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Lack of association between delayed tooth emergence and single nucleotide polymorphisms in estrogen receptors

Isabela Ribeiro Madalena [1], Caio Luiz Bitencourt Reis [2], Daniela Silva Barroso de Oliveira [2], Giovana Daniela Pecharki [3], Paula Cristina Trevilatto [4], Kesly Mary Ribeiro Andrades [5], Julia Carelli [5], Vinicius Laranjeira Barbosa da Silva [5], Flares Baratto-Filho [5], Erika Calvano Küchler [1], João Armando Brancher [4].

[1] Department of Pediatric Dentistry, School of Dentistry of Ribeirão Preto, University of São Paulo, Ribeirão Preto, São Paulo, Brazil.

[2] Department of Clinic and Surgery, School of Dentistry, Federal University of Alfenas, Alfenas, MG, Brazil.

[3] Department of Community Health, Federal University of Parana, Curitiba, PR, Brazil

[4] School of Life Sciences, Pontifícia Universidade Católica do Paraná, Curitiba, PR, Brazil.

[5] School of Dentistry, Univille University, Joinville, SC, Brazil.

Correspondence: Drª. Erika C. Küchler
Department of Pediatric Dentistry, School of Dentistry of Ribeirão Preto, University of São Paulo – USP Avenida do Café s/n, Monte Alegre, 14040-904, Ribeirão Preto, SP, Brazil Phone: +55-16-3315-4057. Fax: +55-16-3633-0999
e-mail: erikacalvano@gmail.com

The purpose of the study was to investigate the association between single nucleotide polymorphisms (SNPs) in genes encoding estrogen receptors (*ESR1* and *ESR2*, respectively) and delayed tooth emergence (DTE). This cross-sectional study was composed of biological unrelated children of both sexes, age ranging from 11 to 13 years old. DTE was defined when the successor primary tooth was still present in the oral cavity after its exfoliation time or the absence of the permanent tooth emergence into the oral cavity. Children were diagnosed with DTE when they had at least one delayed permanent tooth, according to age of exfoliation of each tooth proposed by The American Dental Association. Genomic DNA from saliva was used to evaluate the SNPs in *ESR*1 (rs9340799 and rs2234693) and *ESR2* (rs1256049 and rs4986938) using Real-Time PCR. Chi-square or Fisher exact tests and Logistic Regression adjusted by age and gender were performed. SNP-SNP interaction was accessed by multifactor dimensionality reduction (MDR) analysis also adjusted by gender and age. The established alpha of this study was 5%. Among 537 included children, 296 (55%) were in the "DTE" group and the 241 (45%) were in the "Control" group. Age and gender were not statistically different among the groups (p>0.05). Genotype distribution of the SNPs rs9340799, rs2234693, rs1256049 and rs4986938 were not associated with DTE (p> 0.05). The models elected by MDR were not statistically significant either. Conclusions: The studied SNPs in *ESR1* and *ESR2* were not associated with permanent DTE.

Key Words: Delayed tooth eruption, estrogen receptors, genes

Introduction

Tooth eruption is a long and complex biological process that involves innumerous signaling pathways and includes dental development, movement across alveolar bone, position of occlusion with its antagonist and occlusal arrangements occurring after tooth emergence (1). Tooth eruption is a term often used to indicate the moment of emergence of the tooth into the oral cavity (2). Delayed Tooth Emergence (DTE) is a condition characterized by significant delay of tooth eruption caused by local, systemic, and/or genetic conditions (2). DTE can have psychological implications for the patient, especially if anterior teeth are affected (2), and also leads to a variety of orthodontic problems, once it increases the risk of crowding and malocclusion. A better understanding of DTE etiology is crucial for the orthodontic treatment (2).

Eruption of permanent teeth occurs simultaneously with most major physiological alterations in child development, which is strongly influenced by systemic and local environmental factors (2) and also by individual genetic background (2,3). The role of hormonal factors on DTE are poorly studied. Some studies indicates that the hypofunction condition of the glands and hormones such as Growth Hormone (4) and Parathyroid Hormone (5) have been associated with DTE. Besides, steroid hormones play a wide range in the transition period between childhood and adolescence (6) and studies with animal models clearly supports its involvement in tooth eruption and emergence (7).

