Research, Society and Development, v. 10, n. 7, e29010716487, 2021
(CC BY 4.0) | ISSN 2525-3409 | DOI: http://dx.doi.org/10.33448/rsd-v10i7.16487

Tooth agenesia might be associated with palatine rugae pattern in a tooth Brazilians population

Agenesia dentária pode estar associada ao padrão de rugas palatinas em uma população brasileira

La agenesia dental podría estar asociada al patrón de ruga palatina en una población brasileña

Received: 05/25/2021 | Reviewed: 06/01/2021 | Accept: 06/08/2021 | Published: 06/22/2021

Alice Corrêa Silva-Sousa
ORCID: https://orcid.org/0000-0002-9931-0935
University of São Paulo, Brazil
E-mail: alicesousa@usp.br
Carla Silva Carvalho
ORCID: https://orcid.org/0000-0003-0436-8411
University of Uberaba, Brazil
E-mail: carlacarvalhodt@hotmail.com
Guido Artemio Marañón-Vásquez
ORCID: https://orcid.org/0000-0001-7029-0347
Federal University of Rio de Janeiro, Brazil
E-mail: guido amv@hotmail.com
Mirian Aiko Nakane Matsumoto
ORCID: https://orcid.org/0000-0001-8559-8715
University of São Paulo, Brazil
E-mail: manakanematsu@gmail.com
Maria Bernadete Stuani
ORCID: https://orcid.org/0000-0001-7791-9144
University of São Paulo, Brazil
E-mail: bernadete@forp.usp.br
Maria Angélica Hueb de Menezes Oliveira
ORCID: https://orcid.org/0000-0002-2243-9618
University of Uberaba, Brazil
E-mail: angelicahueb@hotmail.com
Cesar Penazzo Lepri
ORCID: https://orcid.org/0000-0003-4372-9718
University of Uberaba, Brazil
E-mail: cesarlepri@yahoo.com.br
Peter Proff
ORCID: https://orcid.org/0000-0003-1137-5361
University of Regensburg, Germany
E-mail: peter.proff@klinik.uni-regensburg.de
Eva Paddenberg
ORCID: https://orcid.org/0000-0001-8207-5257
University of Regensburg, Germany
E-mail: eva.paddenberg@klinik.uni-regensburg.de
Christian Kirschneck
ORCID: https://orcid.org/0000-0001-9473-8724
University of Regensburg, Germany
E-mail: christian.kirschneck@klinik.uni-regensburg.de
Erika Calvano Küchler
ORCID: https://orcid.org/0000-0001-5351-2526
University of Regensburg, Germany
University of São Paulo, Brazil
E-mail: erikacalvano@gmail.com

Abstract

Tooth and palate development share several molecules during their formation, which could explain some recent studies suggesting that tooth agenesis is associated with palatine rugae pattern. Therefore, the purpose of the se cross sectional study was to investigate the association between palatine rugae phenotypes and tooth agenesis in Brazilian patients. After applying inclusion and exclusion criteria 83 records from orthodontic patients were evaluated. Tooth agenesis cases were diagnosed by evaluation of panoramic radiographs and by anamnesis. The casts and intraoral occlusal photography of each patient were used to evaluated the palatine rugae according to length, shape, direction and unification. All analyses were performed by the same calibrated examiner. All tests were performed with an established alpha of 0.05 ($P \leq .05$). Odds ratio calculations and chi-square or Fisher exact tests were used in the statistical analysis. A total of 17 (20.7%) patients with tooth agenesis was observed. The predominant shape of rugae was wavy (66.3%). The absence of secondary or fragmentary rugae was associated with tooth agenesis ($p = 0.047$; Odds ratio=3.00, Confidence Interval 95%=1.03-9.53). In conclusion, patients with tooth agenesis present a different palatine rugae

pattern. The absence of secondary or fragmentary rugae was associated with isolated tooth agenesis in the population studied.
Keywords: Palate; Tooth agenesis; Maxillofacial development.

