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Association of the estrogen receptor gene with oral health-related quality of life in patients with dentofacial deformities

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Abstract: This study aimed to evaluate the associations between oral health-related quality of life (OHRQoL) and patient-associated factors and polymorphisms in the estrogen receptor 1 (*ESR1*) and 2 (*ESR2*) genes in patients with dentofacial deformities (DFD). This cross-sectional study included 234 adult individuals. Data such as age, sex, and the type of facial profile (I, II, or III), were collected, and the short-form oral health impact profile 14 (OHIP-14) questionnaire was used to assess their OHRQoL. DNA was collected from oral mucosa cells, and the polymorphisms in *ESR1* (*rs2234693* and *rs9340799*) and *ESR2* (*rs1256049* and *rs4986938*) were evaluated using real-time polymerase chain reaction. The data were subjected to statistical analysis at a significance level of 5%. Individuals over 28 years of age exhibited worse OHRQoL ($p = 0.003$) than individuals aged less than or equal to 28 years. Women had worse OHRQoL than men ($p < 0.001$). Profile II individuals had worse OHRQoL in the social disability domain than profile III individuals ($p = 0.030$). Genetic analysis showed that *rs9340799* was associated with OHRQoL in the functional limitation domain, and GG individuals exhibited worse OHRQoL than individuals carrying the AA/AG genotypes ($p < 0.030$). In the social handicap domain, individuals with GG genotype in *rs9340799* exhibited worse OHRQoL than AG individuals ($p < 0.043$). Collectively, our results reveal that factors including age, sex, and type of facial profile, are associated with OHRQoL in patients with DFD. In addition, individuals with the GG genotype in *rs9340799* (*ESR1*) may experience a negative impact on OHRQoL in the functional limitation and social handicap domains.

Keywords: Dentofacial Deformities; Estrogens; Quality of Life.

Introduction

Oral health conditions exert an impact on functional and psychosocial factors affecting an individual's quality of life (QoL). Different approaches can be taken to assess an individual's oral health-related quality of life (OHRQoL).[1,2] The oral health impact profile 14 (OHIP-14) is a widely used tool for evaluating the impact of oral health problems on the OHRQoL. It includes questions related to functional limitation, physical pain,

psychological discomfort, and physical, psychological, and social disabilities, in addition to social handicap.[1]

Dentofacial deformity (DFD) is characterized by developmental changes in facial structure, usually associated with malocclusion,[3] that can impair chewing, swallowing, breathing, and phonation.[3] DFD also has a major impact on an individual's facial aesthetics, which may affect their social life and mental health.[4] Many studies have evaluated OHRQoL in patients with DFD and found that these patients' oral health condition negatively impacts various psychosocial aspects of their lives.[4-7]

Some factors, including age,[4,8] sex,[5] facial profile type,[9] and genetic factors, directly correlate with worsening OHRQoL.[10] Spranger et al.[11] studied different candidate genes that were expected to play a role in the perception of QoL, including the estrogen receptor 1 (*ESR1*), which is associated with depression.[12]

Estrogen is a hormone that promotes synaptic plasticity and modulates the function of various neurotransmitters involved in cognition, including serotonin, norepinephrine, and acetylcholine.[13] There are two subtypes of estrogen receptors (ERs): α and β. ERα is encoded by *ESR1,* and is predominantly expressed in the hypothalamus and amygdala (brain areas involved in autonomic function, emotional regulation, and memory),[14] whereas ERβ is encoded by *ESR2* and is predominantly expressed during formation of the hippocampus and entorhinal cortex (brain areas associated with semantic memory).[14]

Scariot et al.[15] reported that genetic polymorphism in *ESR1* was associated with the state of anxiety in patients with DFD undergoing orthognathic surgery, suggesting that this gene may play a role in the psychologic and emotional states of affected individuals. Although there are no reports on the effects of *ESR2* on psychosocial aspects in this subset of patients, it is associated with an increasing incidence of anxiety in elderly women[16] as well as late-life depression.[12] Thus, we hypothesized that genetic variants of ERs may influence the OHRQoL, especially in individuals with impaired oral conditions, such as DFD.