Estrogen is a steroid hormone present and active throughout the individual's life (6). Although estrogen is primarily responsible for female characteristics, it also plays an important role in the neuroendocrine, vascular, skeletal and immune systems of both genders (females and males) (6). The classical pathway for estrogen response involves intracellular receptors which specifically recognize the

hormone (8) and the most prevalent receptors are the estrogen receptor alpha (ERα) and the estrogen receptor beta (ERβ), encoded by the *ESR1* and *ESR2* genes, respectively (8). Studies evaluating Single Nucleotide Polymorphisms (SNPs) in *ESR1* and *ESR2* have established a significant link between these genes and events that occur in the development (9).

Recently, SNPs in *RANKL* (Receptor Activator of NF-κB Ligand) and *MMP8 (*Matrix metallopeptidase 8) genes were associated with variations in the time of tooth eruption (3,10). The SNPs rs9340799 and rs2234693 in *ESR1* and rs1256049 and rs4986938 in *ESR2* are involved in cell growth and differentiation (9), and can be candidates for DTE investigation. The SNPs rs9340799 and rs2234693 might alter the *ESR1* transcription and affect the quality or quantity of *ESR1* (11). The SNP rs4986938 reduces *ESR2* synthesis (12), while the SNP rs1256049 is possibly involved in mRNA ESR2 stability (13). These SNPs were already associated developmental patters of the craniofacial complex, such as mandible dimensions (9) and tooth measurements (14). So, we can presume that these SNPs in *ESR1* and *ERS2* are involved in DTE of permanent teeth.

Thus, the objective of this study was to investigate the association between SNPs in *ESR1* (rs9340799 and rs2234693) and *ERS2* (rs1256049 and rs4986938) and DTE. The null hypothesis is that these SNPs do not interfere with the permanent tooth eruption.

Material and methods

Ethical aspects

This study was reported following the STREGA (Strengthening the Reporting of Genetic Association) guidelines (15) and was approved by the Human Ethics Committee of the Pontifical Catholic University of Paraná (PUC-PR). Children were included in this study only if the parents/legal guardians returned the informed consent form, and children signed the assent form according to norms of the local Ethical Committee on Research, according to Resolution 196/96 of the Health National Council, register n. 487 and 113/09.

Sample Characterization

This cross-sectional study included 537 biological unrelated children (age ranging from 11 to 13 years old) recruited at public and private schools of Curitiba, Paraná, Brazil. Children were not included if was using orthodontic appliances or with history of any systemic disease (including hormonal alterations), syndrome or oral cleft. Children using systemic antibiotics in the previous 6 months were also excluded. None of them reported hormone therapy nor contraceptive. Clinical examination was performed by two trained dentists. Children were seated in a school chair with artificial light. A dental mirror was used for indirect visualization in the maxillary arch. Tooth gingival emergence was defined by any dental face present in the alveolar mucosa (16). DTE was defined when there was no sign of tooth emergence or the successor primary tooth was still present in the oral cavity after the expected time according to age of teeth exfoliation published by The American Dental Association (17). Children that presented at least one delayed permanent tooth were considered children with DTE.

Genotyping analysis

Samples was obtained from children through a mouthwash with 3% glucose solution and light scrapings of the buccal mucosa. Genomic DNA for molecular analysis was extracted from epithelial buccal cells from saliva. Briefly, the DNA was extracted with a sequential phenol-chloroform solution and precipitated with a salt/ethanol solution according to the method reported by Trevillato and Line (18). Quantification of the concentration and purity of the DNA was determined by spectrophotometer (Nanodrop 1000; Thermo Scientific, Wilmington, DE, USA).

