Tooth agenesis 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

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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 ≤ 0.05). 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.

**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 ≤ 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; Maraño-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; Cuschiere 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 São 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 ≤ .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 |
|-------------------------------|-----------|
| 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.
| 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 |
| Present                                 | 47 | 56.6 |
| **Secondary or fragmentary rugae**      |    |    |
| Absent                                  | 36 | 43.4 |
| Present                                 | 55 | 66.3 |
| Curved                                  | 27 | 32.5 |
| **Rugae unification**                   |    |    |
| Absent                                  | 28 | 33.7 |
| Curved                                  | 27 | 32.5 |
| **Predominant shape**                   |    |    |
| 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)             |         |
| Curved                                  | 23 (34.8)                    | 4 (23.5)             |         |
| Predominant shape                       |                              |                      |         |
| Wavy                                    | 42 (63.6)                    | 13 (76.5)            | 0.569   |
| Straight                                | 1 (1.6)                      | 0 (0.0)              |         |
| Rugae direction (Carrea's classification) |                              |                      |         |
| Only forwardly directed rugae           | 5 (7.6)                      | 0 (0.0)              |         |
| Only perpendicular rugae                | 8 (12.1)                     | 2 (11.8)             | 0.540   |
| 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 | P-value |
|-------------------------------------------|-------------------------|-----------------------------------|---------|
|                                           | Without agenesis | Third Molar agenesis |                  |
| 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       |         |
|                                           | Present                | 43                               | 4       |         |
|                                           | Absent                 | 29                               | 7       |         |
|                                           | Present                | 47                               | 8       | 0.6265 |
|                                           | Absent                 | 25                               | 3       |         |
|                                           | Curved                 | 25                               | 2       |         |
| Predominant shape n                       | Wavy                   | 46                               | 9       | 0.4921 |
|                                           | Straight               | 1                                | 0       |         |
|                                           | Only forwardly directed rugae | 5                             | 0       |         |
|                                           | Only perpendicular rugae | 9                             | 1       | 0.4022 |
|                                           | 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       |          |
|                                                       | Present                  | 50       | 5       | 0.7627  |
| Rugae unification n                                   | Absent                   | 26       | 2       |          |
|                                                       | Curved                   | 23       | 4       | 0.3417  |
|                                                       | Wavy                     | 52       | 3       |          |
| Predominant shape n                                   | Straight                 | 1        | 0       |          |
|                                                       | Only forwardly directed rugae | 5 | 0 | 0.7192 |
|                                                       | Only perpendicular rugae | 9 | 1 |          |
| Rugae direction (Carrea's classification) n           | 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 | Agenesis in maxilla | P-value | Affected arch | Agenesis in mandible | P-value |
|----------------------------------------|--------|---------------------|---------|---------------|----------------------|---------|
|                                        | (Without tooth agenesis) | (Agenesis in maxilla) |         | (Without tooth agenesis) | (Agenesis in mandible) |         |
| Total amount of rugae n                |        |                     |         |               |                      |         |
| < 8 rugae                              | 35     | 3                   | 0.4272  | 33            | 5                    | 0.2850  |
| ≥ 8 rugae                              | 39     | 6                   | 0.6766  | 35            | 10                   |         |
| Left-right symmetry on the amount of the rugae n |        |                     |         |               |                      |         |
| Symmetry                               | 30     | 3                   | 0.3688  | 29            | 4                    | 0.4708  |
| Asymmetry                              | 44     | 6                   | 0.9625  | 41            | 9                    |         |
| Left-right symmetry on the length of primary rugae n |        |                     |         |               |                      |         |
| Symmetry                               | 22     | 4                   | 0.3688  | 22            | 4                    | 0.9625  |
| Asymmetry                              | 52     | 5                   | 0.1501  | 48            | 9                    |         |
| Secondary of fragmentary rugae n       |        |                     |         |               |                      |         |
| Present                                | 43     | 4                   | 0.4348  | 42            | 5                    | 0.1501  |
| Absent                                 | 31     | 5                   | 0.9785  | 28            | 8                    |         |
| Rugae unification n                    |        |                     |         |               |                      |         |
| Present                                | 49     | 6                   | 0.9785  | 44            | 11                   | 0.3471  |
| Absent                                 | 25     | 3                   | 0.8954  | 25            | 3                    |         |
| Curved                                 | 24     | 3                   | 0.4516  | 23            | 4                    | 0.6348  |
| Predominant shape n                    |        |                     |         |               |                      |         |
| Wavy                                   | 49     | 6                   | 0.4516  | 46            | 9                    |         |
| Straight                               | 1      | 0                   | 0       | 1             | 0                    |         |
| Only forwardly directed rugae          | 5      | 0                   | 0       | 5             | 0                    |         |
| Only perpendicular rugae               | 8      | 2                   | 1       | 9             | 1                    | 0.6348  |
| Only backwardly directed rugae         | 9      | 0                   | 0       | 8             | 1                    |         |
| Differently directed rugae             | 52     | 7                   | 1       | 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 more 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 in 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).

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