A knowledge of genes and patient-associated factors impacting OHRQoL will aid in the screening of predisposing factors, facilitating a personalized approach to preventing negative impacts on OHRQoL and predicting treatment outcomes in clinical practice. Additionally, a deeper understanding of the genetic basis of OHRQoL may lead to discoveries that will improve patient management strategies, considering that patient genetic profiles is soon expected to be incorporated into clinical practice to facilitate personalized treatment. Thus, in the present study, we aimed to evaluate the associations between OHRQoL and patient-associated factors and genetic polymorphisms (*ESR1* and *ESR2*) in patients with DFD.

Methodology

Ethical aspects

This study was approved by the local ethics committee under the protocol CAEE 80846317.8.0000.0093. The study was performed in accordance with the ethical standards proposed by the Declaration of Helsinki and its later amendments or comparable ethical standards. All participants were informed regarding the study and signed informed consent forms. The study adhered to the Strengthening the Reporting of Genetic Association Studies (STREGA) Statement.[17]

Study design

This cross-sectional study evaluated a total of 276 individuals with DFD who underwent orthognathic surgery as part of the residency program of Oral and Maxillofacial Surgery at Positivo University and Federal University of Paraná, two universities located in Curitiba, southern Brazil (Figure). Both services were provided by the public sector. The Federal University of Parana is considered a reference center for DFD treatment in southern Brazil, and an average of eight patients receive surgery each month. In the Positivo University service, an average of three patients are operated each month.

This study was performed on a population of patients with DFD, who were previously diagnosed by orthodontists and referred for orthognathic surgery treatment. All patients who underwent orthognathic surgery between January, 2017 and December, 2019, were invited to participate in this study, since the demand for this procedure is low. This study included non-syndromic DFD patients

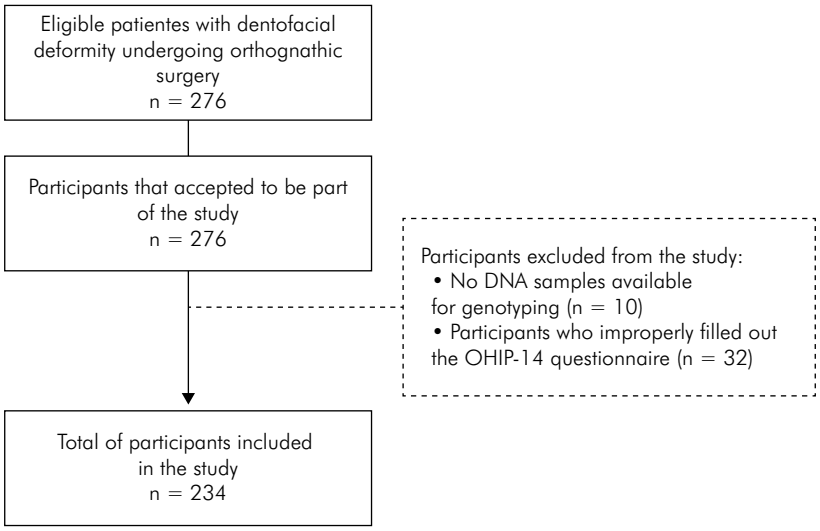

Figure. Flowchart demonstrating the study population selection method.

of both sexes with facial profile types I, II, and III, who required orthognathic surgery and were over 18 years of age. The exclusion criteria were patients with DFD who had undergone previous orthognathic and/or temporomandibular joint (TMJ) surgery, had a history of facial trauma, presence of oral cleft and/or palate, or neurologic disturbances.

