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Association between Estrogen Receptors Alpha and Beta and Developmental Defects of Enamel: Cross-Sectional Study

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Authors' contributions

This work was carried out in collaboration among all authors. Authors KRFV and IRM wrote manuscript. Authors PN-F and MANM acquired the sample and treated the patients. Authors GF-S and JF-S evaluated the developmental defects of enamel. Authors CPT performed the laboratory analysis. Authors ECK critically reviewed the manuscript. Authors CK, CPL, ECK and MAH de M-O conceived the idea and coordinated the study; all authors read and approved the final manuscript.

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ABSTRACT

Background: The genes encoding estrogen receptors *alpha* and *beta (ESR1* and *ESR2)* are expressed during odontogenesis and may be involved in developmental defects of enamel (DDEs).
Aims: To investigate the association between DDE and genetic polymorphisms *ESR1* and *ESR2.*
Study Design: Cross-sectional.
Place: Department of Orthodontics at School of Dentistry of Ribeirão Preto, University of São Paulo (FORP/USP).
Methodology: Ninety-one (91) patients of both sexes were included in this study (mean age 14.1 ± 5.8 years). DDEs were evaluated by a calibrated examiner using the criteria proposed by Ghanim et al. (2015) (Kappa >0.80). Genomic DNA from saliva was used to evaluate four genetic polymorphisms in *ESR1* (*rs2234693* and *rs9340799*) and *ESR2* (*rs1256049* and *rs4986938*). Genotyping was performed through Real-Time PCR. The data were analyzed using the PLINK software. Associations were tested by Chi-square or Fisher exact tests. The established alpha was 5%.
Results: A total of 38.5% of the sample presented some DDE (excluding dental fluorosis). DDE was not associated with the polymorphisms *rs2234693* and *rs9340799* in ESR1 and *rs1256049* and *rs4986938* in *ERS2 (p>0.05).*
Conclusion: Genetic polymorphisms in *ESR1* and *ESR2* were not associated with DDE.

Keywords: Dental enamel hypomineralization; receptor; estrogen; polymorphism; genes.

1. INTRODUCTION

The amelogenesis is a complex process influenced by local, systemic, environmental, and genetic factors [1-5]. Insults during this process may cause alterations in the quantity and/or quality of the enamel matrix deposited under the dental organ, resulting in hypoplastic and/or hypomineralized defects, respectively, called Developmental Defects of Enamel (DDEs) [6]. Clinical conditions such as hypocalcified and hypomature amelogenesis imperfecta, dental fluorosis, hypoplasia, molar-incisor hypomineralization (MIH), and hypomineralization of primary molars and canines are subclassifications of DDEs [5].

The reported prevalence of DDEs in primary dentition varies from 23.9% to 90.4. In permanent dentition, the prevalence can reach 92.1%, depending on the population profile [7-9]. Once DDEs are identified, awareness of their etiology, preventive and therapeutic strategies, as well as clinical implications need to be explored. The literature demonstrates that patients with DDEs present an increased risk of dental caries [10,11], dental hypersensitivity, enamel fractures, aesthetic complaints [9], and worse quality of life [12].

The receptors *ERα* (estrogen receptor alpha) and *ERβ* (estrogen receptor beta) are encoded by the *ESR1* and *ESR2* genes, respectively [13]. Alterations in these receptors signaling are associated with reproductive system diseases, lung cancer, osteoporosis, cardiovascular and urogenital tract disease, neurodegenerative disorders, cutaneous melanoma [14], and dental phenotypes [4]. Previous studies point to the main estrogen receptors in dental tissues [2,15-20]. Arid et al. [4] and Dalledone et al. (2019) [2] found an association between polymorphisms in *ESR1* and DDE. Therefore, the present study aimed to investigate the association between DDE and the genetic polymorphisms in *ESR1* and *ESR2*.

2. MATERIALS AND METHODS

2.1 Sample Characterization

The sample included patients aged between 9 and 40 years old who were undergoing orthodontic treatment at the School of Dentistry of Ribeirão Preto, University of São Paulo (FORP/USP), São Paulo, Brazil. Orthodontic records from patients of both sexes were screened. Healthy patients with dental records and good-quality photographs were included in this study. Patients with consanguineous parents, syndromes, congenital anomalies, craniofacial deformities, hormonal or systemic treatment, dental fluorosis and a previous history of facial trauma were excluded.

