Acknowledgments

Acknowledgments to the participants of the field study for the important contribution to this research study; to the Departments of Health and Education in the municipality of Ibiporã (Paraná), for making available the data used for analysis in this study.

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