Resumo

O desenvolvimento dentário e palatino compartilham diversas moléculas durante sua formação, o que poderia explicar alguns estudos recentes que sugerem que a agenesia dentária está associada ao padrão de rugas palatinas. Portanto, o objetivo do presente estudo transversal foi investigar a associação entre os fenótipos da ruga palatina e a agenesia dentária em pacientes brasileiros. Após a aplicação dos critérios de inclusão e exclusão, 83 registros de pacientes ortodônticos foram avaliados. Os casos de agenesia dentária foram diagnosticados através da avaliação de radiografias panorâmicas e por anamnese. Moldes e fotografias oclusais intrabucais de cada paciente foram utilizados para avaliar as rugas palatinas de acordo com o comprimento, forma, direção e unificação. Todas as análises foram realizadas pelo mesmo examinador calibrado. Todos os testes foram realizados com um alfa estabelecido de 0,05 ($P \leq .05$). Na análise estatística foram utilizados os cálculos da razão de chances e os testes exatos do qui-quadrado ou Fisher. Um total de 17 (20,7%) pacientes com agenesia dentária foi observado. A forma predominante de rugae era ondulada (66,3%). A ausência de ruga secundária ou fragmentária foi associada à agenesia do dente ($p = 0,047$; Odds ratio=3,00, Intervalo de confiança 95%=1,03-9,53). Em conclusão, pacientes com agenesia dentária apresentam um padrão diferente de ruga palatina. A ausência de ruga secundária ou fragmentária foi associada à agenesia isolada de dente na população estudada.
Palavras-chave: Palato; Agenesia dentária; Desenvolvimento maxilofacial.

Resumen

Los procesos de formación dentaria y palatina comparten varias vías moleculares, por lo cual estudios recientes han sugerido que la agenesia dental podría estar asociada con el patrón de las rugas palatinas. El propósito de este estudio transversal fue investigar la asociación entre fenotipos de las rugas palatinas y la agenesia dentaria en pacientes brasileños. Con base en los criterios de inclusión y exclusión establecidos, se seleccionaron 83 registros de pacientes ortodóncicos. Los casos de agenesia dentaria fueron diagnosticados por evaluación de radiografías panorámicas y por medio de anamnesis. El modelo de yeso y la fotografía intraoral oclusal superior de cada paciente fueron utilizados para evaluar las rugas palatinas en relación a su longitud, forma, dirección y unificación. Todos los análisis fueron realizados por el mismo examinador calibrado. Las pruebas estadísticas se realizaron con un alfa de 0,05 ($p \leq 0,05$). Cálculos del Odds ratio, así como la aplicación de las pruebas chi-cuadrado o exacta de Fisher fueron realizadas para el análisis estadístico de los datos. Se observó un total de 17 pacientes (20.7 %) con agenesia dentaria. La forma predominante de ruga fue la ondulada (66,3%). La ausencia de rugas secundarias o fragmentarias se asoció con la presencia de agenesia dentaria ($p = 0.047$; Odds ratio = 3.00, Intervalo de confianza al 95% = 1.03-9.53). En conclusión, los pacientes con agenesia dental presentan un patrón de rugas palatinas diferente. La ausencia de rugas secundarias o fragmentarias se asoció con la agenesia dental aislada en la población estudiada.
Palabras clave: Palacio; Agenesia dentaria; Formación maxilofacial.

1. Introduction

Tooth agenesis is the congenital absence of one or more teeth in the oral cavity (Endo et al., 2006; Marañón-Vásquez et al., 2019). This condition is relatively frequent in humans with a reported global prevalence of 6.4% observed in a systematic review (Khalaf et al., 2014). Although it can affect both dentitions, it is more common in permanent teeth with third molars, premolars and maxillary lateral incisors being the most affected group of teeth (Küchler et al., 2018; Khalaf et al., 2014). Hypodontia is the absence of 1 to 6 permanent teeth, Oligodontia is an uncommon tooth agenesis phenotype, characterized by the absence of of six or more teeth (excluding third molars) and Anodontia is the term used for the congenital absence of all teeth (Küchler et al., 2018, Masood et al., 2018)

Palatine rugae are a set of transverse keratinized ridges that are located in the anterior region of the hard palate, bilaterally to the palatine raphe, behind the incisor papilla (Patil, Patil & Acharya, 2008). The number of these anatomical structures is variable (Moran et al., 2016) with high diversity in their shape, direction and presence of unifications (Silva-Sousa et al., 2020). Palatine rugae have unique characteristics for each person, becoming an alternative method in forensic identification (O'Shaughnessy, 2001).