2.2 Evaluation of Developmental Defects of Enamel

DDEs were diagnosed using the clinical criteria for classification of DDE [21]. The patients were classified into two groups: a control group and a DDE group (when at least one permanent or primary tooth was affected by DDE). The analyses were performed by one calibrated examiner (intra-agreement Kappa=0.0883; inter-agreement Kappa=0.961) evaluating intraoral pictures of orthodontic patients (Fig. 1).

2.3 Genotyping Analysis

Genomic DNA was extracted from saliva cells based on the method reported by Küchler et al. [22]. Four intronic genetic polymorphisms with a minor allele frequency higher than 20% were selected based on the previous studies [17,23,24]. Table 1 presents the characteristics of the studied genetic polymorphisms. The genotype was performed by real-time polymerase chain reactions (Real-Time PCR), using TaqMan assay step OnePlus Real-Time PCR System (Applied Biosystems, Foster City, California, USA).

2.4 Statistical Analysis

Data were analyzed using the PLINK software (Shaun Purcell; http://pngu.mgh.harvard.edu/purcell/plink/) [25]. Chi-square was used to calculate Hardy-Weinberg equilibrium. Chi-square or Fisher's exact tests were used to compare genotype and allele distributions between the "DDE group" and "Control group". For all analyses of this study the alpha value adopted was 5%.

3. RESULTS

A total of 149 orthodontic patients were screened. Of those, 91 were included in this study according to the inclusion/exclusion criteria (Fig. 2). A total of 49 patients (53.8%) were females, while 42 were males (46.2%). The age ranged from 9 to 40 years, with a mean age of 14.1 years (Standard deviation = 5.8). Thirty-five (38.5%) patients presented at least one tooth with DDE. Table 2 shows the genotype distribution according to the groups. There was no statistical association (p>0.05).

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4. DISCUSSION

The exact etiology of DDE is still unknown. However, knowledge about the factors associated with these defects is fundamental once they present high prevalence in some populations and impair the quality of life of affected patients [9,12]. More than 300 genes regulate dental development [26] and some of them are clearly expressed in different stages of amelogenesis [27-30], including hormone receptors.

Fig. 1. Patient presenting the upper left central incisor and canine affect by DDE

Table 1. Characteristics of the studied genetic polymorphisms

Gene	Band	Position (GRCh37)	Reference sequence	Functional consequence	Base change (Context sequence)	MAF (ALFA)
ESR1	6q25.1	152163335	rs2234693	Intron	AGC[C/T]GTT	C=0.449055/27907
ESR1	6q25.1	152163381	rs9340799	Intron	TCT[A/G]GAG	G=0.334827/15317
ESR2	14q23.2	64724051	rs1256049	Intron	CCG[C/T]ACT	T=0.039897/7344
ESR2	14q23.2	64699816	rs4986938	Intron	AGC[C/T]TGT	T=0.367961/65525

MAF – minor allele frequency, ALFA - Allele Frequency Aggregator (NCBI database of Genotypes and Phenotypes [dbGaP]). Sources of information: dbSNP from: http://www.ncbi.nlh.nih.gov/snp/; http://genome.uscs.edu/; and, https://www.thermofisher.com.