Four intronic SNPs were selected, due to the fact that the minor allele frequency was higher than 20%. The SNPs rs9340799 (A>G) and rs2234693 (C>T) located in *ESR*1; and the SNPs rs1256049 (C>T) and rs4986938 (C>T) located in *ESR2* were evaluated. The SNPs were blinded genotyped by real-time polymerase chain reactions (Real-Time PCR), using TaqMan assay step OnePlus Real-Time PCR System (Applied Biosystems, Foster City, California, USA). Real-time PCR reactions were performed in a total volume of 3 µl (4 ng DNA/reaction, 1.5 µl Taqman PCR master mix, 0.075 SNP assay; Applied Biosystems, Foster City, CA). The thermal cycling was carried out by starting with a hold cycle of 95 °C for 10 min, followed by 40 amplification cycles of 92 °C for 15 s and 60 °C for 1 min.

Statistical Analysis

Chi-square was used to calculate Hardy-Weinberg equilibrium (https://wpcalc.com/en/equilibrium-hardy-weinberg/). To compare the groups, children were dived in DTE group and Control group according to their phenotypes. Chi-square or Fisher exact tests were used to compare genotype (co-dominant, dominant and recessive models) among the "DTE" and "control" groups, among "1-4 DTE" and "control", "5 or more DTE" and "control" groups. Haplotype analysis for each gene was performed by PLINK 1.9 (http://pngu.mgh.harvard.edu/purcell/plink/). Kruskal-Wallis was used to compare the mean of DTE among genotypes. Logistic Regression adjusted by age and gender was also performed using Epi Info 7 (Epi Info 7 Software, Atlanta, Georgia, USA).

SNP-SNP interaction was accessed by multifactor dimensionality reduction (MDR) analysis (19). MDR is a non-parametric test which evaluates all the possible combinations of SNPs through 10-fold cross-validation (CV) and testing balanced accuracy (TBA), followed by 1000 permutation test to determine statistical significance to models. Models with TBA > 0.55, 9/10 or 10/10 CV consistency and $p \leq 0.05$ were considered best models. MDR also creates dendrograms and interaction graphs using entropy values, based on the formula by Jakulin and Bratko (20). The analysis was adjusted by gender and age and the established alpha for all analyses of this study was 5%.

The power analysis was performed using clinical.com with an error probability of 0.05.

RESULTS

Among 537 included children, 296 (55%) were in the DTE group and 241 (45%) were in the Control group. The characteristics of the sample is presented in the table 1. The mean of delayed teeth was 4.79 (SD= 3.76). The mean age in years was 11.91 (SD= 0.48) for DTE group and 12.10 (SD= 0.43) for Control group. In DTE group, 115 were boys and 126 were girls, while in Control group, 146 were boys and 150 were girls. There were not statistical differences of age and sex among the groups (p>0.05).

Table 1. Characteristics of sample

	Number of Children	(%)
Gender		
Male	261	
Female	276	
Number of delayed teeth		
0	241	44.8
1-4	185	34.5
5 or more	111	20.7
Type of delayed teeth		
Superior Incisors	10	3.4
Inferior Incisors	0	0.0
Superior Canines	92	31.1
Inferior Canines	21	7.1
Superior First Pre-Molar	39	13.2
Superior Second Pre-Molar	109	36.8
Inferior First Pre-Molar	29	9.8
Inferior Second Pre-Molar	109	36.8
Superior First Molar	1	0.3
Superior Second Molar	246	83.1
Inferior First Molar	1	0.3
Inferior Second Molar	186	62.8

Genotypes distribution were within Hardy-Weinberg equilibrium (chi-square$_{H\text{-}W}$ was 2.70 for rs9340799, 0.02 for rs2234693, 3.33 for rs1256049, and 1.28 for rs4986938). The genotype and allele distributions of the studied SNPs among the groups are presented in Table 2 and logistic regression in Table 3. The SNPs rs9340799 and rs2234693 in the *ERS1* and genetic polymorphisms rs1256049 and rs4986938 in the *ERS2* were not associated with all DTE groups (p>0.05) in genotype (co-dominant, dominant and recessive model).