Data collection

All eligible patients underwent an evaluation by a trained examiner one week before their orthognathic surgery. Data including age, sex, and facial profile type, were collected. Facial profile type evaluation was performed by two trained examiners (KMS and IPB). Both examiners were trained by senior surgeons (RS and DJC) at both universities. During data collection, the examiners were supervised by senior surgeons to verify their assessments of facial profiles. Facial profile type evaluation followed the classification system described by Capelozza Filho[18] to categorize the patients with facial profile types as I, II, or III. Facial profile I was characterized by facial normality. Facial profiles II and III were characterized by positive and negative sagittal steps between the maxilla and mandible, respectively.

OHIP-14 has been designed to assess the effects of oral conditions on the OHRQoL, and includes the following seven domains: functional limitation (items 1 and 2), physical pain (items 3 and 4), psychological discomfort (items 5 and 6), physical disability (items 7 and 8), psychological disability (items 9 and 10), social disability (items 11 and 12), and social handicap (13 and 14). The patients indicated the frequency of their experiences by following a 5-point Likert-type scale: 0-never, 1-rarely, 2-occasionally, 3-often, and 4-always. Scores ranged from 0–56 points. Increasing scores indicate worsening perception of OHRQoL.[1]

DNA collection and genotyping

The two examiners (KMS and IPB) collected DNA samples after rinsing the mouths of the patients with a mouthwash containing 3% glucose for 2 min, followed by light scraping of the cheek mucosa with a sterile wooden spatula.[19] DNA was extracted from the sample according to an established protocol previously published by Line.[20] Briefly, after incubation, the tubes were centrifuged for 10 min at room temperature to pellet the buccal cells. Supernatants were discarded and 1 mL extraction solution [10 mM Tris (pH 8.0), 0.5% sodium dodecyl sulfate, 5 mM ethylenediaminetetraacetic acid (EDTA)] containing 10 µL proteinase K (Sigma Chemical Co., St. Louis, USA) (20 mg/mL) was added to the cell pellet. After overnight incubation, non-digested proteins were removed by adding 500 µL solution containing 8 M ammonium acetate and 1 mM EDTA. The solutions were mixed and centrifuged for 15 min. Supernatants were separated into two 1.5 mL microtubes (700 µL), and DNA was precipitated with 540 µL isopropanol at –20°C for 30 min. After centrifugation for 20 min,

supernatants were discarded, and pellets were washed with 1 mL of 70 % ethanol. Next, ethanol was decanted carefully, and the tubes were inverted and allowed to air dry. DNA was then resuspended in 100 µL Tris-EDTA buffer [10 mM Tris (pH 7.8) containing 1 mM EDTA].

The candidate genetic polymorphisms investigated were *rs223493* and *rs9340799* (*ESR1*) and *rs1256604* and *rs4986938* (*ESR2*), which were blindly genotyped using the same operator (MNM). All selected polymorphisms showed a minimum allelic frequency greater than 10%. DNA was genotyped on real-time PCR (StepOnePlus; Applied Biosystems) using TaqMan technology. The characteristics of *ESR1* and *ESR2* polymorphisms are listed in Table 1.

Statistical analyses

The data were submitted for inferential and descriptive statistical analyses. In addition, patients whose questionnaires were improperly filled, or for whom DNA samples were not available, were excluded. In the Kolmogorov–Smirnov test, the OHIP-14 scores demonstrated a non-normal distribution. Age also displayed a non-normal distribution. Therefore, it was dichotomized by the median (≤ 28 years and > 28 years) to analyze its association with OHRQoL. The associations of OHIP-14 and its domains with patient-associated factors and genetic variables were evaluated using the Mann-Whitney U or Kruskal-Wallis tests for independent samples. Descriptive analysis was represented by the median, minimum, maximum, and interquartile range (IR), which is the difference between the upper and lower quartiles. Statistical significance was set at $p < 0.05$. Data were analyzed using the Statistical Package for the Social Sciences (SPSS; version 21.0; SPSS Inc., Chicago, USA).

Results

Initially, 276 eligible participants were invited to participate in this study. During the survey, 42 patients were excluded: 10 had no DNA samples available for genotyping and 32 did not complete the questionnaire. The final sample was composed of 234 individuals, of which 83 (35.5%) were men and 151 (64.5%) were women. The mean age of the participants was 30.63 ± 10.53 years. In our study, 17, 75, and 138 patients exhibited facial profiles I, II, and III, respectively. Profile I individuals also underwent orthognathic surgery for vertical or transverse deformities.

