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JORDANNA DE MELO TEIXEIRA DO BRASIL

ESTUDO DA MORFOLOGIA DA SELA TÚRCICA, AGENESIA DENTÁRIA E O PAPEL DO GENE PITX2 NOS FENÓTIPOS SUPRACITADOS

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Dissertação apresentada ao Programa de Pós-Graduação em Odontologia - Mestrado Acadêmico da Universidade de Uberaba, como requisito para obtenção do título de Mestre em Odontologia, na Área de Concentração em Clínica Odontológica Integrada.

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RESUMO

As agenesias dentárias são anomalias frequentes na prática clínica e contribuem para desenvolvimento de maloclusões. As fases iniciais da odontogênese coincidem com o desenvolvimento da sela túrcica; que é uma estrutura anatômica localizada na superfície intracraniana no osso esfenoide que envolve a glândula pituitária. A glândula pituitária e os hormônios excretados por ela interferem diretamente no desenvolivmento craniofacial. Desta forma, o presente estudo objetivou 1) realizar uma revisão de literatura sistematizada sobre a associação entre agenesia dentária e sela túrcica; 2) realizar uma revisão de literatura sobre os métodos disponíveis para avaliação da sela túrcica na pesquisa odontológica; 3) investigar a morfologia da sela túrcica em pacientes portadores de agenesia de terceiros molares; e 4) investigar se o gene PITX2 está associado com agenesia de terceiros molares e/ou morfologia da sela túrcica. A revisão de literatura sistematizada foi realizada a partir de estudos publicados até outubro de 2021. A plataforma de dados Pubmed® foi utilizada com os seguintes descritores: "tooth agenesis", "oligodontia", "hypodontia", "congenital missing tooth", "dental agenesis", "congenital missing teeth", "anodontia" and "sella turcica Os critérios de inclusão seguiram as recomendações da declaração PRISMA, seguindo os parâmetros PECOS. Para avaliação dos métodos disponíveis para avaliação da sela túrcica na pesquisa odontológica, uma revisão de literatura foi realizada com os seguintes descritores: "sella turcica", "bridging of sella", "size, shape of sella túrcica" e "sella turcica morphology". As plataformas Pubmed® e Google Scholar® foram utilizadas. Para o artigo de pesquisa original, uma amostra composta de pacientes alemães,13 anos de idade, que iniciaram o tratamento ortodôntico da Universidade de Regensburg foi utilizada. Pacientes sindrômicos e com alterações sistêmicas foram excluídos do estudo. A agenesia dentária foi avaliada por meio das radiografias panorâmicas. As variações morfológicas da sela túrcica foram avaliadas por meio do cefalograma lateral. Variáveis como: altura anterior e posterior, altura média, largura, profundidade, diâmetro, área e distância interclinoide foram avaliadas por meio do software ImageJ. Amostras de DNA foram utilizadas para a genotipagem de polimorfismos genéticos em PITX2. As análises foram realizadas no programa GraphPad Prism 7.04 considerando uma significância de 5%. A revisão de literatura sistematizada concluiu que há uma associação entre agenesia dentária e as variações na morfologia da sela túrcica em determinadas populações. A revisão de literatura sobre métodos para avaliação da sela túrcica na pesquisa odontológica nos demonstra que métodos paramétricos e não-paramétricos podem ser utilizados. Em relação ao artigo de pesquisa

original, a amostra de crianças alemãs não demonstrou associação entre agenesia dentária e fenótipos da sela túrcica ($p>0,05$). Polimorfismos genéticos em PITX2 também não foram associados a agenesia dentária de terceiros molares ($p>0,05$). O polimorfismo genético rs3796902 foi associado ao processo clinóide hipertrófico posterior ($p=0,013$). Os polimorfismos genéticos rs1947187 e rs2595110 foram associados com a ponte da sela túrcica tipo A ($p=0,013$ e $p=0,011$, respectivamente para distribuição dos genótipos). Conclui-se que a agenesia dentária está associada a morfologia da sela túrcica em determinadas populações. Os métodos de avaliação são significativos e precisos. Em crianças alemãs, a morfologia da sela túrcica não foi influenciada pela agenesia de terceiros molares. Polimorfismos genéticos em PITX2 podem estar associados com fenótipos da sela túrcica em crianças alemãs.

Palavras-chave: Agenesia dentária, oligodontia, hipodontia, ausência dentária congênita, agenesia dentária, ausência dentária congênita, anodontia, sela túrcica, ponte de sela, tamanho da sela túrcica, forma da sela túrcica e morfologia da sela túrcica e genes.

ABSTRACT

Dental agenesis are frequent anomalies in clinical practice and have led to the development of malocclusions. The initial phases of odontogenesis coincide with the development of the sella turcica; which is an anatomical structure located on the intracranial surface on the sphenoid bone surrounding the pituitary gland. The pituitary gland and the hormones excreted by it directly interfere with craniofacial development. Thus, the present study aimed to 1) conduct a systematized literature review on the association between tooth agenesis and sella turcica; 2) perform a literature review on available methods for evaluating the sella turcica in dental research; 3) to investigate the morphology of the sella turcica in patients with agenesis of third molars; and 4) investigate whether the PITX2 gene is associated with agenesis of third molars and/or morphology of the sella turcica. A systematic literature review was carried out based on studies published up to October 2021. The Pubmed® data platform was used with the following descriptors: “tooth agenesis”, “oligodontia”, “hypodontia”, “congenital missing tooth”, “ dental agenesis”, “congenital missing teeth”, “anodontia” and “sella turcica The inclusion criteria followed the recommendations of the PRISMA statement, following the PECOS parameters. In order to evaluate the available methods for evaluating the sella turcica in dental research, a literature review was carried out with the following descriptors: “sella turcica”, “bridging of sella”, “size, shape of sella turcica” and “sella turcica morphology”. Pubmed® and Google Scholar® platforms were used. For the original research article, a sample composed of German patients, 13 years old, who started orthodontic treatment at the University of Regensburg was used. Syndromic patients with systemic alterations were excluded from the study. Tooth agenesis was evaluated using panoramic radiographs. The morphological variations of the sella turcica were evaluated using the lateral cephalogram. Variables such as: anterior and posterior height, average height, width, depth, diameter, area and interclinoid distance were evaluated using the ImageJ software. DNA samples were used for genotyping of genetic polymorphisms in PITX2. The analyzes were carried out in the GraphPad Prism 7.04 program considering a significance of 5%. The systematized literature review concluded that there is an association between tooth agenesis and variations in the morphology of the sella turcica in certain populations. The literature review on methods for evaluating the sella turcica in dental research demonstrates that parametric and non-parametric methods can be used. Compared to the original research article, the sample of German children showed no association between tooth agenesis and sella turcica phenotypes ($p>0.05$). Genetic polymorphisms in PITX2 were also not

associated with tooth agenesis of third molars ($p>0.05$). The genetic polymorphism rs3796902 was associated with the posterior hypertrophic clinoid process ($p=0.013$). Genetic polymorphisms rs1947187 and rs2595110 were associated with type A sella turcica bridge ($p=0.013$ and $p=0.011$, respectively for genotype distribution). It is concluded that tooth agenesis is associated with the morphology of the sella turcica in certain populations. The evaluation methods are meaningful and accurate. In German children, the morphology of the sella turcica was not influenced by third molar agenesis. Genetic polymorphisms in PITX2 may be associated with sella turcica phenotypes in German children.

Key-words: Tooth agenesis, oligodontia, hypodontia, congenital missing tooth, dental agenesis, congenital missing teeth, anodontia, sella turcica, bridging of sella, size of sella turcica, shape of sella turcica e sella turcica morphology, genetic polymorphisms and genes.

LISTA DE ABREVIATURAS E SIGLAS

DS Dorso da sela

TS Tubérculo da sela

SF Piso da sela

SA Ponto mais anterior da sela

SP Ponto mais posterior da sela

SM Ponto médio entre DS e TS

FH Plano de Frankfort

SUMÁRIO

1 INTRODUÇÃO

A agenesia dentária é a falta congênita de um ou mais dentes na cavidade bucal, seja na dentição decídua, ou na dentição permanente (AL-ANI *et al.,* 2017; BRASIL *et al.,* 2021). Indivíduos podem apresentar agenesia de um ou vários dentes sendo que a ausência de mais de sete dentes é chamada de oligondontia. A prevalência de agenesia dentária excluindo os terceiros molares é de 6,4% na população geral (KHALAF *et al.,* 2014). os terceiros molares possuem um desenvolvimento longo, estes são os últimos dentes a irromperem na cavidade bucal, por volta dos 17 anos, variando de acordo com a etnia (HERRMANN *et al.,* 2022). A prevalência de agenesia de terceiros molares é maior, afetando 22,6% da população geral (SCHEIWILLER *et al.,* 2020). A etiologia da agenesia dentária é descrita como multifatorial, sendo associada a fatores sistêmicos, fatores genéticos e fatores ambientais (AL-ANI *et al.,* 2017; ASLAM *et al.,* 2020; BRASIL *et al.,* 2021; STEFANI *et al.,* 2021).

A sela túrcica é uma depressão óssea intracraniana localizada no osso esfenoide (KAYA *et al.,* 2021). A sela túrcica é caracterizada por quatro processos clinóides (dois anteriores e dois posteriores), um tubérculo e um dorso (KUCIA *et al.,* 2014). A sela túrcica abriga a glândula pituitária que é uma glândula extremamente importante na secreção de vários hormônios (SCRIBANTE *et al.,* 2017). Estudos anteriores demonstraram variações normais no tamanho e fenótipo da sela túrcica (LEONARDI *et al., 2006;* SCRIBANTE *et al.,* 2017). A sela túrcica é um ponto importante observado nas telerradiografias laterais pelos ortodontistas, pois representa o centro geométrico onde são realizados os traçados cefalométricos (SCRIBANTE *et al.*, 2017; SATO & ENDO, 2020). Os traçados cefalométricos são importantes porque investigam o crescimento do crânio e da face, identifica más oclusões e auxilia o cirurgião-dentista a otimizar estratégias preventivas e terapeuticas (TSOLAKIS *et al.*, 2022).

O desenvolvimento embrionário da sela túrcica ocorre concomitante ao ao desenvolvimento dentário, a partir das células da crista neural (KUCIA *et al.,* 2014; SCRIBANTE, 2017; KAYA *et al.,* 2021). Diante o exposto, hipóteses são sugeridas sobre a associação de variações na morfologia da sela túrcica com anomalias dentofaciais, como agenesia dentária (LEONARDI *et al.,* 2006; SCRIBANTE *et al.,* 2017; SATO & ENDO,2020; ANTONARAKIS *et al.,* 2021; KAYA *et al.,* 2021).

Embora diversos estudos tenham investigado a associação entre agenesia dentária e os aspectos morfológicos da sela túrcica em diversas populações (LEONARDI *et al.,* 2006;

SCRIBANTE *et al.,* 2017; SATO & ENDO,2020; ANTONARAKIS *et al.,* 2021; KAYA *et al.,* 2021), nenhum estudo avaliou indivíduos com agenesia de terceiros molares na população alemã, Assim, o objetivo do presente trabalho foi investigar a associação entre fenótipos da sela túrcica e agenesia dentária.

2 OBJETIVO

2.1 OBJETIVO GERAL

Investigar a associação entre fenótipos da sela túrcica e agenesia dentária.

2.2 OBJETIVOS ESPECÍFICOS

- Realizar uma revisão sistematizada da literatura sobre a associação da morfologia da sela túrcica com agenesia dentária.
- Realizar uma revisão de literatura sobre os métodos disponíveis para avaliação da sela túrcica na pesquisa odontológica;
- Avaliar a morfologia da sela túrcica em pacientes com agenesia de terceiros molares em uma amostra de crianças alemãs.
- Investigar a associação do gene PITX2 com agenesia de terceiros molares em uma amostra de crianças alemãs.
- Investigar a associação do gene PITX2 com morfologia da sela túrcica em uma amostra de crianças alemãs.

3 JUSTIFICATIVA

Agenesia dentária de terceiro molar é uma anomalia de desenvolvimento do complexo craniofacial muito comum e possui etiologia multifatorial. Germes dentários e estruturas constituintes da sela túrcica são formados a partir das mesmas células da crista neural desta forma, este estudo tem o objetivo inédito de explorar aspectos etiológicos envolvidos em ambas as condições para compreender mecanismos envolvidos no processo desenvolvimento craniofacial.

Para melhor compreensão do presente trabalho, a dissertação será apresentada em capítulos de acordo com os artigos delineados.