Odontogenesis, as well as the determination of the pattern of palatal rugae, are processes orchestrated by genetically regulated molecular pathways (Kapadia, Mues & D'Souza, 2007; Trakanant et al., 2019). Tooth development and palate development share several molecules during craniofacial formation and development (Gritli-Linde, 2007; Kouskoura et al., 2011; Graf et al., 2016). Interestingly, it has been observed that alterations in, for example, the Wnt signaling pathway would be

responsible for having both tooth agenesis (Cobourne & Sharpe, 2010) and impaired palatal rugae formation (Lin et al., 2011). In addition, it has been suggested that genetic variations in *WNT* might be associated with tooth agenesis (Kantaputra, P. & Sripathomsawat, 2011; Yu et al., 2019) and variations in the palatine rugae pattern in humans (Silva-Sousa et al., 2020). These findings could suggest that both processes could share common molecular pathways. In fact, previous studies in European samples have suggested that there is variation in the characteristics of palatal rugae in subjects with tooth agenesis and oligodontia (Moran et al., 2016; Armstrong et al. 2020). Assuming that there is phenotypic and genotypic variability between different populations, the present study had the objective of extending previous investigations on the association between palatal rugae phenotypes and tooth agenesis, this time in a Brazilian sample.

2. Methodology

The protocol of this study was approved by the Research Ethics Committee of the School of Dentistry of Ribeirão Preto, University of São Paulo (01451418.3.0000.5419/3.150.551). Informed consent was obtained from all participants and, when necessary, legal guardians. This study was conducted following the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guideline (von Elm et al., 2007; Cuschieri S, 2019)

Sample

The study was based on a consecutive sample including patients who were undergoing orthodontic treatment at graduate clinic of the School of Dentistry of Ribeirão Preto, University of Sao Paulo (Brazil). Patients with craniofacial congenital anomalies or syndromes, oral clefts, severe transverse maxillary deficiency, scar tissue in the palate, previous orthodontic treatment or with poor quality records were excluded from the study. Availability of dental casts, intraoral occlusal photographs and good quality panoramic radiographs was also a prerequisite.

Therefore, pre-orthodontic records from 143 orthodontic patients, both genders, were screened. After the application of inclusion and exclusion criteria, 83 were included. Forty-one (49.4%) patients were men and 42 (50.6%) were women. Their age ranged from 9 to 51 years; their mean age was 14.7 years (standard deviation = 6.5).

Diagnostic criteria for tooth agenesis

Tooth agenesis cases were diagnosed by evaluation of panoramic radiographs and by anamnesis. The absence of at least one permanent tooth, including the third molars, was established as tooth agenesis, if previous tooth loss or extraction could be ruled out by anamnesis. Diagnostic criteria were based on the individual's age and the expected stage of tooth formation seen on the radiographs (Antunes et al., 2013). Participants, for which the absence of teeth was not clearly due to a congenital absence, but rather due to trauma or tooth extraction, were excluded.

Determination of the palatine rugae pattern

Palatine rugae were evaluated via direct visual screening of the casts and intraoral occlusal photography of each patient.

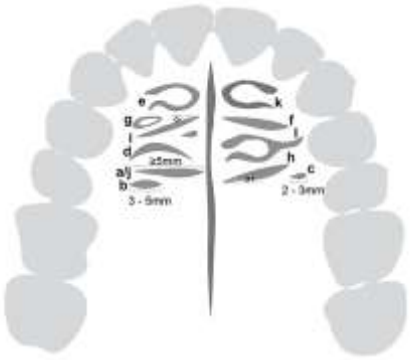
Each of the rugae was classified according to its length (Lysell, 1955), shape (Kapali, Townsend, Richards, & Parish, 1997), direction and unification (Carrea, 1955; Thomas & Kotze, 1983a, 1983b), based on the descriptions presented in Table 1 and Figure 1. From the dental casts, the length of the rugae was directly measured to the nearest 0.01 mm using an electronic hand-held digital caliper (Digimatic CD-15DCX; Mitutoyo®, Kawasaki, Japan). For non-straight rugae, a segment of wire was adapted according to the rugae shape, and then it was rectified for measurement. More details regarding pattern definition and measurements are described in Silva-Sousa et al. (2020).

Table 1. Definitions of the rugae characteristics recorded.

Rugae characteristic	Classification
Length	*Primary* = ≥ 5 mm.
	Secondary = 3 - 5 mm.
	Fragmentary = 2 - 3 mm.
Shape	*Curved* = Rugae curved gently.
	Wavy = Rugae with a curve at the origin or termination of curved rugae.
	Straight = Rugae run directly from their origin to termination.
	Circular = Rugae form a continuous circle.
Direction	*Forwardly directed* = Forming a positive angle.
	Backwardly directed = Forming a negative angle.
	Perpendicular = Perpendicular to the median raphe.
Unification	*Divergent* = Two rugae with the same origin from median raphe but immediately diverged.
	Convergent = Rugae with different origins that joined on their lateral portions.