Age was found to associate with OHRQoL. Patients over 28 years of age had a worse OHRQoL in general ($p = 0.003$) and in the domains related to physical pain ($p = 0.019$), psychological discomfort ($p = 0.027$), physical disability ($p = 0.006$), psychological disability ($p = 0.010$), and social handicap ($p = 0.029$), compared to OHRQoLs in individuals aged less than or equal to 28 years.

Based on OHIP-14 results, women with DFD had worse OHRQoL than men ($p < 0.001$). Women had stronger negative perceptions of OHRQoL in domains related to physical pain ($p < 0.001$), psychological discomfort ($p < 0.001$), physical disability ($p = 0.001$), psychological disability ($p < 0.001$), and social handicap ($p = 0.001$) when compared to men. In OHIP-14 based analyses of the facial profile types, profile II individuals had a worse OHRQoL in the social disability domain than profile III individuals ($p = 0.030$). The associations of OHIP-14 scores with age, sex, and facial profile type are listed in Table 2.

Genetic analyses revealed an association between the genetic polymorphism *rs9340799* in *ESR1* and its functional limitation domain. Homozygous GG individuals had worse OHRQoL in this domain than those with the AA and AG genotypes ($p < 0.030$).

Table 1. Genes and genetic polymorphisms investigated in this study.

Gene	Polymorphism	Position	Base change	Type of alteration	Global MAF
ESR1	*rs2234693**	*6q25.1*	C/T	Intron variant	0.44
	*rs9340799***		A/G	Intron variant	0.28
ESR2	*rs1256049*	*14q23.2*	C/T	Intron variant	0.12
	rs4986938		C/T	Intron variant	0.25

MAF: minor allele frequency; *Also known as PvuII; **Also known as XbaI.
Data sources: dbSNP from: https://www.ncbi.nlh.nih.gov/snp/; http://genome.uscs.edu/; and https://www.thermofisher.com

In the handicap domain, worse OHRQoL was also observed in GG individuals for *rs9340799* compared to AG individuals ($p < 0.043$) (Table 3).

No association was found between the OHRQoL and genetic polymorphisms in *ESR2* (Table 4).

Discussion

The goal of our study was to identify factors that may be associated with OHRQoL in DFD patients who require orthognathic surgery. Overall, we observed that patient-associated factors, such as age, sex, and facial profile type, were associated with OHRQoL. In addition, our study results suggested that genetic aspects may contribute to OHRQoL perception in DFD patients. In our study, *ESR1* (*rs9340799*) was found to be associated with the functional limitation and social handicap domains of OHIP-14.

Skeletal discrepancies in the facial bones of patients with DFD affect not only the individual's facial aesthetics, resulting in low self-esteem,[21] but also physiological problems that affect the oral health and overall perception of OHRQoL.[2,6] Orthognathic surgery usually has a positive impact on OHRQoL by improving the individual's facial aesthetics.[6] For this reason, many patients seek orthognathic surgery to improve their facial aesthetics and restore oral functions.[22] Since there is a high expectation of a positive outcome of this treatment in patients undergoing orthognathic surgery, this study focused on identifying the factors that may be associated with a worse perception of OHRQoL, to avoid psychosomatic disorders after the surgical procedure.

Novel insights into the biological pathways through which genetic factors contribute to patients' negative health experiences will help to improve their health. Elucidating the molecular mechanisms involved in the regulation of OHRQoL will also facilitate the development of new drugs targeting those specific mechanisms. If patients susceptible to a negative OHRQoL can be identified, it would be possible to devise preventive strategies or provide personalized treatment to them that include lifestyle changes, psychological approaches, and/or pharmacological treatment.

Table 2. Associations of the oral health impact profile 14 (OHIP-14) scores with age, gender, and facial profile in patients with dentofacial deformity (DFD).