4 CAPÍTULO 1

IS DENTAL AGENESIS ASSOCIATED WITH SELLA TURCICA MORPHOLOGY? A SYSTEMATIC REVIEW

AGENESIA DENTÁRIA ESTÁ ASSOCIADA A MORFOLOGIA DA SELA TÚRCICA? UMA REVISÃO SISTEMATIZADA

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4.1 ABSTRACT

Tooth development occurs synchronously with the development of the turcica sella; a structure responsible for accommodating the pituitary gland. Recent evidence suggests the relationship between sella turcica morphology and dental anomalies as well as, the influence of hormones excreted by the pituitary gland and craniofacial development. This study aimed to perform a systematic review to explore the association between tooth agenesis and the morphological variations of the sella turcica. The studies were included in this systematic review according to the PRISMA recommendations, following PECOS parameters. The search was carried out in the PubMed database using the following descriptors: tooth agenesis, oligodontia, hypodontia, congenital missing tooth, dental agenesis, congenital missing teeth, anodontia, sella turcica. The data from the included studies were compiled and organized according to the study's characteristics. The search retrieved 20 titles and abstracts. Only six articles were eligible for full article evaluation. Five studies evaluated isolated tooth agenesis, while one study evaluated tooth agenesis in non-syndromic oral cleft patients. Two articles were identified through a manual search. Almost all the studies showed that there is a significant association between sella turcica bridging and tooth agenesis. In conclusion, there is an association between tooth agenesis and the morphological variations of the sella turcica.

Key-words: tooth agenesis, anodontia, sella turcica.

4.2 INTRODUCTION

Tooth agenesis is an anomaly of the craniofacial complex characterized by the congenital absence of development of a tooth/teeth germ (AL-ANI *et al.,* 2017). Tooth agenesis has a multifactorial etiology, involving mainly genetic factors (AL-ANI *et al.,* 2017; LI *et al.,* 2018; ASLAM *et al.,* 2020). Individuals with tooth agenesis have more malocclusions, speech and esthetic problems (COSTA *et al.,* 2017; SAHOO *et al.,* 2019; STEFANI *et al.,* 2021). A systematic review and meta-analysis demonstrated that the prevalence of tooth agenesis varies according to the studied population and type of tooth. They calculated that the overall prevalence was 6.4%, excluding third molars (KHALAF *et al.,* 2014).

Tooth germs are formed from neural crest cells (MESSER; TILL, 2013), the same structure that leads to sella turcica formation (LEONARDI *et al.,* 2006). It is worth mentioning that the sella turcica is an intracranial bone depression located in the sphenoid bone that contains the pituitary gland (TEKINER; ACER; KELESTIMUR, 2015). The pituitary gland and the hormones excreted by it play an important role throughout the development and harmonious maintenance of the craniofacial complex (OMORI *et al.,* 2020; SPILLER *et al.,* 2020; BERGAMO *et al.,* 2021; KÜCHLER *et al.,* 2021; REIS *et al.,* 2021).

Interestingly, in the past two decades, some studies have been proposing the association between tooth agenesis with morphological variations of the sella turcica (LEONARDI *et al.,* 2006; SCRIBANTE *et al.,* 2017; SATO & ENDO, 2020; ZAHEER *et al.,* 2020; ANTONARAKIS, GHISLANZONI & FISCHER, 2021; KAYA *et al.,* 2021). Thus, the purpose of this study was to perform a systematic review to explore the association between tooth agenesis and the morphological variations of the sella turcica.

4.3 METHOD

4.3.1 Protocol, eligibility criteria and focused question

The inclusion criteria were according to the recommendations of the PRISMA statement (Page *et al.,* 2021), following the PECOS parameters, as follows:

P - Patients: patients with and without tooth agenesis in permanent teeth;

E – Exposition: Presence of tooth agenesis

C - Comparison: with and without tooth agenesis;

O - Outcome: variations in the sella turcica;

S - Study type, Study design: clinical studies, observational studies, cohort and cross-sectional studies.

Literature and systematic reviews, case reports, animal studies, in vitro studies, studies missing a control group and book chapters were excluded.

The focus question was: Do tooth agenesis patients present morphological variations in the sella turcica?

4.3.2 Information sources

A broad literature search was performed until October 13, 2021, in the following

databases: MEDLINE (PubMed).

In addition, to ensure a comprehensive literature search, a handsearching was also conducted to identify studies that could have been missed by the primary electronic search.

4.3.3 Search

MeSH (Medical Subject Headings) terms (https://www.ncbi.nlm.nih.gov/pubmed), Health Sciences Descriptors terms (http://decs.bvs.br), related terms and free terms were included. The Boolean operators “AND” and “OR” were applied to combine the keywords “tooth agenesis” OR “oligodontia” OR “hypodontia” OR “congenital missing tooth” OR “dental agenesis” OR “congenital missing teeth” OR “anodontia” AND “sella turcica” through PubMed. Duplicates were later removed.

4.3.4 Sources of evidence, data charting process, data items

Before beginning screening for this review, a data-charting form was jointly developed to determine, which variables to extract. The reviewer charted the data, discussed the results and continuously updated the data-charting form in an iterative process. All these processes were later revised by an experience examiner.

The data from the included studies were compiled and organized according to the study characteristics.

Meta-analysis was not performed due to the heterogeneity of the studies (type of missing tooth investigated and sella turcica analysis variability).

4.4 RESULTS

Our initial search strategy retrieved a total of 20 titles and abstracts. Two articles were identified through the manual search. Upon exclusion, only 6 articles were eligible for full article assessment. These 6 articles were qualified for final analysis. The flow of retrieved, excluded and included articles are summarized in Figure 1.

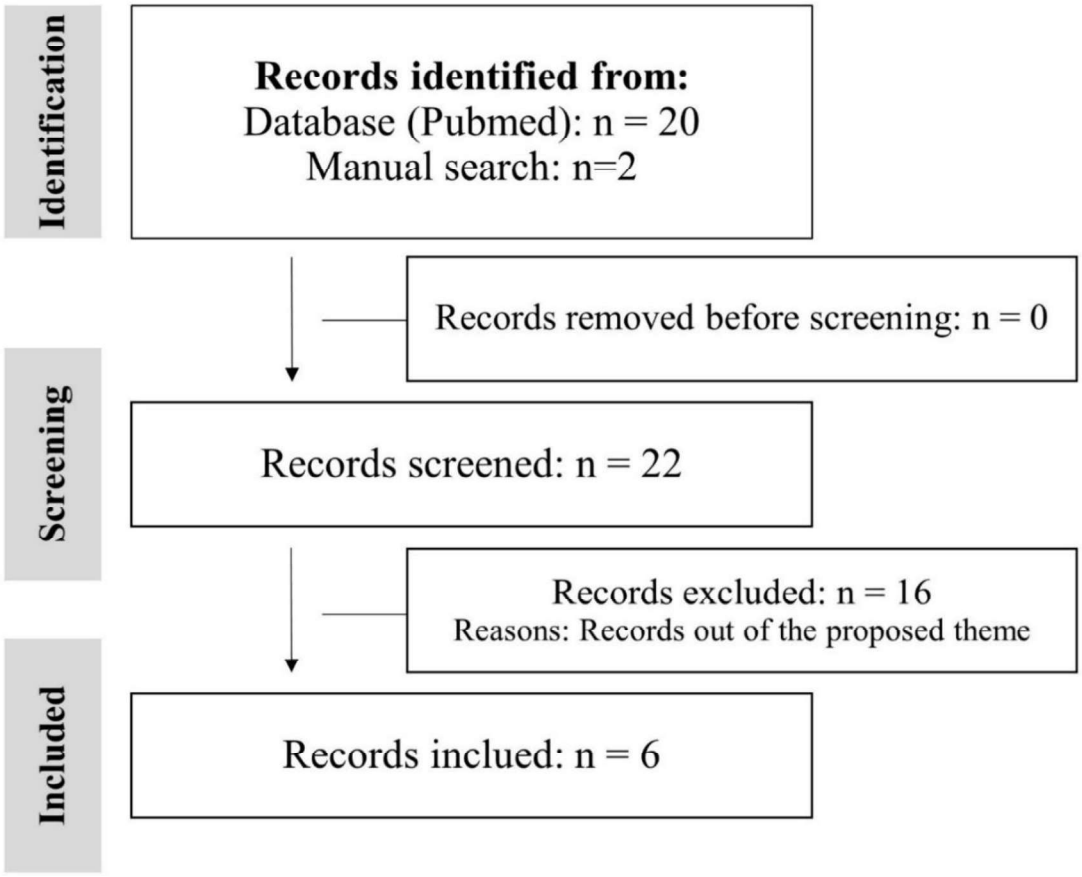

Figure 1. Flow diagram reporting items for systematic reviews.

Table 1 shows the characteristics of the included articles. The sample size ranged from 56 patients (ANTONARAKIS, GHISLANZONI & FISCHER, 2021) to 2995 patients (SATO & ENDO, 2020). Only one study investigated tooth agenesis in non-syndromic oral cleft patients (ANTONARAKIS, GHISLANZONI & FISCHER, 2021), the other studies evaluated patients with isolated tooth agenesis (LEONARDI *et al.,* 2006, SCRIBANTE *et al.,* 2017, SATO & ENDO, 2020; ZAHEER *et al.,* 2020 and KAYA *et al.,* 2021).The methods to investigate sella turcica phenotypes ranged among the studies and are presented in Table 1.

Table 1. Characteristics of the included articles.

Author/year	Studies' aim	Population	Sample size	Evaluated missing teeth	Method to evaluate sella turcica and parameters investigated	Type of measurement
Leonardi *et al.* (2006)	To investigate the association between sella bridging and second mandibular premolar agenesis or the presence of a palatal displaced canine	Italians	Total sample (n=169) Agenesis of mandibular second premolar (n=16) Palatal displaced Canine (n=18) Control (n=135)	Agenesis of mandibular second premolar	Lateral Cephalograms. The degree of sella turcica bridging was scored as type I, II, and III according to length.	Manual measurements
Scribante *et al.* (2017)	To investigate the association between sella turcica dimensions or bridging and canine impaction, tooth agenesis and supernumerary teeth	Italians	Total sample (n=205) Upper lateral incisors agenesis (n=32), lower second premolars agenesis (n=31), supernumerary teeth (n=17) and control group (n=47)	Agenesis of upper lateral incisors and lower second premolars	Lateral cephalograms. The degree of sella turcica bridging was scored as type I, II, and III according to length.	Software measurements. DeltaDent, Outside Format, Paullo, Italy.
Sato; Endo (2020)	To investigate the association between the size and bridging of the sella turcica and tooth agenesis	Japanese	Total sample (n=2995) Maxillary second premolar (n=34) Mandibular second premolar (n=34) Severe tooth agenesis (n=43) Control (n=2867)	Agenesis of second premolars and severe agenesis (five or more teeth missing)	Lateral cephalograms The degree of sella turcica bridging was scored as class I, II, III and IV according to the interclinoid distance.	Software measurements. Image J analysis software program (version 1.51)
Zaheer *et al.* (2020)	To investigate the association between sella turcica bridging with third molar impaction/agenesis	Pakistani	Total sample (n=99) third molar agenesis (n=30) Control (n=69)	Agenesis of third molar	Lateral cephalograms. The degree of sella turcica bridging was scored as type I, II, and III according to length	Manual measurements
Antonarakis; Ghislanzoni; Fischer (2021)	To investigate differences in sella turcica size and bridging in children with unilateral cleft lip and palate with or without dental anomalies.	Canadian	Total sample (n=56) Agenesis of cleft-side maxillary lateral incisor (n=26) Supernumerary cleft-side maxillary lateral incisor (n=7) Peg-shaped maxillary cleft-side lateral incisor (n=19)	Agenesis of cleft-side maxillary lateral incisor	Lateral Cephalograms. The following points of the sella turcica was investigated: most anterior point of the posterior clinoid process, tuberculum, the most posterior, anterior and deepest points of the sella using the Frankfort horizontal plane. The degree of sella turcica bridging was scored as type I, II, and III according to length.	Software measurements. Viewbox 4 cephalometric software (dHAL Software).
Kaya *et al.* (2021)	To compare the bridging and dimensions of the sella turcica and calcification of the ponticulus posticus in subjects with different dental anomalies	Turkish	Total sample (n=550) Impacted canines (n=95), mandibular second premolar agenesis (n=45), maxillary lateral incisor agenesis (n=75), tooth transpositions (n=25), peg-shaped maxillary lateral incisors (n=30), third molar agenesis (n=145) and control group (n=145)	Agenesis of mandibular second premolar, maxillary lateral incisor and third molar	Lateral cephalograms. The degree of sella turcica bridging was scored as type I, II, and III according to length.	Manual measurements

Table 2 shows the results and conclusions of the included articles. Five studies investigated the calcification of sella turcica bridging and showed that there is a significant association between sella turcica bridging and tooth agenesis (LEONARDI *et al.,* 2006, SCRIBANTE *et al.,* 2017, SATO & ENDO, 2020, KAYA *et al.,* 2021 and ANTONARAKIS; GHISLANZONI & FISCHER, 2021). Children with unilateral cleft lip and palate and sella turcica bridging are more likely to present tooth agenesis of the cleft-side maxillary lateral incisor (ANTONARAKIS; GHISLANZONI & FISCHER,2021).