Source: Authors.

Figure 1. Graphic description of rugae characteristics. Length: (a) Primary, (b) Secondary and (c) Fragmentary rugae. Shape: (d) Curved, (e) Wavy, (f) Straight and (g) Circular. Direction: (h) Forwardly, (i) Backwardly, and (j) Perpendicular. Unification: (k) Divergent and (l) Convergent



Source: Authors.

Statistical analysis

All available materials were examined by the same calibrated evaluator (ACSS) using the same protocol. Five random patients were evaluated twice within an 8-week interval, and then Cohen's kappa (κ) was applied to check the intraexaminer coefficient of agreement. The intraclass correlation coefficient (ICC) was used to determine the rater consistency of the repeated evaluations of rugae length. All ICC and κ values were above 0.9 ($p < 0.001$).

Data were analyzed using Graph Pad Prism 5.0a. All tests were performed with an established alpha of 0.05 ($P \leq .05$). To evaluate the association between tooth agenesis and palatine rugae patterns, the odds ratio calculations and chi-square or Fisher exact tests were used.

3. Results

Frequencies of tooth agenesis phenotypes are presented in Table 2. Seventeen patients presented agenesis of at least one permanent tooth (20.5%) (Table 2). The number of congenital missing teeth ranged from 1 to 15 with an average of 3.6 missing teeth per patient (standard deviation = 3.7). The most common congenitally missing tooth type was the third molar.

Table 2. Frequency of tooth agenesis phenotypes (n=83).

Phenotype	Frequency	
	n	%
No tooth agenesis	66	79.5
Tooth agenesis	17	20.5
Type of missing tooth/teeth		
Third Molar agenesis	11	13.3
Premolar agenesis	7	8.4
Upper lateral incisor agenesis	1	1.2
Other agenesis	4	4.8
Affected dental arch		
Agenesis in the maxilla	9	10.8
Agenesis in the mandible	13	15.7

Source: Authors.

The frequency distribution of palatine rugae patterns is presented in Table 3. The predominant shape of rugae was wavy (66.3%). It showed a high frequency of asymmetry in the size of the primary rugae (68.7%) and in the amount of rugae (60.2%). Rugae unification was observed in 66.3% of the patients and 56.6% presented secondary or fragmentary rugae. In addition, 54.2% had eight or more rugae.

Table 3. Frequency of palatal rugae phenotypes (n=83).

Phenotype		Frequency	
		n	%
Total amount of rugae	< 8 rugae	38	45.8
	≥ 8 rugae	45	54.2
Left-right symmetry on the amount of the rugae	Symmetry	33	39.8
	Asymmetry	50	60.2
Left-right symmetry on the length of primary rugae	Symmetry	26	31.3
	Asymmetry	57	68.7
Secondary or fragmentary rugae	Present	47	56.6
	Absent	36	43.4
Rugae unification	Present	55	66.3
	Absent	28	33.7
Predominant shape	Curved	27	32.5
	Wavy	55	66.3
	Straight	1	1.2
Rugae direction (Carrea's classification)	Only forwardly directed rugae	5	6.0
	Only perpendicular rugae	10	12.0
	Only backwardly directed rugae	9	10.8
	Differently directed rugae	59	71.2

There was an association between the presence of secondary/fragmentary rugae and the absence of tooth agenesis [($p = 0.047$); Odds ratio=3.00, Confidence Interval 95%=1.03-9.53)]. The absence of secondary rugae was significantly higher in patients with tooth agenesis. No other association between any palatine rugae patterns and presence of tooth agenesis was observed ($p > 0.05$) (Table 4).
Source: Authors.

Table 4. Tooth agenesis subgroups distribution according to the palatal rugae morphology.

Rugae morphology		Without tooth agenesis n (%)	Tooth agenesis n (%)	P-value
Total amount of rugae	< 8 rugae	32 (48.5)	6 (35.3)	0.330
	≥ 8 rugae	34 (51.5)	11 (64.7)	
Left-right symmetry on the amount of the rugae	Symmetry	27 (40.9)	6 (35.3)	0.673
	Asymmetry	39 (59.1)	11 (64.7)	
Left-right symmetry on the length of primary rugae	Symmetry	20 (30.3)	6 (35.3)	0.771
	Asymmetry	46 (69.7)	11 (64.7)	
Secondary or fragmentary rugae	Present	41 (62.1)	6 (35.3)	**0.046**
	Absent	25 (37.9)	11 (64.7)	
Rugae unification	Present	42 (63.6)	13 (76.5)	0.318
	Absent	24 (36.4)	4 (23.5)	
Predominant shape	Curved	23 (34.8)	4 (23.5)	0.569
	Wavy	42 (63.6)	13 (76.5)	
	Straight	1 (1.6)	0 (0.0)	
Rugae direction (Carrea's classification)	Only forwardly directed rugae	5 (7.6)	0 (0.0)	0.540
	Only perpendicular rugae	8 (12.1)	2 (11.8)	
	Only backwardly directed rugae	8 (12.1)	1 (5.8)	
	Differently directed rugae	45 (68.2)	14 (82.4)	