Table 2. Genotype distribution among control and DTE groups

Gene	SNP	Genotype	Control n (%)	DTE n (%)	p-value	OR (CI95%)
ESR1	rs9340799	AA	110 (47.2)	146 (50.5)	Ref.	-
		AG	92 (39.5)	113 (39.1)	0.68	0.92 (0.63-1.34)
		GG	31 (13.3)	30 (10.4)	0.26	0.72 (0.42-1.29)
	rs2234693	TT	88 (37.1)	98 (34.0)	Ref.	-
		CT	112 (47.3)	154 (53.5)	0.27	1.23 (0.85-1.78)
		CC	37 (15.6)	36 (12.5)	0.87	0.87 (0.50-1.49)
ESR2	rs1256049	CC	188 (95.4)	234 (92.1)	Ref	-
		CT	7 (3.6)	18 (7.1)	0.14	2.06 (0.83-5.38)
		TT	2 (1.0)	2 (0.8)	0.99*	0.80 (0.12-5.17)
	rs4986938	CC	97 (41.4)	121 (41.5)	Ref.	-
		CT	113 (48.3)	140 (48.1)	0.97	0.99 (0.69-1.42)
		TT	24 (10.3)	30 (10.4)	0.99	1.00 (0.54-1.79)

Note: * Fisher's exact test.

Table 3: Multiple Logistic Regression for DTE

Gene	SNP	Genotype reference	Genotype	Unadjusted			Adjusted		
				Coefficient	OR (CI 95%)	p-value	CO	OR (CI 95%)	p-value
ESR1	rs9340799	AA	AG	-0.01	0.98 (0.69–1.40)	0.92	-0.04	0.95 (0.66–1.37)	0.82
			GG	-0.28	0.75 (0.44–1.29)	0.30	-0.23	0.78 (0.44–1.38)	0.40
	rs2234693	TT	TC	0.24	1.28 (0.90–1.81)	0.15	0.24	1.27 (0.89–1.81)	0.17
			CC	-0.25	0.77 (0.46–1.26)	0.30	-0.25	0.77 (0.46–1.28)	0.32
ESR2	rs1256049	CC	CT	0.72	2.07 (0.88–5.41)	0.11	0.68	1.98 (0.83–5.24)	0.13
			TT	-0.25	0.77 (0.09–6.49)	0.79	-0.26	0.76 (0.09–6.45)	0.79
	rs4986938	CC	CT	-0.01	0.98 (0.69–1.38)	0.92	-0.02	0.97 (0.68–1.38)	0.96
			TT	0.01	1.01 (0.57–1.79)	0.97	-0.10	0.90 (0.50–1.61)	0.72

Note: The multiple linear regression was adjusted by gender and age.

The comparisons between the mean number of DTE among genotypes in rs9340799, rs2234693, rs1256049 and rs4986938 were not statistically different (p>0.05). Haplotype analysis for both genes are demonstrated in the Table 4.

Table 4: Haplotype analysis for *ESR1* and *ESR2*.

Gene	SNPs	Haplotype	Fa[1]	Fu[2]	*p-value*
ESR1	rs9340799 - rs2234693	G-C	0.27	0.30	0.27
		A-C	0.11	0.08	0.11
		G-T	0.02	0.02	0.96
		A-T	0.58	0.58	0.96
ESR2	rs1256049 - rs4986938	C-T	0.33	0.34	0.77
		T-C	0.04	0.02	0.25
		C-C	0.61	0.62	0.87

Note: [1]means frequency in cases; [2]means frequency in controls.

The haplotype analysis between rs9340799 - rs2234693 in *ESR1* were not associated with DTE (p>0.05). The haplotype analysis between rs1256049 - rs4986938 in *ESR2* genes also showed no association (p>0.05).

The results of MDR analysis are in table 5. The models elected by MDR were not statistically significant. The dendrogram and circle graph revealed weak interaction and low values of entropy (Figure 1). The power analysis indicated that this sample would present a power ranging from 18 to 29%.

Table 5: Results of the MDR analysis.