Table 2. Main results and conclusions of the included articles.

Author/year	**Authors' main results and conclusion**
Leonardi *et al.* (2006)	The prevalence of a sella turcica bridge in dental anomalies patients is increased compared to controls.
Scribante *et al.* (2017)	The frequency of partial and complete calcification of the sella turcica in patients with dental anomalies is higher. No statistically significance was observed in sella dimensions.
Sato;Endo (2020)	Maxillary second premolar agenesis and severe tooth agenesis were associated with a reduced interclinoidal distance and increased prevalence of sella turcica bridging.
Zaheer *et al.* (2020)	An insignificant correlation was found between third molar agenesis and sella turcica bridging. Increased incidence of third molar impaction was associated with third molar agenesis. All skeletal classes were found to be ubiquitous in partial bridging category. Chances of sella turcica bridging increase with age.
Antonarakis; Ghislanzoni; Fischer (2021)	Children with unilateral cleft lip and palate and sella turcica bridging are more likely to present tooth agenesis of the cleft-side maxillary lateral incisor.
Kaya *et al.* (2021)	Type II bridging prevalence was lower in patients with mandibular second premolar agenesis, maxillary lateral incisor agenesis, and third molar agenesis, while type III bridging prevalence was significantly higher only in patients with third molar agenesis.

4.5 DISCUSSION

In the present systematic review, we explored the association between two craniofacial phenotypes. The development of the dental-craniofacial complex includes many networks and pathways, which are shared by different structures, such as bone and teeth. The sella turcica is a structure that develops from the same tissues that originate teeth (LEONARDI *et al.,* 2006). Furthermore, it is also supposed that morphological variations of the sella turcica can alter the

morphology of the pituitary gland and, consequently, cause variations in the hormones excreted by the pituitary gland (KAJEAR, 2015). In fact, hormones play an important role in craniofacial and tooth development (OMORI *et al.,* 2020; SPILLER *et al.,* 2020; BERGAMO *et al.,* 2021; KÜCHLER *et al.,* 2021; REIS *et al.,* 2021). It is also possible that the connection between variation in the sella turcica and pituitary gland is through the genes that participate in the formation in both structures.

Several studies have been investigating the morphological variations of the sella turcica in different conditions, such as dental anomalies (LEONARDI *et al.,* 2006; SCRIBANTE *et al.,* 2017; SATO & ENDO, 2020; ANTONARAKIS; GHISLANZONI & FISCHER, 2021; KAYA *et al.,* 2021; JANKOWIK *et al.,* 2021), oral cleft (ALAM & ALFAWZAN, 2020), down syndrome (KORAYEM & ALKOFID, 2015) and other genetic syndromes (ROOMANEY & CHETTY, 2021). Given the above, the aim of this study was to systematically evaluate the findings related to the association between tooth agenesis and sella turcica morphology in non-syndromic patient with and without oral cleft.

Our results demonstrate that there is an agreement between the studies included in this systematic review, which suggest that both phenotypes, sella turcica morphological variations and tooth agenesis, are connected (LEONARDI *et al.,* 2006; SCRIBANTE *et al.,* 2017; SATO & ENDO, 2020; ANTONARAKIS; GHISLANZONI & FISCHER, 2021; KAYA *et al.,* 2021). The included studies suggested that morphological variations of the sella turcica were mainly associated with mandibular agenesis of second premolar (LEONARDI *et al.,* 2006; SCRIBANTE *et al*., 2017; SATO & ENDO, 2020; KAYA *et al.,* 2021), incisor superior lateral agenesis (SCRIBANTE *et al.,* 2017 ANTONARAKIS; GHISLANZONI & FISCHER, 2021) and third molar agenesis (KAYA *et al.,* 2021), which are the most common missing teeth in humans. The same occurred in cleft patients with higher chance of incisor agenesis in the cleft area (ANTONARAKIS; GHISLANZONI & FISCHER, 2021).

The included manuscripts used different methods to investigate the morphological variations in the sella turcica. Although all studies investigated the morphology using lateral cephalograms (LEONARDI *et al.,* 2006; SCRIBANTE *et al.,* 2017; 2020; ZAHEER *et al.,* 2020; ANTONARAKIS; GHISLANZONI & FISCHER, 2021; KAYA *et al.,* 2021), which is a type of radiography widely used in orthodontic treatment (McNAMARA JR & FRANCHI, 2018), the studies differed in the method used for the evaluation of the sella turcica. Leonardi *et al.* (2006), Zaheer *et al.* (2020) and Kaya *et al.* (2021) performed manually, while Scribante

et al. (2017), Sato & Endo (2020) and Antonarakis, Ghislanzoni & Fischer (2021) performed the measurements using a specific software. Also, sella turcica classifications and measurements ranged according to the studies and therefore it was difficult to extract homogeneous results (same type of missing teeth and same classification used to evaluate the sella turcica) in order to perform a meta-analysis.

Another important aspect to be highlighted is that only few populations were investigated and the sample size investigated in some of these studies was small. Therefore, more studies investigating the association between sella turcica variations and isolated tooth agenesis or tooth agenesis associated with syndromes and oral clefts are necessary.

Finally, the analysis of the included studies supports the hypothesis that tooth agenesis and sella turcica morphology variations are associated. This fact could be due to the concomitant development of the sella turcica and teeth (LEONARDI *et al.,* 2006) and the genes involved in the formation of both structures, but is also possible that the pituitary gland influences tooth development. It is also important to highlight that additional well-designed studies are necessary in different populations.

4.6 CONCLUSION

There is an association between tooth agenesis and the morphological variations of the sella turcica.

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5 CAPITULO 2

THE SELLA TURCICA: A BRIEF REVIEW OF THE MORPHOLOGY ANALYSIS IN DENTAL RESEARCH

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5.1 ABSTRACT

Introduction: Sella turcica is an intracranial bone depression located in the sphenoid bone that houses the pituitary gland, which is an important gland in the secretion of various hormones. **Literature review:** Variations in the morphology of the sella turcica can alter the morphology of the pituitary, which can lead to changes in hormone secretion and dental anomalies. There are studies that evaluate the sella turcica using metric methods and other studies that evaluate them with non-metric methods. Researchers use lateral radiographs and/or computed tomography to visualize the sella turcica. The purpose of this brief review was to revise the methods used to study sella turcica morphology in dental research. The literature search for

sella turcica morphology was carried out with the following key words (sella turcica, bridging of sella, size, shape of sella turcica and sella turcica morphology) and using the search engines (Pubmed and Google scholar). According to the research, three methods of analyzing the sella turcica were observed, according to the measurements (length, width, diameter, area, depht, sella height posterior, sella height anterior), degree of calcification (class I / type I / group I, class II / type II / group II, class III / type III / group III) and format (normal sella turcica, sella turcica bridge type A – ribbon-like fusion, sella turcica bridge type B – extension of the clinoid processes, incomplete bridge, hypertrophic posterior clinoid process, hypotrophic posterior clinoid process, irregularity in the posterior part of the sella turcica, pyramidal shape of the dorsum sella, double contour of the floor, oblique anterior wall, oblique contour of the floor) of the sella turcica. **Conclusion:** It is expected that the three methods exposed in this review will help dental researchers to analyze sella turcica.

Key-words: sella turcica; intracranial bone; hormones; morphology; dental anomalies

5.2 INTRODUCTION

Sella turcica is an intracranial bone depression located in the sphenoid bone that houses the pituitary gland, which is an important gland in the secretion of various hormones. The pituitary gland controls the function of most other endocrine glands and is called the master gland [19]. By detecting the levels of hormones produced by target glands under the pituitary's control, the hypothalamus or the pituitary gland can determine stimulation level that the target glands need [14].

The sella turcica morphology ranges according to the individuals and have been associated with a variety of conditions, including dental phenotypes such as dental transposition, tooth agenesis, supernumeraries tooth and impacted teeth [1-7, 9-11, 15, 17, 18], oral cleft [1, 2] and syndromes such as William's Syndrome, Cri du chat syndrome, Down's Syndrome among others [8, 16]. The s-point is one of the fix points used to determine the cranial base angle and the nasion–sella line connecting the nasion and the sella s-point. The accuracy or reproducibility of the s-point is crucial in orthodontic treatment and research.

The studies performing morphological analysis of the sella turcica have been using lateral cephalograms or computed tomography image to define the phenotypic variations.

Leonardi *et al.* [15], Scribante *et al.* [18], Kaya *et al.* [11], Sato and Endo [17], Antonarakis *et al.* [2], Alam and Alfawzan [1] and Roomaney and Chetty [16] used lateral cephalograms to analyze the sella turcica. Hasan *et al.* [7], Islam *et al.* [9], Hasan *et al.* [8] and Roomaney and Chetty [16] used computed tomography to analyze the sella turcica.

Therefore, the purpose of this brief review was to revise the methods used to study sella turcica morphology in dental research. The literature search for sella turcica morphology was carried out with the following key words (sella turcica, bridging of sella, size, shape of sella turcica and sella turcica morphology) and using the search engines (Pubmed and Google scholar).

Sella turcica morphology

The phenotypic determination of the sella turcica ranged according to the study. Data on the size of the sella turcica have been well-reported in the dental literature. The size of sella turcica assessed from radiographs and computed tomography can be either linear or various methods of area and volume measurements. The linear measurements used by the studies and landmarkers, such as height/ depth, anterior height, posterior height, diameter, length, area and width to assess the sella turcica of patients are described in the table I.

Some studies classified the sella turcica according to the calcification of the clinoid processes. Leonardi *et al.* [15], Scribante *et al.* [18], Antonarakis *et al.* [2], Kaya *et al.* [11] and Sato and Endo [17] classified in Class I / Type I (no calcification): the length was greater than three-quarters of the diameter; class II / type II (partially calcified): the length was less than or equal to three quarters of the diameter; and Class III / type III for a radiographically visible diaphragm sella. This is described in the table II.

Sella turcica is also evaluated according to the its shape as normal sella turcica, sella turcica bridge type A – ribbon-like fusion, sella turcica bridge type B – extension of the clinoid processes, incomplete bridge, hypertrophic posterior clinoid process, hypotrophic posterior clinoid process, irregularity (notching) in the posterior part of the sella turcica, pyramidal shape of the dorsum sella, double contour of the floor, oblique anterior wall, oblique contour of the floor. The table III describes the studies that evaluated sella turcica shape. The morphological variation is shown in figure 1.

Table I – Linear and area measurements description

Measurements	Description	Reference
Length	Distance between the dorsum sella (DS) and the tuberculum sella (TS)	Leonardi *et al.* [15]; Scribante *et al.* [18]; Kaya *et al.* [11]; Islam *et al.* [9]; Hasan *et al.* [7]; Hasan *et al.* [8]; Alam and Alfawzan [1]; Sato and Endo [17]; Baidas *et al.* [3]
Diameter	Distance between the tuberculum sella to the most posterior point on the inner wall of the pituitary fossa	Leonardi *et al.* [15]; Scribante *et al.* [18]; Kaya *et al.* [11]; Hasan *et al.* [7]; Hasan *et al.* [8]; Alam and Alfawzan [1]; Sato and Endo [17]; Islam *et al.* [9]; Baidas *et al.* [3]
Width	Distance between the point most posterior (SP) and the point most anterior (SA) perpendicular to the Frankfort plane (FH)	Antonarakis *et al.* [2]; Islam *et al.* [9]; Hasan *et al.* [7]; Hasan *et al.* [8]; Alam and Alfawzan [1]
Sella height posterior	Distance between DS and deepest point (SF), perpendicular to FH	Antonarakis *et al.* [2]; Islam *et al.* [9]; Hasan *et al.* [7]; Hasan *et al.* [8]; Alam and Alfawzan [1]
Sella height anterior	Distance between tuberculum sella and SF, perpendicular to FH	Antonarakis *et al.* [2]; Islam *et al.* [9]; Hasan *et al.* [7]; Hasan *et al.* [8]; Alam and Alfawzan [1]
Depth / Sella height median	Distance between midpoint clinoid process DS and TS to SF, perpendicular to FH	Scribante *et al.* [18]; Antonarakis *et al.* [2]; Islam *et al.* [9]; Hasan *et al.* [7]; Hasan *et al.* [8]; Alam and Alfawzan [1]; Kaya *et al.* [11]; Sato and Endo [17]; Baidas *et al.* [3]
Area	TS – SA – SF – SP – DS	Antonarakis *et al.* [2]; Hasan *et al.* [7]; Hasan *et al.* [8]; Islam *et al.* [9]; Alam and Alfawzan [1]; Sato and Endo [17]