Note: In bold means statistically significance difference ($P < 0.05$).

Source: Authors.

Tooth agenesis subgroups were not associated with palatine rugae patterns ($p > 0.05$) (Tables 5, 6 and 7).

Table 5. Third molar tooth agenesis distribution according to the palatal rugae morphology.

Rugae morphology		Groups	Type of congenitally missing tooth	
		Without agenesis	Third Molar agenesis	P-value
Total amount of rugae n	< 8 rugae	35	3	0.1858
	≥ 8 rugae	37	8	
Left-right symmetry on the amount of the rugae n	Symmetry	28	5	0.6786
	Asymmetry	44	6	
Left-right symmetry on the length of primary rugae n	Symmetry	22	4	0.6989
	Asymmetry	50	7	
Secondary of fragmentary rugae n	Present	43	4	0.1454
	Absent	29	7	
Rugae unification n	Present	47	8	0.6265
	Absent	25	3	
Predominant shape n	Curved	25	2	0.4921
	Wavy	46	9	
	Straight	1	0	
Rugae direction (Carrea's classification) n	Only forwardly directed rugae	5	0	0.4022
	Only perpendicular rugae	9	1	
	Only backwardly directed rugae	9	0	
	Differently directed rugae	49	10	

Source: Authors.

Table 6. Premolar agenesis subgroups distribution according to the palatal rugae morphology.

Rugae morphology		**Groups**	**Type of congenitally missing tooth**	
		Without agenesis	Premolar agenesis	P-value
Total amount of rugae n	< 8 rugae	36	2	0.4007
	≥ 8 rugae	40	5	
Left-right symmetry on the amount of the rugae n	Symmetry	32	1	0.1501
	Asymmetry	44	6	
Left-right symmetry on the length of primary rugae n	Symmetry	23	3	0.4918
	Asymmetry	53	4	
Secondary of fragmentary rugae n	Present	43	4	0.9770
	Absent	33	3	
Rugae unification n	Present	50	5	0.7627
	Absent	26	2	
Predominant shape n	Curved	23	4	0.3417
	Wavy	52	3	
	Straight	1	0	
Rugae direction (Carrea's classification) n	Only forwardly directed rugae	5	0	0.7192
	Only perpendicular rugae	9	1	
	Only backwardly directed rugae	9	0	
	Differently directed rugae	54	5	

Source: Authors.

Table 7. Maxillary and mandibular tooth agenesis distribution according to the palatal rugae morphology.

Rugae morphology		Groups			Affected arch		
		Without tooth agenesis	Agenesis in maxilla	P-value	Without tooth agenesis	Agenesis in mandible	P-value
Total amount of rugae n	< 8 rugae	35	3	0.4272	33	5	0.2850
	≥ 8 rugae	39	6		35	10	
Left-right symmetry on the amount of the rugae n	Symmetry	30	3	0.6766	29	4	0.4708
	Asymmetry	44	6		41	9	
Left-right symmetry on the length of primary rugae n	Symmetry	22	4	0.3688	22	4	0.9625
	Asymmetry	52	5		48	9	
Secondary of fragmentary rugae n	Present	43	4	0.4348	42	5	0.1501
	Absent	31	5		28	8	
Rugae unification n	Present	49	6	0.9785	44	11	0.3471
	Absent	25	3		25	3	
Predominant shape n	Curved	24	3	0.9399	23	4	0.8954
	Wavy	49	6		46	9	
	Straight	1	0		1	0	
Rugae direction (Carrea's classification) n	Only forwardly directed rugae	5	0	0.4516	5	0	0.6348
	Only perpendicular rugae	8	2		9	1	
	Only backwardly directed rugae	9	0		8	1	
	Differently directed rugae	52	7		48	11	

Source: Authors.