Variable	Age		p-value	Sex		p-value	Facial profile			p-value
	≤ 28 years Median (min-max)	> 28 years Median (min-max)		Male	Female		I	II	III	
	IR	IR		Median (min-max)	Median (min-max)		Median (min-max)	Median (min-max)	Median (min-max)	
OHIP-14 GERAL	15 (0–51) 12	20 (0–44) 14	0.003	14 (0–51)	20 (0–48)	< 0.001	19 (6–33)	20 (0–51)	16.5 (0–41)	0.244
Functional limitation	2 (0–8) 2	2 (0–8) 2	0.490	1 (0–8)	2 (0–8)	0.050	2 (0–5)	2 (0–8)	2 (0–7)	829
Physical pain	3 (0–8) 3	4 (0–8) 3	0.019	2 (0–8)	4 (0–8)	< 0.001	4 (2–6)	4 (0–8)	3 (0–8)	0.491
Psychological discomfort	4 (0–8) 2	4 (0–8) 3	0.027	4 (0–6)	4 (0–8)	< 0.001	4 (1–7)	4 (0–8)	4 (0–8)	0.221
Physical disability	1 (0–6) 3	2 (0–12) 3	0.006	1 (0–6)	2 (0–12)	0.001	2 (0–5)	2 (0–12)	2 (0–6)	0.825
Psychological disability	3 (0–8) 3	4 (0–8) 3	0.010	3 (0–7)	4 (0–8)	< 0.001	4 (0–6)	4 (0–8)	3 (0–8)	0.885
Social disability	2 (0–8) 2	3 (0–8) 3	0.128	2 (0–8)	3 (0–8)	0.001	3 (0–6)[ab]	3 (0–8)[a]	2 (0–7)[b]	0.030
Social handicap	0 (0–7) 2	1 (0–7) 3	0.029	0 (0–7)	1 (0–6)	0.094	2 (0–4)	1 (0–7)	1 (0–7)	0.393

Mann–Whitney U or Kruskal–Wallis test for independent samples with a significance level of 0.05; IR: interquartile range. Bold values indicate statistically significant differences. Different letters indicate significant differences.

Table 3. Association between OHIP-14 scores and genetic polymorphisms in the estrogen receptor 1 (*ESR1*).

Variable	rs2234693				rs9340799			
	Median (min – max)			p-value	Median (min – max)			p-value
	CC	CT	TT		AA	AG	GG	
OHIP-14 GERAL	23 (1–48)	18 (0–51)	16 (0–39)	0.091	18 (0–44)	16 (0–51)	22.50 (2–39)	0.178
Functional limitation	2 (0–5)	2 (0–8)	2 (0–6)	0.287	2 (0–6)[a]	2 (0–8)[a]	3 (0–6)[b]	**0.030**
Physical pain	4 (0–8)	3 (0–8)	3 (0–8)	0.060	3 (0–8)	4 (0–8)	4 (0–8)	0.530
Psychological discomfort	4 (0–8)	4 (0–8)	2 (0–8)	0.611	4 (0–8)	4 (0–8)	4.5 (0–8)	0.380
Physical disability	2 (0–6)	2 (0–12)	2 (0–6)	0.654	2 (0–12)	2 (0–6)	2 (0–5)	0.762
Psychological disability	4 (0–8)	3 (0–8)	3 (0–8)	0.166	4 (0–8)	3 (0–8)	3.5 (0–7)	0.155
Social disability	3 (0–8)	3 (0–8)	2 (0–7)	0.159	2 (0–8)	2 (0–8)	3 (0–7)	0.716
Social handicap	1 (0–6)	1 (0–6)	0 (0–4)	0.070	1 (0–6)[ab]	0 (0–6)[a]	2 (0–6)[b]	**0.043**

Mann–Whitney U or Kruskal–Wallis test for independent samples with a significance level of 0.05; ID: interquartile distance. Bold values indicate statistically significant differences. Different letters indicate significant differences.