Locus number	Best Combination	CV[1]	TBA[1]	p-value[3]
2	rs9340799 (*ESR1*), rs1256049 (*ESR2*)	9/10	0.550	0.13
3	rs2234693 (*ESR1*), rs1256049 (*ESR2*), rs4986938 (*ESR2*)	4/10	0.528	0.39
4	rs9340799 (*ESR1*), rs2234693 (*ESR1*), rs1256049 (*ESR2*), rs4986938 (*ESR2*)	10/10	0.536	0.28

Note: [1]Cross-validation consistency. [2]Testing Balanced Accuracy. [3]P-values were based on 1000 permutations test. The MDR analysis was adjusted by gender and age.

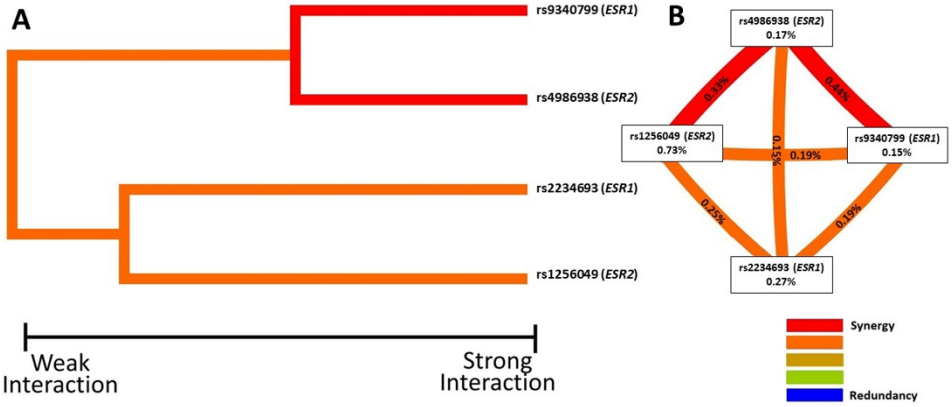

Figure 1. Epistasis analysis. A) Dendrogram. Dendrogram's keys represent the SNP-SNP interaction. B) Epistasis Map. Percentage of entropy (PE). The PE of each SNP is in the box, and percentages on the connection lines are the entropy value resulting from the interaction. The red or orange lines represent synergy (SNP-SNP interaction PE is greater than the sum of the percentages of each SNP).

Discussion

In the present study, the null hypothesis was confirmed, in which the SNPs in *ESR1* (rs9340799 and rs2234693) and *ERS2* (rs1256049 and rs4986938) were not associated with DTE. Deviations from tooth eruption and tooth emergence time standards are often observed in the clinical practice (2). In many cases, DTE is the main or the only manifestation of a local or systemic pathology, which can cause the development of dental caries, malocclusion and periodontal disease (2). Although in few cases it is easy to link permanent DTE to a local oral or a systemic cause, in the majority of the cases the etiological factor involved in DTE is unknown, and is probably linked with the individual genetic background. Many previous studies highlighted the possible influence of genetic factors on tooth eruption (2,3), including the fact that more than fifty chromosomal syndromes have already been linked to DTE (2).

The tooth eruption process depends on a complex molecular network between hormones, cell receptors and genes, which are involved in bone resorption, dental follicle quality, and cellular events. Molecular interaction initiates eruption and regulates the cellular events, and cell receptors, and hormones decoding genes program its chronology, quantity, quality and localization. Mutations in decoding genes might modify the molecular network and disturb the tooth eruption process (21). In fact, SNPs in *RANKL*, *BMP4*, *MMP8*, and *ADK* genes were already associated with DTE (3,10,22). Therefore, it is reasonable to hypothesize that SNPs in craniofacial development-related genes, like *VDR*, *PTH*, *ESR1* and *ESR2* can be also involved with DTE.