4. Discussion

Several studies have been exploring the etiology and the factors associated with tooth agenesis in humans. Tooth agenesis can be part of a syndromic phenotype, but it is commonly an isolated trait. Isolated tooth agenesis is frequent in oral cleft patients and, interestingly, their non-affected family members are more commonly affected by tooth agenesis than the general population (Küchler et al., 2011; Marzowk et al., 2020). Patients with tooth agenesis have a higher risk to present other developmental dental anomalies (Küchler et al., 2008a, 2008b; Choi, Lee & Song, 2017). Interestingly, some recent studies have also been postulating a possible connection between tooth agenesis and the risk for different types of cancer (Küchler et al., 2013; Al-Muzian et al., 2021). The association between tooth agenesis and palatine rugae pattern has also been previously observed in some studies (Moran et al., 2016; Armstrong et al. 2020) and is poorly explored so far. Therefore, the present study aimed to evaluate the association between these two conditions.

In our study, we evaluated a sample of orthodontic patients from Brazil. We were able to observe an association between the presence of secondary or fragmentary rugae and the presence of tooth agenesis. This concurs with a recent study by Armstrong et al. (2020) from the United Kingdom. The authors observed that patients with tooth agenesis presented different palatine rugae patterns, including the number of secondary rugae and fragmentary rugae. Another study, also from the United Kingdom, observed that oligodontia presented different palatine rugae patterns, of which the curved shape was mode frequent in patients with oligodontia (Moran et al., 2016). Different from our study and from Armstrong et al. (2020), Moran et al. (2016) evaluated only patients with oligodontia, which is the congenital absence of six or more permanent teeth (excluding third molars). In our study, none of the patients presented oligodontia and we also included third molar agenesis. Armstrong et al. (2020) also observed different patterns according to the group of teeth missing. Secondary and fragmentary rugae were different mainly in patients presenting molar and premolar agenesis. In our study, a statistically significant difference was not observed according to the type of agenesis. It is possible that the sample size was a limitation for this stratified analysis and these results represent a type II error.

Palatine rugae pattern (Surekha et al., 2012; Ibeachu, Didia & Arigbede, 2014) and tooth agenesis (Khalaf et al., 2014) vary according to the ethnicity of the population. The prevalence of tooth agenesis ranges from 4.4% to 13.4% (excluding third molars) (Khalaf et al., 2014). In our manuscript, 20.5% of the evaluated patients had agenesis of at least one tooth. This prevalence is high due to the fact that third molar agenesis was included. Previous studies have shown a 10.3% prevalence of congenital agenesis of one or more third molars (Atay, Ozveren & Serindere, 2020). Mani, Mohsin & John (2014) reported that only the absence of third molars represented 27.7% of patients. Therefore, other studies should investigate the rugoscopy of patients with tooth agenesis in different populations as well as different types of tooth agenesis (hypodontia and oligodontia).

Although the number of patients is a limitation of our study, we were able to determine that patients with tooth agenesis present a different pattern of palatine rugae in accordance with previous studies (Moran et al., 2016; Armstrong et al., 2020). Our results suggest a common developmental pathway during the establishment of these structures (palatine rugae pattern and tooth pattern). Further studies are needed to investigate the molecular mechanisms involved in the relationship among these two conditions.

5. Conclusion

In conclusion, patients with tooth agenesis present a different palatine rugae pattern. The absence of secondary or fragmentary rugae was associated with isolated tooth agenesis in the population studied.

Acknowledgments

This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) Finance Code 001 (ACSS, CCSS, ECK and CK) and the Alexander-von-Humboldt-Foundation (ECK and CK, accepted in July 4th, 2019).

References

Al-Muzian, L.; Almuzian, M.; Mohammed, H.; Ulhaq, A.; Keightley, A. J. (2021) Are developmentally missing teeth a predictive risk marker of malignant diseases in non-syndromic individuals? A systematic review. *Journal of Orthodontics* 18;1465312520984166. Online ahead of print.

Altug-Atac, A. T.; Erdem, D. (2007) Prevalence and distribution of dental anomalies in orthodontic patients. *American Journal of Orthodontics and Dentofacial Orthopedics*, 131(4): 510–514.

Antunes, L. S.; Küchler, E. C.; Tannure, P. N.; Dias, J. B.; Ribeiro, V. N.; Lips, A.; Costa, M. C. Antunes, L. A.; Granjeiro, J. M. Genetic variations in MMP9 and MMP13 contribute to tooth agenesis in a Brazilian population. *J Oral Sci.*, 2013;55(4):281-6. doi: 10.2334/josnusd.55.281. PMID: 24351915.