Table 4. Association between OHIP-14 and genetic polymorphisms in estrogen receptor 2 (*ESR2*).

Variable	rs1256049				rs4986938			
	Median (min–max)			p-value	Median (min–max)			p-value
	CC	CT	TT		CC	CT	TT	
OHIP-14 GERAL	18 (0–44)	16.5 (1–48)	-	0.218	18 (0–48)	18 (1–51)	16 (0–34)	0.428
Functional limitation	2 (0–8)	2 (0–5)	-	0.215	2 (0–8)	2 (0–8)	2 (0–5)	0.762
Physical pain	3 (0–8)	4 (0–8)	-	0.378	3 (0–8)	3 (0–8)	2 (0–7)	0.286
Psychological discomfort	4 (0–8)	4 (0–8)	-	0.306	4 (0–8)	4 (0–8)	4 (0–8)	0.136
Physical disability	2 (0–12)	2 (0–6)	-	0.256	2 (0–6)	2 (0–12)	1 (0–5)	0.257
Psychological disability	4 (0–8)	3 (0–8)	-	0.208	3 (0–8)	3 (0–8)	3 (0–7)	0.805
Social disability	2 (0–8)	3 (0–8)	-	0.532	2 (0–8)	2 (0–8)	2 (0–7)	0.454
Social handicap	1 (0–6)	1 (0–6)	-	0.516	1 (0–6)	1 (0–7)	0 (0–5)	0.228

Mann–Whitney U or Kruskal–Wallis test for independent samples with a significance level of 0.05; Bold values indicate statistically significant differences. No individual presented with the TT genotype for *rs1256049*.

Age affects the perception of OHRQoL.[4,8] In our study, the old-age group had an overall worse perception of OHRQoL and in domains related to physical pain, physical disability, psychological discomfort, psychological disability, and social handicap. Bortoluzzi et al.[8] (2015) also reported that older individuals have a worse perception of facial aesthetics and oral functions. Considering this premise, it is important to note that these individuals may have experienced various negative effects over the years, where physical and psychosocial factors may have already been affected.

We also observed that individuals with facial profile II had a worse perception in the social disability domain than those with facial profile III. According to De Ávila et al.,[23] individuals with facial features that deviate from the acceptable standard have difficulties in interpersonal relationships. In 2010, Johnston and colleagues also showed that facial profile II individuals felt a greater degree of unhappiness and insecurity than profile III individuals.[21] This may occur due to differences in facial profile aesthetics, in which profile II individuals could have a greater discrepancy in facial bones and overall deformity.[9]

One notable point in our study was the unequal sample sizes of male and female participants; women were overrepresented in our sample group. The demand for health services is known to be more frequent among females. They are more concerned about facial aesthetics, which motivates them to seek

treatment.[21] Our results showed that women had a worse OHRQoL than men. These data corroborate the available evidence that women are up to two times more likely to report negative impacts on their OHRQoL.[24] This worsened perception in women with DFD was found in the preoperative and postoperative periods of orthognathic surgery.[5]

Our results also showed that women with DFD had worse perception of physical pain. Women exhibit more symptoms of pain compared to men.[25] Several factors could be associated with sex differences in pain perception and the higher prevalence of chronic pain conditions in women.[26] Biological factors, such as sex hormones, menstrual cycle, and age, are believed to be the main factors influencing these differences.[26] Psychological changes are also affected in a gender-specific manner. Women are usually more affected by mental disorders, such as depression and psychological distress, than men.[27,28] The domains of discomfort and psychological disability were also associated with worsening perception of OHRQoL in women in our study. This may be due to sex differences in brain activity during emotional regulation and emotional processing.[29] Psychological factors are also associated with changes in the endocrine system, which controls the reproductive system.[30] Postmenopausal women, for example, experience considerable biological and psychological changes, including reduced levels of estrogen, which may be related to depression.[31]