Table II – Sella turcica classification according to the calcification of the clinoid processes

Type of sella	Description	Reference
Class I / type I / Group I (no calcification)	the length was greater than three-quarters of the diameter	Leonardi *et al.* [15]; Scribante *et al.* [18]; Antonarakis *et al.* [2]; Kaya *et al.* [11]; Sato and Endo [17]
Class II / type II / Group II (partial calcified)	the length was less than or equal to three quarters of the diameter	Leonardi *et al.* [15]; Scribante *et al.* [18]; Antonarakis *et al.* [2]; Kaya *et al.* [11]; Sato and Endo [17]
Class III / type III / Group III	radiographically visible diaphragm sella	Leonardi *et al.* [15]; Scribante *et al.* [18]; Antonarakis *et al.* [2]; Kaya *et al.* [11]; Sato and Endo [17]

Table III – Sella turcica's shape

Shape of the sella turcica	Author
Normal sella turcica	Kucia *et al.* [13]; Islam *et al.* [9]
Sella turcica bridge type A – ribbon-like fusion	Kucia *et al.* [13]
Sella turcica bridge type B – extension of the clinoid processes	Kucia *et al.* [13]
Hypertrophic posterior clinoid process	Kucia *et al.* [13]
Hypotrophic posterior clinoid process	Kucia *et al.* [13]
Pyramidal shape of the dorsum sellae	Kucia *et al.* [13]; Islam *et al.* [9]
Oblique contour of the floor	Kucia *et al.* [13]
Oblique anterior wall	Kucia *et al.* [13]; Islam *et al.* [9]
Double contour of the floor	Kucia *et al.* [13]; Islam *et al.* [9]
Irregularity (notching) in the posterior part of the sella turcica	Kucia *et al.* [13]; Islam *et al.* [9]
Incomplete bridge	Kucia *et al.* [13]
Sella turcia bridge	Islam *et al.* [9]; Alam and Alfawzan [1]; Leonardi *et al.* [15]; Scribante *et al.* [18]; Antonarakis *et al.* [2]; Kaya *et al.* [11]; Sato and Endo [17]

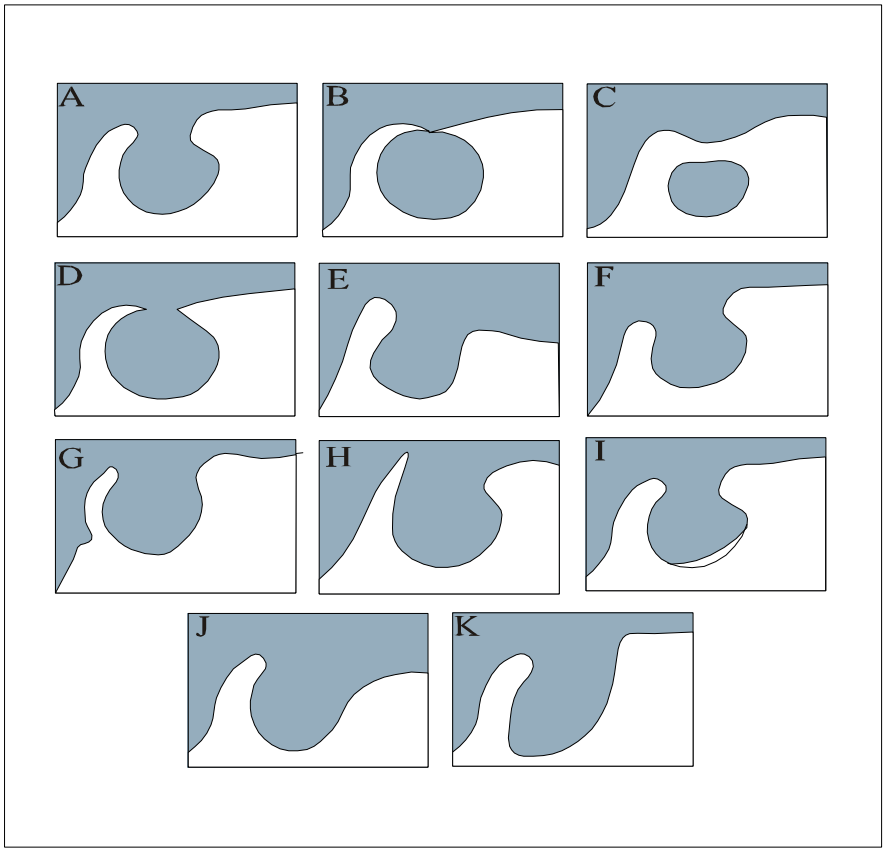

Figure 1 – A) normal sella turcica; B) sella turcica bridge type B – extension of the clinoid processes; C) sella turcica bridge type A – ribbon-like fusion; D) incomplete bridge; E) hypertrophic posterior clinoid process; F) hypotrophic posterior clinoid process; G) irregularity (notching) in the posterior part of the sella turcica; H) pyramidal shape of the dorsum sella; I) double contour of the floor; J) oblique anterior wall; K) oblique contour of the floor

5.3 FINAL CONSIDERATIONS AND FUTURE DIRECTIONS

The sella turcica is an important anatomical reference in the orthodontic field. The s-point, which is placed centrally in the sella region, is a central fix point in cephalometric analysis and partly because the contour of the anterior wall is used in the analysis of the craniofacial growth [12]. However, it is possible that the sella turcica is also a valuable marker to predict dental anomalies and, therefore, the knowledge regarding its morphology and the association with other developmental alteration is important in future studies, specially in dental research.

Recent original studies [1-3, 5-9, 11, 15, 17, 18] and systematic reviews [4, 10 16] that investigated the relationship between sella turcica morphology and dental anomalies concluded that developmental dental alterations are associated with specific types of sella turcica phenotypes. Jankowski *et al.* [10] in a systematic review concluded that there is an association

between dental abnormalities (palatally displaced canines and tooth agenesis) and sella turcica bridge. The authors used cephalometric radiographs and computed tomography to investigate sella turcica morphology. Brasil *et al.* [4] also performed a recent systematic review and also concluded that patients with tooth agenesis and patients with oral clefts are more likely to have alterations in the morphology of the sella turcica. Although these studies and reviews clearly supported that craniofacial developmental alterations are associated with sella turcica morphological variations, more studies with larger sample size are necessary.

In conclusion, morphological variations of the sella turcica may be indicative of some craniofacial developmental alterations, such as dental anomalies (tooth agenesis, tooth transposition, dental impaction, supernumerary tooth) and oral cleft. Therefore, dental researchers in this area should be aware of the methods used to investigate sella turcica morphology.

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6 CAPÍTULO 3

Exploring the association between genetic polymorphisms in PITX2, sella turcica phenotypes and third molars agenesis

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6.1 ABSTRACT

Dental agenesis are frequent anomalies in clinical practice and contributes to the development of malocclusions. It is worth mentioning that the initial phases of odontogenesis coincide with the development of the sella turcica; an anatomical structure located on the intracranial surface on the sphenoid bone surrounding the pituitary gland. The pituitary gland and the hormones excreted by it directly interfere with craniofacial development. Thus, the present study evaluated the association between tooth agenesis and morphological variations of the sella turcica. The sample consisted of German patients aged approximately 13 years who started orthodontic treatment at the University of Regensburg. Syndromic patients with systemic alterations were excluded from the study. Tooth agenesis was evaluated using panoramic

radiographs. The morphological variations of the sella turcica were evaluated using the lateral cephalogram. Variables such as: anterior and posterior height, average height, width, depth, diameter, area, and interclinoid distance were evaluated using the ImageJ software. The morphological aspect of the sella turcica was classified according to the protocol by Kucia *et al.,* 2014. The analyzes were performed using the GraphPad Prism 7.04 program considering a significance of 5%. There was no association between tooth agenesis and sella turcica phenotypes ($p>0.05$). Genetic polymorphisms in PITX2 were also not associated with tooth agenesis of third molars ($p>0.05$). Genetic polymorphisms in rs3796902 were associated with hypertrophic posterior clinoid process ($p=0.013$). Genetic polymorphisms in rs1947187 and rs2595110 were associated with sella turcica bridge type A ($p=0.013$ and $p=0.011$ respectively for genotype distribution). In conclusion, genetic polymorphisms in PITX2 are associated with sella turcica morphology in patients with agenesis of third molars in a sample of German children.

Key words: Sella turcica, tooth agenesis, anodontia

6.2 INTRODUCTION

Tooth agenesis is an anomaly of the craniofacial complex characterized by the congenital absence of development of one of the tooth germs (AL-ANI *et al.,* 2017). In a systematic review with meta-analysis, the prevalence of tooth agenesis, excluding third molars, could be stated in 6.4% of the population (KHALAF *et al.,* 2014). Studies on the prevalence of dental agenesis of third molars in particular, bring an even higher prevalence, with variations between 12.6% and 51.1% of affected individuals (GARCÍA-HERNÁNDEZ *et al.,* 2008; CELIKOGLU & KAMAK, 2012; FERNANDEZ *et al.* al., 2018; ERCAL & TAYSI, 2020). It is estimated that the decrease in masticatory activity in the population, polygenic inheritance, and environmental factors significantly contribute to such phenotypic variation and is an evolutionary trend (COCOS & HALAZONETIS, 2017; OESCHGER *et al.,* 2020; XU *et al.,* 2022). It is also estimated that evolutionary trends about agenesis of third molars could act on craniofacial dimensions (MOGHADAM, ETEMADI & NARJES AKBARI, 2018; SCHEIWILLER *et al.,* 2020; GKANTIDIS *et al.,* 2021).

At the same time, it is worth mentioning that the sella turcica is a structure that develops from the same tissues that originate the teeth (LEONARDI *et al.,* 2006). The sella turcica is an

intracranial bony depression located on the sphenoid bone that contains the pituitary gland (TEKINER, ACER & KELESTIMUR, 2015). Several studies have investigated the morphological variations of the sella turcica in different conditions, such as in patients with oral fissures (ALAM & ALFAWZAN, 2020), genetic syndromes (KORAYEM & ALKOFID, 2014, ROOMANEY & CHETTY, 2021) and tooth development anomalies (LEONARDI *et al.,* 2006; SCRIBANTE *et al.,* 2017; SATO & ENDO, 2020; ANTONARAKIS, GHISLANZONI; FISCHER & 2021; KAYA *et al.,* 2021; JANKOWSKI *et al.,* 2021). The hypothesis that tooth agenesis of third molars and variations in the morphology of the sella turcica is suggested (KAYA *et al.,* 2021).

Evidence to elucidate the delimited participation of genetics in the agenesis of third molars and morphological variations of the sella turcica is scarce. We hypothesized that genetic polymorphisms in PITX2 could be related to the agenesis of third molars and morphological variations of the sella turcica. Genetic polymorphisms are alterations that occur naturally due to modifications in the genetic material with more than one variation, with a population frequency greater than 1% (SHERRY *et al.,* 1999; YE, 2001; NIELSEN, 2004). Although most genetic polymorphisms are functionally neutral, some of them may exert an allele-specific effect on the regulation of gene expression and/or on the function of the protein encoded by it, which leads to different characteristics among individuals. PITX2 is a protein involved in the development of eyes, abdominal organs and teeth (FOOTZ *et al.,* 2009; YU *et al.,* 2020; TRAN & KIOUSSI, 2021). Mutations in PITX2 have already been hypothesized to be associated with morphological variations of the sella turcica (FOOTZ *et al.,* 2009). Therefore, the present study aimed to investigate whether genetic polymorphisms in PITX2 are associated with sella turcica morphology in patients with agenesis of third molars in a sample of German children.

6.3 MATERIALS AND METHODS

6.3.1 Ethical aspects

The approval for this research was obtained by the local Ethics Committee from the University of Regensburg (# 19-1549-101). Informed consent was obtained from all included patients and the assent was also obtained from any participant younger than 18 years during dental appointment.

The guideline STREGA (Strengthening the Reporting of Genetic Association) was followed for this cross-sectional study (LITTLE *et al.,* 2009).

6.3.2 Subjects of the study

This is a cross-sectional phenotype-genotype study performed in patients aged 12 to 35 years old who was undergoing orthodontic treatment at the University of Regensburg and private orthodontic practices in Regensburg, Germany. The study sample was composed of cephalometric radiographs and dental orthopantomograms from patients. All radiographs were made for orthodontic treatment purposes. The patients included in this study were recruited from 2020 to 2021. The sample was obtained for convenience.

The exclusion criteria were incomplete records, the presence of syndromes, oral clefts, clearly visualization of the sella turcica, other types of tooth agenesis besides third molar agenesis, and previous extraction of third molars. To minimize genetic variance, only patients with a Central-European ancestry and one patient per family were included.