Armstrong, J.; Seehra, J.; Andiappan, M.; Jones, A. G, Papageorgiou, S. N., Cobourne, M. T. (2020) Palatine rugae morphology is associated with variation in tooth number. *Sci Rep* 10(1):19074.

Atay, M.T.; Ozveren, N.; Serindere G. (2020) Evaluation of third molar agenesis associated with hypodontia and oligodontia in turkish pediatric patients. *European Oral Research* 54(3):136-141.

Carrea, J. U. (1955). Fotostenograms of palate folds, a new identification technic. *Deutsche Zahnarztliche Zeitschrift*, 10:11–17.

Choi, S. J.; Lee, J. W.; Song, J. H. (2017) Dental anomaly patterns associated with tooth agenesis. *Acta Odontol Scand* 75(3):161-165.

Cobourne, M. T.; Sharpe, P. T. (2010) Making up the numbers: The molecular control of mammalian dental formula. *Semin Cell Dev Biol*, 21(3):314-24.

Cuschieri, S. (2019) The STROBE guidelines. *Saudi J Anaesth*, 13(1): S31-S34.

Endo, T.; Ozoe, R.; Kubota, M.; Akiyama, M.; Shimooka, S. (2006) A survey of hypodontia in Japanese orthodontic patients. *American Journal of Orthodontics and Dentofacial Orthopedics*, 129(1):29–35.

Fauzi, N. H.; Ardini, Y. D.; Zainuddin, Z.; Lestari, W. (2018) A review on non-syndromic tooth agenesis associated with PAX9 mutations. *Japanese Dental Science Review*, 54(1): 30–36.

Gritli-Linde, A. (2007) Molecular control of secondary palate development. *Dev Biol*, 301(2):309-26.

Ibeachu, P. C.; Didia, B. C.; Arigbede, A. O. (2014) A comparative study of palatine rugae patterns among Igbo and Ikwerre ethnic groups of Nigeria: a university of port harcourt study. *Anat. Res. Int*, 2014:123925.

Kapali, S.; Townsend, G.; Richards, L.; Parish, T. (1997) Palatine rugae in Australian aborigenes and Caucasians. *Australian Dental Journal*, 42:129–133.

Kantaputra, P.; Sripathomsawat, W. (2011) WNT10A and isolated hypodontia. *Am. J. Med. Genet. A* 155A:1119–1122.

Khalaf, K.; Miskelly, J.; Voge, E.; Macfarlane, T. V. (2014) Prevalence of hypodontia and associated factors: a systematic review and meta-analysis. *Journal of Orthodontics*, 41(4):299–316.

Kouskoura, T.; Fragou, N.; Alexiou, M.; John, N.; Sommer, L.; Graf, D.; Katsaros, C.; Mitsiadis, T. A. (2011) The genetic basis of craniofacial and dental abnormalities. Schweiz Monatsschr Zahnmed 121(7-8):636-46.

Küchler, E. C.; Risso, P. A.; Costa, M. C.; Modesto, A.; Vieira, A. R. (2008a) Studies of dental anomalies in a large group of school children. *Arch Oral Biol* 53(10):941-6.

Küchler, E. C.; De Andrade Risso, P.; De Castro Costa, M.; Modesto, A.; Vieira, A. R. (2008b) Assessing the proposed association between tooth agenesis and taurodontism in 975 paediatric subjects. *Int J Paediatr Dent.* 18(3):231-4.

Küchler, E. C.; da Motta, L. G.; Vieira, A. R.; Granjeiro, J. M. (2011) Side of dental anomalies and taurodontism as potential clinical markers for cleft subphenotypes. *Cleft Palate Craniofac J*, 48(1):103-8.

Küchler, E. C.; Lips, A.; Tannure, P. N.; Ho, B.; Costa, M. C.; Granjeiro, J. M.; Vieira A. R. (2013) Tooth agenesis association with self-reported family history of cancer. *J Dent Res*, 92(2):149-55.

Lin, C.; Fisher, A. V.; Yin, Y.; Maruyama, T.; Veith, G. M.; Dhandha, M.; Huang, G. J.; Hsu, W.; Ma, L. (2011) The inductive role of Wnt-β-Catenin signaling in the formation of oral apparatus. *Dev Biol*, 356(1):40-50.

Lysell, L. (1955) Plicae palatine transversae and papilla incisive in man: A morphologic and genetic study. *Acta Odontologica Scandinavica*, 13:5–137.