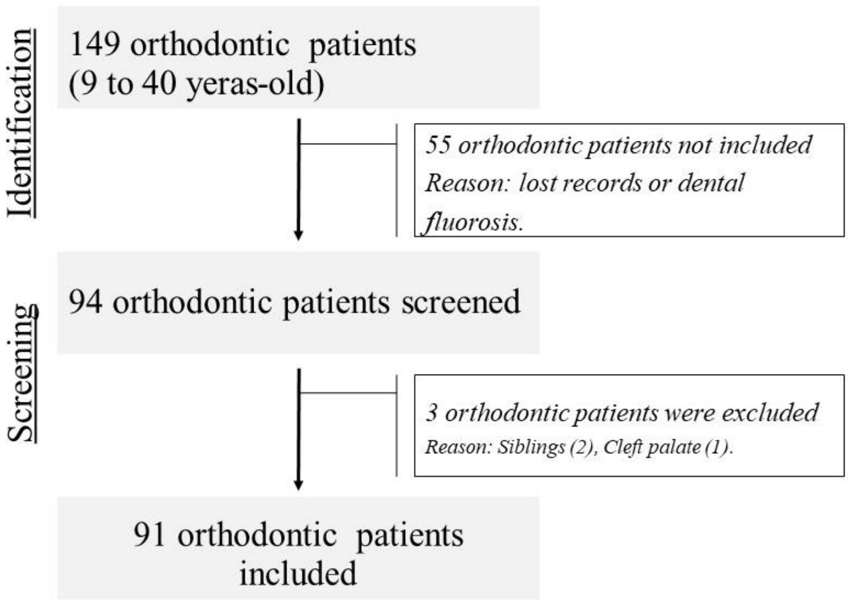

Fig. 2. Flow chart of the study

Although estrogen is an androgen hormone whose primary function is the development of female sexual characteristics, it plays a role in both females and males, acting in the bone metabolism, cardiovascular system, and central nervous system) [31,32]. The actions of estrogen are mediated by binding its receptors, *ERα* and *Erβ,* codified by ESR1 and ESR2 genes, respectively [13]. The actions of estrogen and its receptors in buccal tissues were described in animal studies [18,19,23,33-35] and have been extrapolated in studies about genetic polymorphisms in humans [17, 23,36,37].

Genetic polymorphisms consist of alterations of a specific DNA sequence occurring in a population with a frequency of 1% or higher [38,39]. Even though most polymorphisms do not affect gene function, some of them result in changes in the protein produced and may increase the risk of development of certain diseases [40-42]. Thus, this study aimed to evaluate the association between genetic polymorphisms in *ESR1* and *ESR2* and DDE in a Brazilian sample.

Estrogen receptors were observed in ameloblast during phases of proliferation, differentiation, and maturation in amelogenesis [16,27]. Scientific evidence also suggests that estrogen and their receptors may influence in calcium and phosphate homeostasis, affecting dental mineralization [15, 43]. Previous studies found an association between genetic polymorphisms in *ESR1* (*rs2234693* and *rs9340799*) and *ESR2* (*rs1256049* and *rs4986938*) tooth abnormalities, including DDEs [2,4,15]. Such evidence supports the need for further studies investigating the role of estrogens and their receptors during amelogenesis and in the occurrence of DDE.

Table 2. Evaluation of the SNP according to the groups in the codominant, dominant, and recessive models, in relation to DDE

SNP	Phenotype	Genotype frequencies, n (%)			Association test *p-values*		
					Codominant model	**Dominant model**	**Recessive model**
rs2234693		CC	CT	TT	CC vs. CT vs. TT	CC+CT vs. TT	CC vs. CT+TT
	DDE	4 (12.5)	15 (46.9)	13 (40.6)	0.761	>0.999	0.668
	no DDE	10 (18.5)	23 (42.6)	21 (38.9)			
rs9340799		AA	AG	GG	AA vs. AG vs. GG	AA+AG vs. GG	AA vs. AG+GG
	DDE	18 (54.5)	11 (33.3)	4 (12.1)	0.497	0.476	>0.999
	no DDE	30 (54.5)	22 (40.0)	3 (5.5)			
rs1256049		CC	CT	TT	CC vs. CT	CC+CT vs. TT	CC vs. CT+TT
	DDE	32 (91.4)	3 (8.6)	0 (0.0)	>0.999	---	---
	no DDE	52 (92.9)	4 (7.1)	0 (0.0)			
rs4986938		CC	CT	TT	CC vs. CT vs. TT	CC+CT vs. TT	CC vs. CT+TT
	DDE	10 (31.3)	18 (56.3)	4 (12.5)	0.854	>0.999	0.747
	no DDE	19 (37.3)	26 (51.0)	6 (11.8)			

In the present study, no association between genetic polymorphisms in *ESR1* and *ESR2,* and DDE was found. Dental alterations result from complex interactions between genetic, epigenetic, and genetic factors [44]. For example, xenoestrogens associated with MIH, such as bisphenol A (BPA), can bind to *ERα* in ameloblasts, influencing their function [45]. A previous study hypothesized that polymorphisms in *ESR1* may alter the capacity of binding, changing BPA kinetics and, consequently, its effects on amelogenesis [46]. It may suggest that DDEs result from gene-environmental interactions, not from isolated genetic or environmental factors. Thus, future studies should consider both factors in their evaluation. Another point to be considered about this study is the small sample size, which may explain the lack of association between the evaluated variables.

5. CONCLUSION

Genetic polymorphisms in *ESR1* and *ESR2* were not associated with DDE in permanent dentition. However, it is known that dental alterations may result from gene-environmental interactions. Thus, it is suggested that future studies on this topic consider the correlation between these factors.

CONSENT AND ETHICAL APPROVAL

This cross-sectional phonotype-genotype study was approved by the Human Ethics Committee of the School of Dentistry of Ribeirão Preto, University of São Paulo (FORP/USP), São Paulo, Brazil (CAAE: 01451418.3.0000.5419). Informed consent was obtained from all participants and their legal guardians.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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