6.3.3 Phenotype definition - Dental orthopantomograms analysis

All dental orthopantomograms were digital panoramic radiographs that were examined in a dark room using the same protocol. In all cases third molar agenesis were clearly evident from the panoramic radiographs alone using a method previously reported (KÜCHLER *et al.,* 2008). In case of doubt, a follow-up orthopantomograms of the same patient in the course of orthodontic treatment was examined to confirm the agenesis diagnosis, as reported in Herrmann *et al.* (2022). If tooth agenesis could not be confirmed, the patient was excluded. Each panoramic orthopantomograms was evaluated by one dentist. For intra-examiner reliability and inter-examiner reliability, 10% of the orthopantomograms were randomly chosen and the investigations were conducted twice in a 2-weeks interval. The Kappa statistics showed perfect agreement to both tests for third molar agenesis (Kappa for all third molar agenesis was 1).

Tooth agenesis was defined based on the age of patients and when initial third molar should be visible in the radiographs (KÜCHLER *et al.,* 2008). Patients were considered with

third molar agenesis when at least one third molar was. Patients with all 32 permanent teeth were considered as non-tooth agenesis patients.

6.3.4 Phenotype definition - Cephalometric analysis

All the cephalometric radiographs were also taken in Frankfort horizontal plane parallel to the floor in a rigid cephalostat. The sella turcica calcification was evaluated in three aspects: 1) no calcification, 2) partial calcification and, 3) complete calcification of the interclinoid ligament (SCRIBANTE *et al.,* 2017; LEONARDI *et al.,* 2006; KAYA *et al.,* 2021; ANTONARAKIS *et al.,* 2020) as shown in the Figure 1. The sella turcica patterns were also evaluated according to the protocol described by Kucia *et al.* [16] and is shown in Figure 2. All cephalometric radiographs were examined by only one trained and calibrated examiner. For inter-examiner reliability, 10% of the sample were randomly chosen for a second analysis in a 2-week interval. The Kappa statistics showed perfect agreement (Kappa=1) for sella calcification and for sella turcica pattern.

The method for measuring the size of the sella turcica and its structures was also used. The landmarkers were established for each radiograph using the Frankfurt plane (FH) as the horizontal reference direction. The total of six points defined the measurements performed (Figure 3).

The following linear and area measurements were calculated sella measurements: 1) Sella length: Distance between the dorsum sellae (DS) and the tuberculum sella (TS), 2) Sella depth: Distance between midpoint clinoid process DS and TS to SF, perpendicular to FH, 3) Sella diameter: Distance between the tuberculum sella to the most posterior point on the inner wall of the pituitary fossa, 4) Sella height anterior: The vertical distance, as measured perpendicular to the FH plane, from Tuberculum sella (TS) to the sella floor (SF), 5) Sella height posterior: The vertical distance, as measured perpendicular to the FH plane, from DS to the sella floor (SF), 6) Sella width: Distance between of the point most posterior (SP) and the point most anterior (SA) perpendicular to the Frankfurt plane (FH), 7) Sella area: the area included by the outline of the sella and capped by a line joining TS- SA – SF – SP – DS.

All measurements were performed after adjusting for the magnification of the radiographs in a room with dimmed light. The ImageJ software version 1.53a (Rasband, W.S.,

ImageJ, U.S. National Institutes of Health, Bethesda, MD, USA) was used. To calculate the error of the method, 20 radiographs were randomly selected and re-analysed. The intraclass correlation coefficient (ICC) was used to evaluate the inter-examiner agreement, and the ICC ranged from 0.915 to 0.998.

6.3.5 DNA extraction and genotyping analysis

The intronic SNPs rs3796902, rs1947187, and rs2595110 in PITX2 were screened from the dbSNP database (http://www.ncbi.nlm.nih.gov/snp/) based on their MAF (minor allele frequency) (≥ 10% in the global population).

The genomic DNA of each included patient was used for the genotyping analysis. The DNA was isolated from epithelial cells collected with cytobrushes using extraction solution (Tris-HCl 10 mmol/L, pH 7.8; EDTA 5 mmol/L; SDS 0.5%, 1 mL) and proteinase K (100 ng/mL) and ammonium acetate to remove non-digested proteins. The DNA was precipitated with isopropanol and resuspended, and later quantified by spectrophotometry (Nanodrop 1000; Thermo Scientific, Wilmington, DE, USA). All 3 SNPs were blindly genotyped using real-time Polymerase chain reaction (real time-PCR) in the Mastercycler® ep realplex-S thermocycler (Eppendorf AG, Hamburg, Germany). The TaqMan technology, which uses extremely sensitive allele-specific probes (VIC™ and FAM™ dyes were used for the alleles), was used in this study. One negative control template (omitting the DNA) was used in each reaction plate. Additionally, 10% of the samples were randomly selected for repeated analysis (presented 100% concordance). DNA samples that failed to be genotyped were considered missing data and was excluded from the statistical analysis.

6.3.6 Statistical analysis

The Hardy-Weinberg Equilibrium was calculated for each SNP Chi-square test (wpcalc.com/en/equilibrium-hardy-weinberg). Epi Info was used for statistical analysis. Sella turcica phenotypes were compared among third molar agenesis and controls groups. Also, SNPs in PITX2 were analyzed according to tooth agenesis and sella turcica phenotypes (regardless tooth agenesis condition). Chi-square test or Fisher's exact test were used to compare genotype and allele distribution according to the phenotypes. ANOVA with Tukey's multiple-comparison

test and t test were also used to compare the means among groups and genotypes. SNP-SNP interaction was also tested. The significance level was set as 5% ($p<0.05$) for all comparisons.

6.4 RESULTS

A total of 163 patients were included. Fourth-one (20 males and 21 females) patients presented third molar agenesis and 122 (62 males and 60 females) were patients without tooth agenesis (controls). Gender distribution among tooth agenesis groups was not statistically significant different ($p=0.821$).

Calcification sella turcica was more common phenotype, 107 patients presented partially phenotype sella, 20 presented completely calcified sella and 36 presented no calcification. Sella turcica bridge type B was the most common type (n=45), followed by the normal sella turcica (n=36). Table 1 shows the sella turcica phenotypes frequency and distribution among third molar agenesis and control groups. There were no statistical differences among the groups ($p>0.05$ for all comparisons).

The association of the SNPs rs3796902, rs1947187 and rs2595110 with third molar agenesis is presented in the table 2. The genotype distribution was not statistically significant different among the groups ($p>0.05$).

Sella turcica linear and area measurements among genotypes are presented in the Table 3. Means differences were not observed among genotypes ($p>0.05$).

Table 4 shows the genotype distribution among degree of calcification phenotypes are presented in the table 4. The genotype distribution was not associated with the degree of calcification ($p>0.05$). Allele distribution was also not associated with the degree of calcification ($p>0.05$).

Table 5 shows genotype and allele distribution among sella turcica patterns. The rs3796902 was associated with hypertrophic posterior clinoid process ($p=0.039$ for genotype distribution and $p=0.050$ for allele distribution). The rs1947187 and rs2595110 were associated with sella turcica bridge type A ($p=0.013$ and $p=0.011$ respectively for genotype distribution). To carry the genotypes GG-CC-AG (rs3796902- rs1947187- rs2595110) had 7.2 higher chance

to present sella turcica bridge type A (p=0.002; Odds ratio=7.2, Confidence interval 95% 2.04-27.04).

6.5 DISCUSSION

Third molar tooth agenesis is a very common developmental anomaly of the craniofacial complex (KHALAF *et al.,* 2014; GARCÍA-HERNÁNDEZ *et al.,* 2008; CELIKOGLU & KAMAK, 2012 FERNANDEZ *et al.* al., 2018; ERCAL & TAYSI, 2020); has a multifactorial etiology (AL-ANI *et al.,* 2017; LI *et al.,* 2018; ASLAM *et al.,* 2020) and is estimated to be significant in the harmonious development of craniofacial dimensions (MOGHADAM, ETEMADI & NARJES AKBARI, 2018; SCHEIWILLER *et al.,* 2020; GKANTIDIS *et al.,* 2021). Agenesis of third molars and sella turcica phenotypes are currently supposed associations (ZAHEER *et al.,* 2020; KAYA *et al.,* 2021). Dental germs and constituent structures of the sella turcica are formed from the same neural crest cells (LEONARDI *et al.,* 2006; MESSER & TILL, 2013). In view of the implication of epigenetics in current phenotypes, the aim of this study was to investigate genetic polymorphisms in PITX2 and their relationship with the morphology of the sella turcica in patients with agenesis of third molars in a sample of German children. Our results demonstrated that genetic polymorphisms in PITX2 were related to the degree of calcification of the hypertrophic posterior clinoid process and sella turcica bridge type A.

Third molars are the last teeth to form and erupt in the oral cavity depending on the population (HERRMANN *et al.,* 2022). Due to the decrease in masticatory activity, some evidence points to its physiological and adaptive disappearance (SCHEIWILLER *et al.,* 2020). Therefore, it is also worth mentioning that tooth agenesis of third molars also becomes a product of a mutation and selection process based on heredity. Additive genetic factors significantly influence the formation of third molar follicles (TRAKINIENĖ *et al.,* 2018). The agenesis of third molars implies a distinct craniofacial morphology (COCOS *et al.,* 2017), contributing to better delimitations of preventive, therapeutic and health promotion strategies.

The sella turcica in turn is a structure that develops from the same tissues that originate from teeth (LEONARDI *et al.,* 2006). Some authors support hypotheses that dental agenesis and variations in the morphology of the sella turcica are associated due to the concomitant development of the sella turcica and the teeth (LEONARDI *et al.,* 2006), due to genes involved

in the formation of both structures and also, due to the possibility of the hypophysis influencing the development of the teeth. Indeed, hormones secreted by the pituitary gland play an important role in craniofacial and dental development (OMORI *et al.,* 2020; SPILLER *et al.,* 2020; BERGAMO *et al.,* 2021; KÜCHLER *et al.,* 2021; REIS *et al.,* 2021; MADALENA *et al.,* 2022). Therefore, evidence is needed to clarify the other hypotheses.

Initially, the association between tooth agenesis of third molars and sella turcica phenotypes was tested. Our results did not demonstrate an association between these variables, in opposition to the related and specific literature. Morphological variations of the sella turcica were mainly associated with mandibular agenesis of the second premolar (LEONARDI *et al.,* 2006; SCRIBANTE *et al.*, 2017; SATO & ENDO, 2020; KAYA *et al.,* 2021), maxillary incisor lateral agenesis (SCRIBANTE *et al.,* 2017; ANTONARAKIS, GHISLANZONI & FISCHER, 2021) and agenesis of third molars (KAYA *et al.,* 2021), which are the most commonly missing teeth in humans. The same occurred in cleft patients with a greater chance of incisor agenesis in the cleft area (ANTONARAKIS, GHISLANZONI & FISCHER, 2021). It is suggested that this result is justified by differences in population, age of participants and method employed. Not a single work analyzed the German population, the studied populations were: Italian, Canadian, Turquoise, Japanese and Pakistani population. Regarding the sample size, the mean of the studies was 679 patients, while in this study the sample was 163 (BRASIL *et al.,* 2022).

Therefore, the association of genetic polymorphisms in PITX2 and agenesis of third molars was also tested. PITX2 is a protein involved in the development of eyes, abdominal organs, and teeth (FOOTZ *et al.,* 2009; YU *et al.,* 2020; TRAN & KIOUSSI, 2021). Mutations in PITX2 have been described as potential to cause dental anomalies in non-syndromic patients since the specific location in the C-terminal domain of PITX2 is exclusively required for tooth development (INTARAK *et al.,* 2018; FAN *et al.,* 2019). Our results showed no association; however, PITX2 is considered to be one of the earliest markers exclusively expressed in dental epithelium during tooth development (HJALT *et al.,* 2000; MUCCHIELLI *et al.,* 1997). PITX2 mutations have also been described in association with craniofacial and dental aberrations such as maxillary retrognathia, Class III skeletal relationship, tooth hypoplasia, and sella turcica anomalies (MEYER-MARCOTTY *et al.,* 2008).

Our results demonstrate an association of genetic polymorphisms in rs3796902 and hypertrophic posterior clinoid process and genetic polymorphisms in rs1947187, rs2595110, and sella turcica bridge type A. The hypertrophic posterior clinoid process is one of the

alterations found that could not be classified based on the literature (KUCIA *et al.,* 2014). Our results highlight the importance of further studies exploring this structure. As for the sella turcica bridge type, a previous study demonstrated that 70% of individuals who had a Type A sella turcica bridge were submitted to an operation to correct a mandibular overjet and 30% to a maxillary overjet (KUCIA *et al.,* 2014). The hypothesis is supported that third molar agenesis and formation of the sella turcica are interconnected and that such a proposition could cause craniofacial dimensional changes. Therefore, further studies investigating the genetic polymorphisms in PITX2, tooth agenesis, and morphology of the sella turcica are necessary.