Mani, S. A.; Mohsin, W. S.; John, J. (2014) Prevalence and patterns of tooth agenesis among Malay children. *Southeast Asian J Trop Med Public Health*, 45(2):490-8.

Marañón-Vásquez, G. A.; Spada, P. P.; Omori, M. A.; Zielak, J.; Ferreira, J. T. L.; Araújo, M. T. S.; Matsumoto, M. A. N.; Küchler, E. C. (2019) Genetic polymorphism in ESR2 and risk of tooth genesis. *Revista Científica do CRO-RJ (Rio de Janeiro Dental Journal)*, 4(1): 28-33.

Marzouk, T.; Alves, I. L.; Wong, C. L.; DeLucia, L.; McKinney, C. M.; Pendleton, C.; Howe, B. J.; Marazita, M. L.; Peter, T. K.; Kopycka-Kedzierawski, D. T.; Morrison, C. S.; Malmstrom, H.; Wang, H.; Shope, E. T. (2020) Association between Dental Anomalies and Orofacial Clefts: A Meta-analysis. JDR Clin Trans Res. 8:2380084420964795. Epub ahead of print.

Masood, F.; Benavides, E. (2018) Alterations in Tooth Structure and Associated Systemic Conditions. *Radiol Clin North Am.*, 56(1):125-140.

Moran, A.; Tippett, H.; Manoharan, A.; Cobourne, M. T. (2016) Alteration of palatine ruga pattern in subjects with oligodontia: A pilot study. *American Journal of Orthodontics and Dentofacial Orthopedics*, 150(2): 295-302.

O'Shaughnessy, P. E. (2001) Introduction to forensic science. *Dent Clin North Am*, 45(2):217-27.

Paliwal, A.; Wanjari, S.; Parwani, R. (2010) Palatine rugoscopy: Establishing identity. *Journal of Forensic Dental Sciences* 2(1):27-31.

Patil, M. S.; Patil, S. B.; Acharya, A. B. (2008) Palatine Rugae and Their Significance in Clinical Dentistry. *The Journal of the American Dental Association*, 139(11):1471–1478.

Rakhshan, V.; Rakhshan, H. (2016) Meta-analysis and systematic review of the number of non-syndromic congenitally missing permanent teeth per affected individual and its influencing factors *Eur J Orthod*, 38(2):170-7.

Silva-Sousa, A. C.; Marañón-Vásquez, G. A.; Gerber, J. T.; Judachesci, C. S.; Stuani, M. B. S.; Nakane Matsumoto, M. A.; Coletta, R. D.; Scariot, R.; Küchler, E. C. (2020) Left-right asymmetry in palatal rugae is associated with genetic variants in WNT signaling pathway. *Arch Oral Biol* 110:104604.

Surekha, R.; Anila, K.; Reddy, V. S.; Hunasgi, S.; Ravikumar, S.; Ramesh, N. (2012) Assessment of palatal rugae patterns in Manipuri and Kerala population. *J Forensic Dent Sci*, 4(2):93-6.

Sweat, Y. Y.; Sweat, M.; Yu, W.; Sanz-Navarro, M.; Zhang, L.; Sun, Z.; Eliason, S.; Klein, O. D.; Michon, F.; Chen, Z.; Amendt, B. A. (2020) Sox2 Controls Periderm and Rugae Development to Inhibit Oral Adhesions. *J Dent Res* 99(12):1397-1405.

Thomas, C. J.; Kotze, T. J. (1983a) The palatine rugae pattern in six southern African human populations, Part I: A description of the populations and a method for its investigation. *Journal of The Dental Association South Africa*, 38:547–553.

Thomas, C. J.; Kotze, T. J. (1983b) The palatine rugae pattern: A new classification. *Journal of The Dental Association South Africa*, 38:153–157.

Trakanant, S.; Nihara, J.; Kawasaki, M.; Meguro, F.; Yamada, A.; Kawasaki, K.; Saito, I.; Takeyasu, M.; Ohazama, A. (2020) Molecular mechanisms in palatal rugae development. *J Oral Biosci*, 62(1):30-35.

von Elm, E.; Altman, D. G.; Egger, M.; Pocock, S. J.; Gøtzsche, P. C.; Vandenbroucke, J. P. (2007) STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Epidemiology*, 18:800–804.

Yu, M.; Wong, S. W.; Han, D.; Cai, T. (2019) Genetic analysis: Wnt and other pathways in nonsyndromic tooth agenesis. *Oral diseases* 25(3):646–651.