Estrogens are sex hormones that perform several functions apart from those affecting the reproductive system.[33] ERs are located in many brain regions, such as the synaptic terminals and dendritic spines, axons, mitochondria, and glial cells.[32] Thus, ERs regulate various brain areas responsible for cognitive function, emotion, memory, and behavior.[33] They are also involved in the preservation of bone mass and regulation of lipoprotein synthesis and insulin levels.[34] Moreover, they act in other parts of the human body, such as the musculoskeletal,[35] cardiovascular, and immune systems.[36]

We observed an association between *rs9340799* polymorphism and the functional limitation domain in OHIP-14. Homozygous GG individuals had a worse perception of OHRQoL in this domain than AA and AG individuals. This association may be explained by the broad spectrum of estrogens in the central nervous system of both sexes;[32] therefore, the amended levels of this hormone can negatively affect some functions in the human body. Additionally, lack of estrogen may lead to an imbalance in physiological activities and indirectly result in physical and functional limitations. For example, ERα expression impacts TMD in animal models[37], and *ESR1* is associated with TMJ pain in the postoperative period of orthognathic surgery,[38] which can lead to stress, anxiety, psychosocial comorbidities, and risk of functional limitation. More studies are necessary to elucidate the exact effects of estrogen on the functional and physical aspects of patients with DFD.

Additionally, an association was observed between *rs9340799* and the social handicap domain. Homozygous GG individuals have a worse OHRQoL in this domain than AG individuals. These results indicate that *ESR1* may be involved in the perception of social behavior. In fact, previous research found associations among the altered expression levels of ERs in the brain and social recognition and social learning.[39] Also, studies performed in mice have shown that ER deficiency generates deficits in social recognition tasks.[40] Therefore, estrogens have repeatedly been shown to be associated with a wide range of social behaviors. Further investigations related to the impacts of estrogen and ER on social aspects of quality of life are required to elucidate their effects on social behavior and, more specifically, to advance our understanding of sex differences and flexibility in social interactions among humans.

In the present study, *ESR2* polymorphisms were not associated with OHRQoL in patients with DFD. Although *ESR2* was previously reported to be associated with anxiety disorders[16] and depression,[11] studies to date regarding this gene are too few to draw solid conclusions. Furthermore, the majority of studies on *ESR2* were performed in women. Thus, the effect of this gene in men remains unclear. The lack of association between *ESR2* and OHRQoL may be attributed to the fact that both sexes were evaluated in our study, and the analysis was not adjusted for patient-associated factors. Second, the sample size may have impeded the detection

of subtle effects of both *ESR2* polymorphisms. Thus, future studies should include a larger sample population and evaluate the entire extension of *ESR2* to validate these results.

Although the findings of this study are promising, their limitations merit further discussion. First, the OHRQoL is a highly multifactorial element, and other variables may account for its overall perception, including psychological comorbidities, depression, DFD severity, environmental factors, and anxiety levels. These confounding factors were not considered in our analyses, and might have affected our results because physical and emotional aspects are largely determined by interactions between environmental and genetic factors. Second, the OHIP-14 scores were used as non-parametric variables; therefore, it was not possible to perform an adjusted analysis with patient-associated factors or to calculate the statistical power. Thus, the results obtained here must be further parsed, considering other aspects that can worsen or attenuate relationships between genetic components and OHRQoL in patients. Another limitation that should be overcome in the future is the sample size. Sample size calculation was not performed because this study only included a conveniently identified population that sought orthognathic treatment. Therefore, future studies should also include a general population to confirm these results.

Despite the limitations of this study, it is the first one to attempt to identify the genetic contributions of *ESR1* and *ESR2* to the OHRQoL in patients with DFD. Although our results do not show the exact mechanism by which estrogen affects the OHRQoL, we provide statistical evidence that *ESR1* and various patient-associated factors may be involved in this process, and these data should be further examined in future studies.

Conclusion

Several factors, including age, sex, and facial profile type, can contribute to worsened OHRQoL. In addition, individuals with GG genotype in *rs9340799* (*ESR1)* had a worse impact on the OHRQoL in the functional limitation and social handicap domains in patients with DFD.

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