6.6 CONCLUSION

In conclusion, third molar agenesis is not associated with sella turcica morphology. The genetic polymorphisms in PITX2 are associated with sella turcica morphology but not with third molars agenesis in a sample of German children.

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6.9 TABLES

Table 1. Sella turcica phenotypes among third molar agenesis and controls.

Parameter	Third molar agenesis (N=41)	Control (N=122)	*p-value*
	Mean (SD)	**Mean (SD)**	
Length in mm	8.58 (1.66)	8.79 (1.94)	0.506
Depth in mm	8.28 (1.14)	8.16 (1.30)	0.582
Posterior height in mm	8.46 (1.32)	8.24 (1.50)	0.391
Anterior height in mm	8.10 (1.48)	8.07 (1.56)	0.909
Width in mm	8.65 (1.31)	8.68 (1.53)	0.900
Diameter in mm	10.67 (1.36)	10.96 (1.93)	0.291
Area in mm^2	61.12 (13.55)	62.33 (16.93)	0.645
Degree of calcification	**N (%)**	**N (%)**	
No calcification	7 (17.1)	29 (23.8)	
Partially calcified	28 (68.3)	79 (64.7)	0.627
Completely calcified	6 (14.6)	14 (11.5)	
Format of Sella turcica	**N (%)**	**N (%)**	
Normal ST	8 (19.5)	30 (24.6)	
ST bridge type A	6 (14.6)	13 (10.6)	
ST bridge type B	12 (29.3)	33 (27.0)	
Incomplete bridge	2 (4.9)	10 (8.2)	
Hypertrophic posterior clinoid process	8 (19.5)	21 (17.2)	
Hypotrophic posterior clinoid process	0 (0)	1 (0.8)	0.657
Irregularity in the posterior part of the ST	2 (4.9)	1 (0.8)	
Pyramidal shape of the dorsum of the ST	0 (0)	2 (1.6)	
Double contour of the floor	0 (0)	1 (0.8)	
Oblique anterior wall	1 (2.4)	8 (6.6)	
Oblique contour of the floor	2 (1.6)	2 (4.8)	

Note: t test was used. SD means standard deviation

Table 2. Genotype frequency distribution between third molar agenesis group and control group and comparison.

SNP		**rs3796902**		***p-value***	
Genotypes	**AA**	**AG**	**GG**	**Genotype**	**Allele**
Control	4 (3.6)	38 (34.2)	69 (61.2)	0.459	0.356
Third molar agenesis	0 (0)	11 (31.4)	24 (68.6)		
SNP		**rs1947187**		**Genotype**	**Allele**
Genotypes	**CC**	**CT**	**TT**		
Control	86 (78.9)	19 (17.4)	4 (3.7)	0.681	0.618
Third molar agenesis	25 (73.9)	8 (23.5)	1(2.9)		
SNP		**rs2595110**		**Genotype**	**Allele**
Genotypes	**AA**	**AG**	**GG**		
Control	40 (35.4)	55 (48.7)	18 (15.9)	0.950	0.998
Third molar agenesis	13 (36.1)	17 (47.2)	6 (16.7)		

Note: Chi-square was used.

Table 3. Means comparisons of Sella Turcica's parameters according to the genotypes.

SNP	**rs3796902**				**rs1947187**				**rs2595110**			
Parameters	**AA**	**AG**	**GG**	**p-value**	**CC**	**CT**	**TT**	**p-value**	**AA**	**AG**	**GG**	***p-value***
Length in mm	83.75 (18.21)	86.85 (18.44)	86.20 (17.25)	0.936	86.66 (17.19)	86.16 (16.70)	79.58 (19.55)	0.665	87.45 (18.57)	86.75 (16.92)	82.25 (16.42)	0.458
Depth in mm	80.43 (8.15)	83.13 (12.39)	82.01 (12.00)	0.826	82.22 (12.17)	82.72 (11.73)	80.40 (9.75)	0.922	82.23 (13.49)	82.71 (11.60)	82.44 (10.55)	0.976
Posterior height in mm	83.62 (8.56)	85.58 (13.89)	82.96 (14.21)	0.573	83.46 (14.71)	86.75 (11.81)	81.71 (8.67)	0.517	81.10 (16.56)	80.32 (13.73)	82.76 (16.05)	0.745
Anterior height in mm	76.03 (10.44)	81.22 (15.07)	80.96 (15.28)	0.803	80.98 (15.41)	78.99 (14.51)	79.24 (13.35)	0.814	81.10 (16.56)	80.32 (13.73)	82.76 (16.05)	0.873
Width in mm	83.99 (19.34)	87.16 (13.29)	86.45 (14.09)	0.892	86.13 (13.16)	89.12 (14.34)	87.01 (18.74)	0.591	86.48 (14.82)	87.07 (12.80)	86.68 (14.92)	0.971
Diameter in mm	10.05 (12.59)	10.58 (14.29)	10.79 (16.62)	0.523	10.72 (16.05)	10.68 (12.63)	10.63 (22.49)	0.984	10.62 (18.18)	10.84 (14.04)	10.45 (14.10)	0.519
Area in mm²	56.43 (13.54)	62.64 (14.54)	60.94 (14.99)	0.643	60.70 (14.32)	63.83 (14.52)	57.10 (15.09)	0.487	62.01 (16.19)	61.63 (14.18)	60 .30 (13.12)	0.893

Note: ANOVA and Tukey's post hoc test were used

Table 4. Genotype frequency distribution and comparison between degree of calcification.

SNP	**rs3796902**				**rs1947187**				**rs2595110**			
Degree of calcification	**AA**	**AG**	**GG**	***p-value***	**CC**	**CT**	**TT**	***p-value***	**AA**	**AG**	**GG**	***p-value***
No calcification	0 (0.0)	12 (37.5)	20 (62.5)		24 (77.4)	7 (22.6)	0 (0.0)		10 (31.3)	14 (43.7)	8 (25.0)	
Partially calcified	3 (3.2)	3 (34.8)	59 (62.1)	0.564	70 (75.3)	19 (20.4)	4 (4.3)	0.360	39 (39.8)	45 (45.9)	14 (14.3)	0.207
Completely calcified	1 (5.3)	4 (21.0)	14 (73.7)		17 (89.5)	1 (5.3)	1 (5.3)		4 (21.0)	13 (68.4)	2 (10.6)	

Note: Chi-square was used.

Table 5. Genotype frequency distribution and comparison between degree of calcification.

SNP	**rs3796902**					**rs1947187**					**rs2595110**				
Patterns	AA	AG	GG	***p-value Genotype***	***p-value Allele***	**CC**	**CT**	**TT**	***p-value Genotype***	***p-value Allele***	**AA**	**AG**	**GG**	***p-value Genotype***	***p-value Allele***
Normal sella turcica	1 (2.9)	13 (38.2)	20 (58.9)	Reference		25 (75.8)	6 (18.2)	2 (6.0)	Reference		14 (41.2)	11 (32.3)	9 (26.5)	Reference	
ST bridge type B	2 (5.1)	16 (41.0)	21 (53.9)	0.849	0.621	26 (68.4)	10 (26.3)	2 (5.3)	0.715	0.677	17 (42.5)	18 (45.0)	5 (12.5)	0.265	0.340
ST bridge type A	0 (0.0)	4 (25.0)	12 (75.5)	0.478	0.290	18 (100)	0 (0.0)	0 (0.0)	0.075	0.013*	3 (17.6)	13 (76.5)	1 (5.9)	0.011*	0.887
Incomplete bridge	0 (0.0)	6 (66.7)	3 (33.3)	0.296	0.198	6 (66.7)	3 (33.3)	0 (0.0)	0.501	0.482	3 (30.0)	4 (40.0)	3 (30.0)	0.811	0.892
Hypertrophic posterior clinoid process	1 (3.5)	3 (10.3)	25 (86.2)	0.039*	0.050*	22 (78.6)	5 (17.9)	1 (3.6)	0.891	0.782	10 (34.5)	16 (55.2)	3 (10.3)	0.121	0.318
Hypotropic posterior clinoid process	0 (0.0)	1 (100)	0 (0.0)	0.462	0.562	1 (100)	0 (0.0)	0 (0.0)	0.853	0.872	0 (0.0)	0 (0.0)	1 (100)	0.271	0.922
Irregularity in the posterior part of the ST	1 (20.0)	1 (20.0)	3 (60.0)	0.237	0.872	3 (100)	0 (0.0)	0 (0.0)	0.839	0.792	0 (0.0)	2 (66.7)	1 (33.3)	0.331	0.832
Pyramidal shape of the dorsum sella	0 (0.0)	2 (100)	0 (0.0)	0.227	0.235	0 (0.0)	2 (100)	0 (0.0)	0.028	0.133	1 (50.0)	1 (50.0)	0 (0.0)	0.592	0.899
Double contour of the floor	0 (0.0)	1 (100)	0 (0.0)	0.462	0.562	1 (100)	0 (0.0)	0 (0.0)	0.853	0.872	1 (100)	0 (0.0)	0 (0.0)	0.503	0.628
Oblique anterior wall	0 (0.0)	1 (12.5)	7 (87.5)	0.308	0.285	7 (100)	0 (0.0)	0 (0.0)	0.346	0.588	2 (25.0)	5 (62.5)	1 (12.5)	0.285	0.632
Oblique contour of the floor	0 (0.0)	2 (50.0)	2 (50.0)	0.509	0.289	2 (66.7)	1 (33.3)	0 (0.0)	0.792	0.690	2 (50.0)	2 (50.0)	0 (0.0)	0.484	0.559

Note: Chi-square was used. * means statistical significance difference

6.10 FIGURES

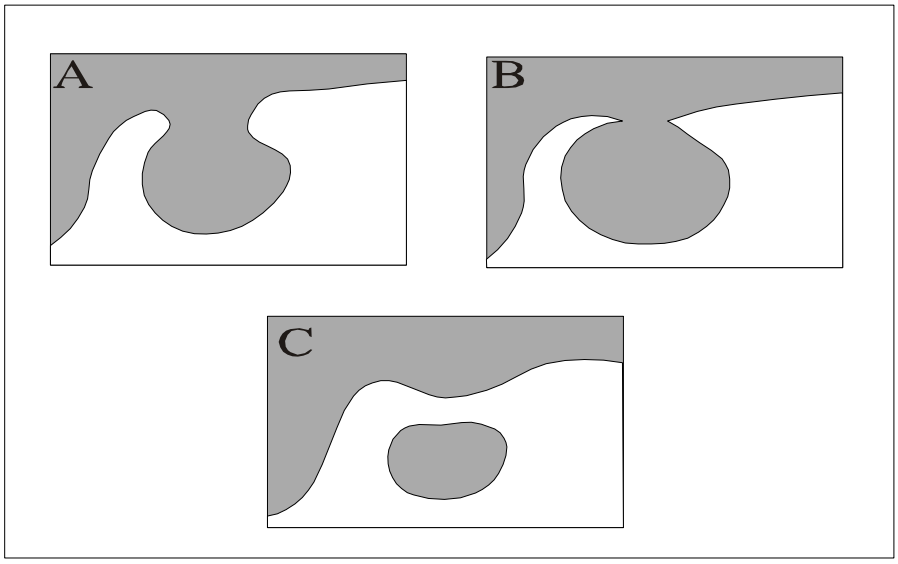

Figure 1. Sella turcica calcification phenotypes. A- calcification; B- partially calcified); C- completely calcified.