ESR1 and *ESR2* receptors act in bone resorption (23) and regulate the odonto/osteogenic differentiation (24). Both processes are necessary for tooth eruption process (21). Therefore, we decided

to investigate if SNPs in genes encoding estrogen receptors could contribute to DTE. The rs9340799 and rs2234693 SNPs in *ESR1* and rs1256049 and rs4986938 SNPs in *ESR2* were previously associated with craniofacial and dental development phenotypes (9,14). These indicated that SNPs in *ESR1* and *ESR2* may have an important role in the development of the maxilla and mandible of children and adolescents. Interestingly, rs9340799 in *ESR1*was observed as one of the risk factors for the formation of fetal macrosomy, a condition that may be associated with DTE (25).

It is well known that tooth eruption is influenced by ethnic and sexual factors (Suri). Although the population from Curitiba city is predominant European descendent (IBGE) ethnicity mixture is a characteristic of our population and could be a limitation in genetic studies. Regarding well-known sexual dimorphism observed in DTE, it is possible that sexual hormones, such as estrogen, are involved in these characteristics. Estrogen is mainly produced in the ovaries, but is also produced by the adipose tissue and brain of both sexes and important for the development of males and females (8). Therefore, we decided to include both genders in our study, however, in the logistic regression and MDR analysis, we adjusted by gender, once estrogen may play a different role according to the gender.

It is assumed that the expression of the polymorphic genes may occur in different ways according to tissues and cells, since the expression profiles of estrogen receptors are quite different (8). In addition, estrogen signaling may be due to interaction both at the nuclear level and in the plasma membrane (8). At the nuclear level, the main signaling pathway is described by directly linking estrogen to regulatory elements of DNA (8).

`The knowledge that dental tissues, including periodontal ligament, express estrogen receptors are not new. Thus, although our results do not show an association between the SNPs in *ESR1* (rs9340799, rs2234693) and *ESR2* (rs1256049, rs4986938) and DTE, it is suggested that further studies should investigate other candidate SNPs in estrogen receptors or SNPs in different genes. Finally, some conditions such as cysts, odontogenic tumors, premolar tooth agenesis and supernumerary teeth could be involved DTE and are visible only in image exams. Although these conditions are uncommon in the population and may not influence significantly the results of our study, the absence of radiographic images was a limitation.

The search for biomarkers of DTE could impact the clinical practice, aiding pediatric dentists and orthodontists to design a personalized treatment for each patient in the dental practice. Therefore, future studies should evaluate genetic factors associated with DTE including image exams. In conclusion, the studied SNPs in estrogens receptors encoding genes (*ESR1* and *ESR2*) were not associated with delayed tooth emergence in Brazilian children.

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Conflict of interest

The authors declare no conflict of interest.

RESUMO

O objetivo do presente estudo foi investigar a associação entre polimorfismos de nucleotídeo único (SNPs) em genes que codificam receptores de estrógeno (*ESR1* e *ESR2*, respectivamente) e o retardo na emergência dentária (DTE). Este estudo transversal foi composto por crianças biológicas não relacionadas de ambos os sexos, com idades entre 11 e 13 anos. O DTE foi definido pela presença do dente decíduo na cavidade bucal após seu tempo e também, quando as crianças apresentaram pelo menos um dente permanente com atraso. O DNA genômico foi usado para avaliar os SNPs em *ESR1* (rs9340799 e rs2234693) e *ESR2* (rs1256049 e rs4986938) usando PCR em tempo real. Foram realizados testes Qui-quadrado ou exato de Fisher e Regressão Logística ajustados por idade e sexo. A interação SNP-SNP foi acessada pela análise de redução de dimensionalidade multifatorial (MDR), também ajustada por sexo e idade. O alfa de 5% foi estabelecido. Entre 537 crianças incluídas, 296 (55%) estavam no grupo "DTE" e 241 (45%) estavam no grupo "Controle". A idade e o sexo não foram estatisticamente diferentes entre os grupos (p> 0,05). A distribuição de genótipos dos SNPs rs9340799, rs2234693, rs1256049 e rs4986938 não foi associada ao DTE (p> 0,05). Os modelos eleitos pelo MDR também não foram estatisticamente significativos. Conclusões: Os SNPs estudados na *ESR1* e *ESR2* não foram associados ao DTE na dentição permanente.

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