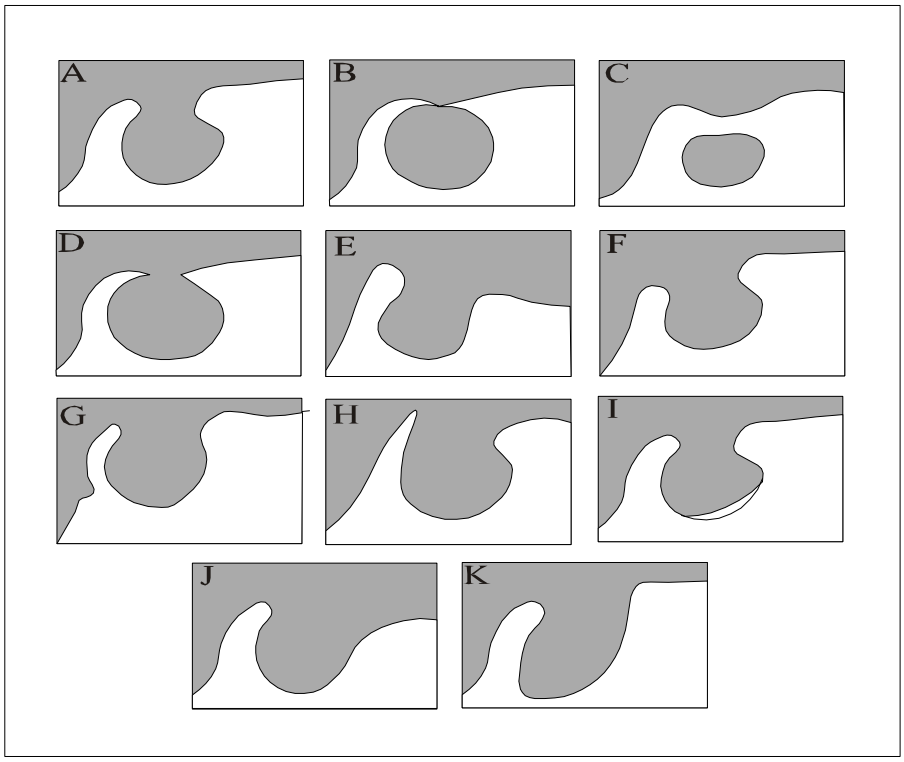

Figure 2. Sella turcica patterns. A- normal sella turcica; B- sella turcica bridge type B- extension of the clinoid process; C- sella turcica bridge type A- ribbon-like fusion; D- incomplete bridge; E- hypertrophic posterior clinoid process; F- hypotrophic posterior clinoid process; G- irregularity (notching) in the posterior part of the sella turcica; H- pyramidal shape of the dorsum sella; I- double contour of the floor; J- oblique anterior wall; K- oblique contour of the floor.

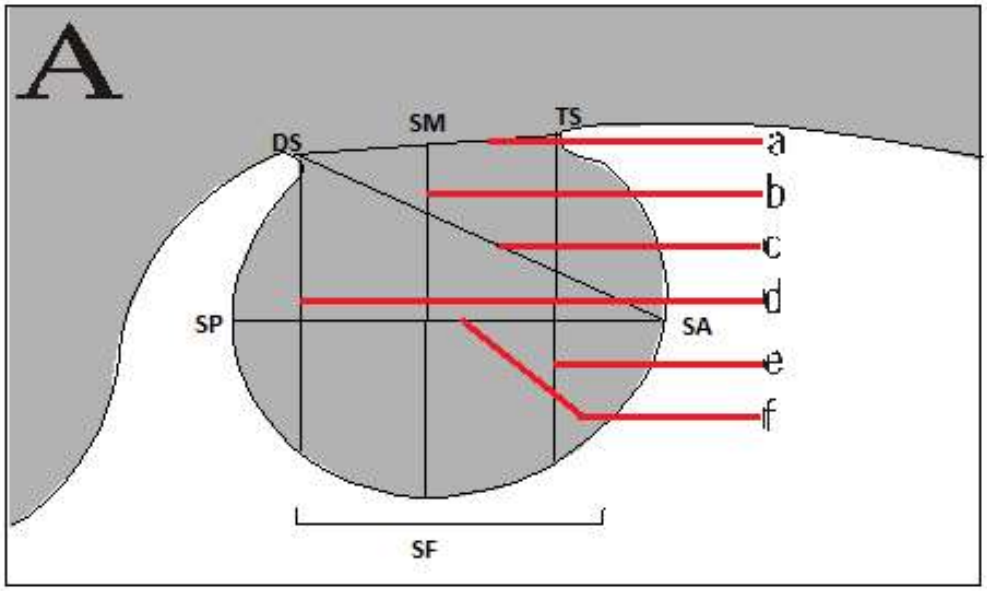

Figure 3. Sella turcica landmarkers and linear measuremts. a: length; b: depth; c: diameter; d: anterior height; e: posterior height; f: width

7 CONCLUSÃO

Diante a revisão de literatura sistematizada, a morfologia da sela túrcica pode ser influenciada pela agenesia dentária em determinadas populações. Métodos métricos e não-métricos são bem executados para avaliação dos fenótipos da sela túrcica. A população de crianças alemãs foi mais uma população que não encontrou associação entre fenótipos de sela túrcica e agenesia dentária de terceiros molares. Em contrapartida, pôde-se demonstrar que polimorfismos genéticos em PITX2 estão associados com alguns fenótipos da sela túrcica em pacientes com agenesia de terceiros molares na população de crianças alemãs.

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ANEXOS

Anexo 1. Carta de aprovação do Comitê de Ética na Universidade de Regensburg.

Universität Regensburg

Ethikkommission
an der Universität Regensburg

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13.11.2019

Unser Zeichen: **19-1549-101**

Beratung nach § 15 Abs. 1 Berufsordnung für die Ärzte Bayerns
für das Forschungsvorhaben:

Studientitel: **AUFDECKUNG MÖGLICHER ÄTIOLOGISCHER ZUSAMMENHÄNGE ZWISCHEN BIOLOGISCHEN FAKTOREN BZW. GENETISCHEN POLYMORPHISMEN UND DENTOFAZIALEN SOWIE KIEFEROR-THOPÄDISCHEN PHÄNOTYPEN**

Antragssteller: Dr. med. dent. Christian Kirschneck

Die Ethikkommission der Universität Regensburg hat in Ihrer Sitzung am 13.11.2019 über das o.g. Forschungsvorhaben auf Grundlage der im Anhang aufgeführten Unterlagen beraten. Es ergeben sich daraus keine berufsethischen oder rechtlichen Bedenken gegen das vorgelegte Forschungsvorhaben.

Es wird auf folgendes grundsätzlich hingewiesen:

1. Unabhängig vom Beratungsergebnis verbleibt die ärztliche und juristische Verantwortung beim Forscher und seinen Mitarbeitern. Eine Nichtbeachtung des Beratungsergebnisses kann berufs- und haftungsrechtliche Folgen nach sich ziehen.

2. Die Auflagen der Deklaration von Helsinki des Weltärztebundes in ihrer aktuellen Fassung hinsichtlich ethischen und rechtlichen Aspekten biomedizinischer Forschung am Menschen sind strikt zu beachten.

3. Die Ethikkommission erwartet bei Interventionsstudien, dass ihr alle schwerwiegenden oder unerwarteten unerwünschten Ereignisse (u.a. Todesfälle), die während der Studie auftreten und die Sicherheit der Studienteilnehmer oder die Durchführung der Studie beeinträchtigen können, unverzüglich schriftlich mitgeteilt werden. Dieses sollte in Verbindung mit einer Stellungnahme des Antragsstellers geschehen, ob aus seiner Sicht die Nutzen-Risiko-Relation des Vorhabens verändert ist.

4. Die Ethikkommission bittet darum, dass ihr der Abbruch oder Abschluss einer Studie mitgeteilt werden.

5. Dieses Schreiben ist mit den Studienunterlagen jederzeit sorgfältig aufzubewahren. Duplikate oder Abschriften dieses Schreibens können im Nachhinein nicht erstellt werden.
   Auf die Rechtspflichten zum Umgang mit dienstlichem Schriftgut bzw. Urkunden wird verwiesen.

6. Auf Grundlage dieser rein berufsrechtlichen Beratung können Sie nachträgliche Änderungen am Protokoll dieses Forschungsvorhabens vornehmen, ohne dafür eine erneute Beratung (umgangssprachlich 'Amendmentvotum') durch die Ethikkommission beantragen zu müssen. Zur Begrenzung rechtlicher Risiken wird eine solche Beratung aber gleichwohl dringend empfohlen.

   Sobald Sie jedoch ein neues Forschungsvorhaben durchführen wollen, müssen Sie dieses einer eigenständigen Beratung durch die Ethikkommission zuführen. Hierfür gilt gemäß Grundsatzbeschluss unserer Ethikkommission vom 02.08.2016:

   In der Regel handelt es sich noch um ein und dasselbe Forschungsvorhaben ohne eine erneute Beratungspflicht, wenn sich lediglich ergänzende Fragestellungen im Rahmen der selben Hypothese, methodische Erweiterungen oder Beschränkungen oder Erweiterungen oder Beschränkungen in der Studienpopulation nachträglich ergeben. Um ein neues Forschungsvorhaben handelt es sich aber in der Regel, wenn die Formulierung einer neuen Hypothese, wesentliche Änderungen am Studiengegenstand bzw. der Entität sowie wesentliche Änderungen an der wissenschaftlichen oder technischen Vorgehensweise vorgenommen werden sollen, was dann eine Pflicht zur neuerlichen Beratung durch die Ethikkommission begründet. Gesetzliche Vorschriften bleiben unberührt.

7. Die Ethikkommission bestätigt die Bearbeitung gemäß der GCP/ICH-Richtlinien.

8. Die Ethikkommission empfiehlt im Einklang mit der Deklaration von Helsinki nachdrücklich die Registrierung der Studie vor Studienbeginn in einem öffentlich zugänglichen Register, das die von der WHO geforderten Voraussetzungen erfüllt.

9. Falls kein gesetzlicher Kostenbefreiungstatbestand greift, wird ein gesonderter Kostenbescheid für die Gebühren und Auslagen der Ethikkommission ergehen.

10. **Die Übermittlung personenbezogener Daten einschließlich DNA-tragender Biomaterialien in datenschutzrechtlich unsichere Drittstaaten, wie etwa die USA, bedarf einer gesonderten datenschutzrechtlichen Beurteilung und Risikoaufklärung.**

11. **Datenschutzrecht wird durch die Ethikkommission grundsätzlich nur kursorisch geprüft. Dieses Votum ersetzt mithin nicht die Konsultation des zuständigen Datenschutzbeauftragten.**

Prof. Edward K. Geissler, PhD
Vorsitzender der Ethikkommission

3

Liste der eingereichten Unterlagen:

Anlageelement	Datei-Name	Eingangs-datum
Prüfplan	01 Protokoll.pdf	23.09.2019
Gegenstand des Forschungsvorhabens	02 Gegenstand des Forschungsvorhabens.pdf	23.09.2019
Angaben zum Nutzen für die Heilkunde/ wissenschaftl. Erkenntniswert	03 Angaben zum Nutzen für die Heilkunde bzw. wissenschaftlicher Erkenntniswert.pdf	23.09.2019
Nutzen-Risiko-Bewertung	04 Informationen zu Abwägung zwischen Risiko und Nutzen für den Patienten bzw. Probanden.pdf	23.09.2019
Angaben zu Anzahl, Alter und Geschlecht	05 Angaben zu Anzahl, Alter und Geschlecht der Versuchspersonen.pdf	23.09.2019
Angaben zur ethischen Problematik	06 Angaben zur ethischen Problematik.pdf	23.09.2019
Vereinbarungen zur Vergütung	07 Angaben zum Honorar für Versuchspersonen.pdf	23.09.2019
Patienteninformation	08 Aufklärungsdokument.pdf	23.09.2019
Patienteninformation	08 Aufklärungsdokument_Kinder.pdf	23.09.2019
Patienteneinwilligung	09 Einwilligungsdokument.pdf	23.09.2019
Vorgesehene Untersuchungsmethoden/ Abweichung von der üblichen Praxis	10 Beschreibung der vorgesehenen Untersuchungsmethoden und eventuelle Abweichungen von den in der medizinischen Praxis üblichen Untersuchungen.pdf	23.09.2019
Literaturverzeichnis	11 Literaturverzeichnis.pdf	23.09.2019
Angaben zur Methodik der Erfassung/ Verarbeitung personenbezogener Daten	12 Angaben zur Methodik der Erfassung und Verarbeitung personenbezogener oder personenbeziehbarer Daten.pdf	23.09.2019
Kurzbeschreibung	Kurzbeschreibung.pdf	23.09.2019

An dieser Entscheidung der Ethikkommission in Ihrer Sitzung vom 13.11.2019 haben mitgewirkt:

Prof. Dr. Karin Pfister
Prof. Dr. Karl Peter Ittner
RiAG Dr. Wolfhard Meindl
Prof. Dr. Michael Melter
Prof. Dr. Stefan Wüst
Dr. Sophie Schlosser
RAR Werner Stelzl
PD Dr. Anja-Kathrin Wege
PD Dr. Anika Bundscherer
Michael Ertl

Anexo 2. Tradução para a língua inglesa da Carta de aprovação do Comitê de Ética na Universidade de Regensburg.

Universität Regensburg

Ethics Committee
at the University of Regensburg

Ethics Committee University of Regensburg 93040 Regensburg

University Hospital Regensburg
Polyclinic for Orthodontics
Dr. med. *dent.* Christian *Kirschneck*
Franz-Josef-Strauß-Allee 11
93053 Regensburg

Prof. Edward K. Geissler. PhD, Vorsitzender

Ass. jur. Jan von Hassel, Geschäftsführer

Office:
Telefon +49 941 94 3 -5370
Telefax +49 941 943-5369
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Universitat Regensburg
ETHICS COMMITTEE
D-93040 Regensburg

ethikkommission@klinik uni-regensburg. de
http://ethikkommisston.uni-regensburg.de

1 3.1 1.2019

Unser Zeichen. 19-1549-101

Consultation according to § 1 5 Abs. 1 Professional code for the doctors of Bavaria for the research project:

Study title: **IDENTIFICATION OF POSSIBLE ETIOLOGICAL CORRELATIONS BETWEEN BIOLOGICAL FACTORS OR GENETIC POLYMORPHISMS AND DENTOFACIAL AND ORTHODONTIC PHENOTYPES**

Applicant: Dr. med. dent. Christian Kirschneck

The Ethics Committee of the University of Regensburg discussed the above-mentioned research project at its meeting on 13.11.2019 on the basis of the documents listed in the appendix. There are no ethical or legal objections to the submitted research project.

The following is generally pointed out:

1 Regardless of the outcome of the consultation, the medical and legal responsibilityremains with the researcher and his/her collaborators. Non-observance of the result of the consultation can result in professional and liability law consequences.

2 The requirements of the Declaration of Helsinki of the World Medical Association in its current version regarding ethical and legal aspects of biomedical research involving human subjects are to be strictly observed.

3 In the case of intervention studies, the ethics committee expects to be informed immediately in writing of any serious or unexpected adverse events (including deaths) that occur during the study and may affect the safety of the study participants or the conduct of the study. This should be done in conjunction with a statement from the applicant as to whether, in his or her view, the benefit-risk ratio of the project has changed.

4 The Ethics Committee requests to be informed of the termination or completion of a study.

5 This letter must be carefully kept with the study documents at all times. Duplicates or copies of this letter cannot be made subsequently.
Reference is made to the legal obligations regarding the handling of official documents.

6 On the basis of this purely professional advice, you can make subsequent changes to the protocol of this research project without having to apply for a new consultation (colloquially known as an 'amendment vote') by the ethics committee. However, in order to limit legal risks, such advice is strongly recommended.

However, as soon as you want to carry out a new research project, you must submit it to an independent consultation with the ethics committee. This applies in accordance with the basic decision of our Ethics Committee of 02.08.2016:

As a rule, it is still one and the same research project without a renewed obligation to consult if only supplementary questions within the framework of the same hypothesis, methodological extensions or limitations, or extensions or limitations in the study population subsequently arise. However, a new research project is usually involved if the formulation of a new hypothesis, substantial changes to the object of study or the entity, as well as substantial changes to the scientific or technical procedure are to be undertaken, which then justifies an obligation for renewed consultation by the ethics committee. Statutory regulations remain unaffected.

7. The ethics committee confirms the processing according to the GCP/ICH guidelines.

8. In accordance with the Declaration of Helsinki, the Ethics Committee strongly recommends the registration of the study prior to study initiation in a publicly accessible registry that meets the requirements demanded by the WHO.

9. If no statutory exemption from costs applies, a separate cost order will be issued for the fees and expenses of the ethics committee.

10. The transfer of personal data, including DNA-bearing biomaterials, to third countries that are insecure in terms of data protection law, such as the USA, requires a separate data protection assessment and risk clarification.

11. Data protection law is only examined by the ethics committee in a cursory manner. This vote therefore does not replace consultation with the responsible data protection officer.

Prof. Edward K. Geissler, PhD
Vorsitzender der Ethikkommission

List of documents received:

Investment element	File-Name	Received date
Test plan	01 Protocol.pdf	23.09.2019
Subject of the research project	02 Subject of the research project.pdf	23.09.2019
Information on the benefit for medical science / scientific knowledge value	03 Information on the benefit for medical science or scientific investigative value.pdf	23.09.2019
Benefit-Risk Assessment	04 Information on weighing up the risk and benefit for the patient or test person.pdf	23.09.2019
Information on number, age and gender	05 Information on the number, age and sex of the test subjects.pdf	23.09.20s 9
Information on the ethical problem	06 Information on the ethical problem.pdf	23.09.2019
Remuneration agreements	07 Details of the fee for test subjects.pdf	23.09.2019
Patient information	08 Reconnaissance document.pdf	23.09.2019
Patient information	08 Reconnaissance document children.pdf	23.09.2019
Patient Informed Consent	09 Informed consent document.pdf	23.09.2019
Intended examination methods/ deviation from usual Practice	1 0 Description of the intended examination methods and any deviations from the usual examinations in medical practice.pdf	23.09.20J 9
References	11 References.pdf	23.09.2019
Information on the methodology of collection/processing of personal Data	12 Information on the methodology of collection and processing of personal or personal-related data. pdf	23.09.2019
Brief description	Brief description.pdf	23.09.2019

The following participated in this decision of the Ethics Committee in your meeting of 13.11.2019.

Prof. Dr. Karin Pfister

Prof. Dr. Karl Peter Ittner

RiAG Dr. Wolfhard Meindl

Prof. Dr. Michael Melter

Prof. Dr. Stefan Wüst

Dr. Sophie Schlosser

RAR Werner Stelzl

PD Dr. Anja-Kathrin *Vege*

PD Dr. Anika Bundscherer

Michael Ertl

Anexo 3: Normas para publicação no periódico Head Face Medicine.

Preparando seu manuscrito

As informações abaixo detalham os títulos das seções que você deve incluir em seu manuscrito e quais informações devem estar em cada seção.

Observe que seu manuscrito deve incluir uma seção 'Declarações' incluindo todos os subtítulos (consulte abaixo para obter mais informações).

Folha de rosto

A página de título deve:

- apresentar um título que inclua, se apropriado, o desenho do estudo, por exemplo:
  - "A versus B no tratamento de C: um estudo randomizado controlado", "X é um fator de risco para Y: um estudo de caso-controle", "Qual é o impacto do fator X no sujeito Y: uma revisão sistemática"
  - ou para estudos não clínicos ou sem pesquisa, uma descrição do que o artigo relata

- listar os nomes completos e endereços institucionais de todos os autores
  - se um grupo de colaboração deve ser listado como autor, liste o nome do grupo como autor. Se você deseja que os nomes dos membros individuais do Grupo possam ser pesquisados por meio de seus registros individuais do PubMed, inclua essas informações na seção "Agradecimentos" de acordo com as instruções abaixo
  - Modelos de linguagem grandes (LLMs), como ChatGPT , atualmente não atendem aos nossos critérios de autoria . Notavelmente, uma atribuição de autoria traz consigo a responsabilidade pelo trabalho, que não pode ser efetivamente aplicada aos LLMs. O uso de um LLM deve ser devidamente documentado na seção Métodos (e se uma seção Métodos não estiver disponível, em uma parte alternativa adequada) do manuscrito.

- indique o autor correspondente

Resumo

O Resumo não deve exceder 350 palavras. Minimize o uso de abreviaturas e não cite referências no resumo. Os relatórios de ensaios clínicos randomizados devem seguir a extensão CONSORT para resumos. O resumo deve incluir as seguintes seções separadas:

- **Contexto:** o contexto e o objetivo do estudo
- **Métodos:** como o estudo foi realizado e os testes estatísticos utilizados
- **Resultados:** as principais descobertas
- **Conclusões:** breve resumo e possíveis implicações
- **Registro do estudo:** Se o seu artigo relatar os resultados de uma intervenção de saúde em participantes humanos, ele deve ser registrado em um registro apropriado e o número de registro e a data do registro devem ser declarados nesta seção. Caso não tenha sido cadastrado prospectivamente (antes da inscrição do primeiro participante), deverá incluir a expressão 'cadastrado retrospectivamente'. Consulte nossas políticas editoriais para obter mais informações sobre o registro de avaliação

Palavras-chave

Três a dez palavras-chave que representam o conteúdo principal do artigo.

Fundo

A seção Antecedentes deve explicar os antecedentes do estudo, seus objetivos, um resumo da literatura existente e por que este estudo foi necessário ou sua contribuição para o campo.

Métodos

A seção de métodos deve incluir:

- o objetivo, o design e o cenário do estudo
- as características dos participantes ou descrição dos materiais
- uma descrição clara de todos os processos, intervenções e comparações. Nomes genéricos de medicamentos geralmente devem ser usados. Quando marcas proprietárias forem usadas na pesquisa, inclua os nomes das marcas entre parênteses
- o tipo de análise estatística usada, incluindo um cálculo de poder, se apropriado

Resultados

Isso deve incluir os resultados do estudo, incluindo, se apropriado, os resultados da análise estatística que devem ser incluídos no texto ou na forma de tabelas e figuras.

Discussão

Esta seção deve discutir as implicações das descobertas no contexto da pesquisa existente e destacar as limitações do estudo.

Conclusões

Este deve indicar claramente as principais conclusões e fornecer uma explicação sobre a importância e relevância do estudo relatado.

Lista de abreviações

Se abreviaturas forem usadas no texto, elas devem ser definidas no texto no primeiro uso, e uma lista de abreviações deve ser fornecida.

Referências

Exemplos do estilo de referência Vancouver são mostrados abaixo.

Veja nossas políticas editoriais para orientação do autor sobre boas práticas de citação

Links da Web e URLs: Todos os links da Web e URLs, incluindo links para os sites dos próprios autores, devem receber um número de referência e ser incluídos na lista de referências, e não no texto do manuscrito. Devem ser fornecidos completos, incluindo o título do site e a URL, bem como a data em que o site foi acessado, no seguinte formato: The Mouse Tumor Biology Database. http://tumor.informatics.jax.org/mtbwi/index.do . Acessado em 20 de maio de 2013. Se um autor ou grupo de autores puder ser claramente associado a um link da web, como para weblogs, eles devem ser incluídos na referência.

Exemplo de estilo de referência:

Artigo dentro de um jornal

SmithJJ. O mundo da ciência. Am J Sci. 1999;36:234-5.

Artigo dentro de um jornal (sem números de página)

Rohrmann S, Overvad K, Bueno-de-Mesquita HB, Jakobsen MU, Egeberg R, Tjønneland A, *et al.* Consumo de carne e mortalidade - resultados da Investigação Prospectiva Europeia sobre Câncer e Nutrição. BMC Medicina. 2013;11:63.

Artigo dentro de um jornal pelo DOI

Slifka MK, Whitton JL. Implicações clínicas da produção desregulada de citocinas. Dig J Mol Med. 2000; doi:10.1007/s801090000086.

Artigo dentro de um suplemento de revista

Frumin AM, Nussbaum J, Esposito M. Asplenia funcional: demonstração da atividade esplênica por varredura da medula óssea. Blood 1979;59 Supl 1:26-32.

Capítulo de livro ou um artigo dentro de um livro

Wyllie AH, Kerr JFR, Currie AR. Morte celular: o significado da apoptose. In: Bourne GH, Danielli JF, Jeon KW, editores. Revisão Internacional de Citologia. Londres: Acadêmico; 1980. pág. 251-306.

OnlinePrimeiro capítulo de uma série (sem designação de volume, mas com DOI)

Saito Y, Hyuga H. A equação de taxa aproxima-se da amplificação do excesso enantiomérico e da quebra de simetria quiral. Top Curr Chem. 2007. doi:10.1007/128_2006_108.

Livro completo, autoria

Blenkinsopp A, Paxton P. Sintomas na farmácia: um guia para o manejo de doenças comuns. 3ª ed. Oxford: Blackwell Science; 1998.

Documento on-line

Doe J. Título do documento subordinado. In: O dicionário de substâncias e seus efeitos. Sociedade Real de Química. 1999. http://www.rsc.org/dose/title do documento subordinado. Acessado em 15 de janeiro de 1999.

banco de dados on-line

Base de Conhecimento Healthwise. US Pharmacopeia, Rockville. 1998. http://www.healthwise.org. Acessado em 21 de setembro de 1998.

Material suplementar/página inicial privada

Doe J. Título do material suplementar. 2000. http://www.privatehomepage.com. Acessado em 22 de fevereiro de 2000.

site da universidade

Doe, J: Título da pré-impressão. http://www.uni-heidelberg.de/mydata.html (1999). Acessado em 25 de dezembro de 1999.

Site FTP

Doe, J: Trivial HTTP, RFC2169. ftp://ftp.isi.edu/in-notes/rfc2169.txt (1999). Acessado em 12 de novembro de 1999.

Site da organização

Centro Internacional ISSN: O registro ISSN. http://www.issn.org (2006). Acessado em 20 de fevereiro de 2007.

Conjunto de dados com identificador persistente

Zheng LY, Guo XS, He B, Sun LJ, Peng Y, Dong SS, *et al.* Dados do genoma do sorgo doce e granulado (Sorghum bicolor). Banco de Dados GigaScience. 2011. http://dx.doi.org/10.5524/100012 .