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Genetic bases related to the development of non-syndromic dental agenesis: a literature review

Bases genéticas relacionadas ao desenvolvimento de agenesia dentária não sindrômica: uma revisão de literatura

Bases genéticas relacionadas con el desarrollo de agenesia dental no sindrómica: revisión de literatura

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Iago Demétrio da Silva
ORCID: https://orcid.org/0000-0002-3591-3278
State University of Maringá, Brazil
E-mail: iagodemetrio95@gmail.com
Caio Cesar Santos Patron Luiz
ORCID: https://orcid.org/0000-0003-1695-838X
State University of Maringá, Brazil
E-mail: caiopatron@hotmail.com
Andressa Bolognesi Bachesk
ORCID: https://orcid.org/0000-0002-4123-5186
State University of Maringá, Brazil
E-mail: andressabachesk@gmail.com
Brenda da Silva Balassa
ORCID: https://orcid.org/0000-0002-8180-8938
Ingá University Center, Brazil
E-mail: balassabh@icloud.com

Abstract

Non-syndromic dental agenesis is characterized as the most common developmental anomaly in humans, causing the lack of one or more teeth, in deciduous or permanent dentition. Mutations in specific genes of dental development are pointed as etiological factors of this anomaly. To perform this work, two electronic databases were consulted to conduct a literature survey, including PubMed and BVS. The descriptor "Anodontia" was used in both. The articles were filtered from 2010 to 2020, including full texts, in english, portuguese and spanish.

Dissertations, theses and book chapters were discarded. In PubMed, from 508 articles found, 13 were included for review. In the BVS, from 304 articles found, 07 were included for review, totaling 20 articles. Studies have shown that mutations by nucleotide subitusing and deletion were more present in genes that cause dental agenesis (PAX9, MSX1, AXIN2, WNT). In epidemiologic studies, women showed greater involvement than men, both in deciduous and permanent dentition, in a ratio of 3:2. In addition, leukoderms showed greater involvement than melanoderms. Knowledge of the genotype-phenotype correlation between mutations and dental agenesis is important for the dental surgeon, as it assists in diagnosis, genetic counseling, treatment and prognosis.

Keywords: Genetics; Mutation; Dental anomaly.

Resumo

A agenesia dentária não sindrômica se caracteriza como a anomalia de desenvolvimento mais comum nos seres humanos, ocasionando a falta de um ou mais dentes, na dentição decídua ou permanente. Mutações em genes específicos do desenvolvimento dentário são apontadas como fatores etiológicos desta anomalia. Para a realização deste trabalho duas bases de dados eletrônicas foram consultadas para fazer um levantamento de literatura, sendo elas: PubMed e BVS. Em ambas utilizou-se o descritor “Anodontia”. Os artigos foram filtrados no período de 2010 a 2020, incluindo textos completos, em idioma inglês, português e espanhol. Descartaram-se dissertações, teses e capítulos de livros. No PubMed, de 508 artigos encontrados, 13 foram incluídos para a revisão. Na BVS, de 304 artigos encontrados, 07 foram incluídos para a revisão, totalizando 20 artigos. Os estudos demonstraram que mutações por substituição de nucleotideo e deleção mostraram-se mais presentes nos genes causadores da agenesia (PAX9, MSX1, AXIN2, WNT). Nos estudos epidemiologicos as mulheres mostraram maior acometimento que os homens, tanto na dentição decidua quanto na permanente, com uma proporção de 3:2. Além disso, os leucodermas apresentaram maior acometimento que os melanodermas. O conhecimento da correlação genótipo-fenótipo entre mutações e agenesia dentária é importante para o cirurgião dentista, pois auxilia no diagnóstico, aconselhamento genético, tratamento e prognóstico.

Palavras-chave: Genética; Mutação; Anomalia dentária.

Resumen

La agenesia dental no sindrómica se caracteriza como la anomalía del desarrollo más común en los seres humanos, causando la falta de uno o más dientes, en la dentición primaria o

permanente. Las mutaciones en genes específicos del desarrollo dental se señalan como factores etiológicos de esta anomalía. Para llevar a cabo este trabajo, se consultaron dos bases de datos electrónicas para llevar a cabo una encuesta de literatura, incluyendo PubMed y BVS. El descriptor "Anodontia" se utilizó en ambos. Los artículos se filtraron de 2010 a 2020, incluyendo textos completos, en inglés, portugués y español. Se descartaron disertaciones, tesis y capítulos de libros. En el PubMed de 508 artículos encontrados, 13 fueron incluidos para su revisión. En el BVS de 304 artículos encontrados, 07 fueron incluidos para la revisión, con un total de 20 artículos. Los estudios han demostrado que las mutaciones por nucleótido sulis y la deleción estaban más presentes en los genes causantes de la agenesia (PAX9, MSX1, AXIN2, WNT). En estudios epidemiológicos, las mujeres mostraron una mayor implicación que los hombres, tanto en la dentición primaria y permanente, en una proporción de 3:2. Además, leucodermos mostraron una mayor implicación que melanoderms. El conocimiento de la correlación genotipo-fenotipo entre mutaciones y agenesia dental es importante para el dentista, ya que ayuda en el diagnóstico, asesoramiento genético, tratamiento y pronóstico.

Palabras clave: Genética; Mutación; Anomalía dental.

1. Introduction

Dental agenesis is characterized as a congenital lack of one or more teeth, which may occur in deciduous or permanent dentition, and represents the most common morphological abnormality in humans (Chishti, et al., 2006). The term hypodontia applies for the absence of one to six teeth (excluding the third molars), oligodontia for the absence of more than six teeth (excluding the third molars) and anodondia when a total absence of teeth occurs (Chishti, et al., 2006).

This anomaly can be embryologically determined and may occur in several phases of fetal development, specifically during the initial formation of dental germs (Carvalho & Tavano, 2008). The agenesis can occur isolated, non-syndromic, or associated with syndromes (Klein, et al., 2013). When it occurs in a non-syndromic manner, the genetic factor is pointed as its main etiology.

Mutations in genes that encoding transcription factors MSX1, PAX9, or genes that encoding proteins involved in wnt canonical signaling (AXIN2) are the main etiological factors pointed in the studies (Chhabra, et al., 2014). The aim of this was to identify in the literature of the last 10 years, studies that demonstrate the genetic alterations that lead to the development of non-syndromic dental agenesis.

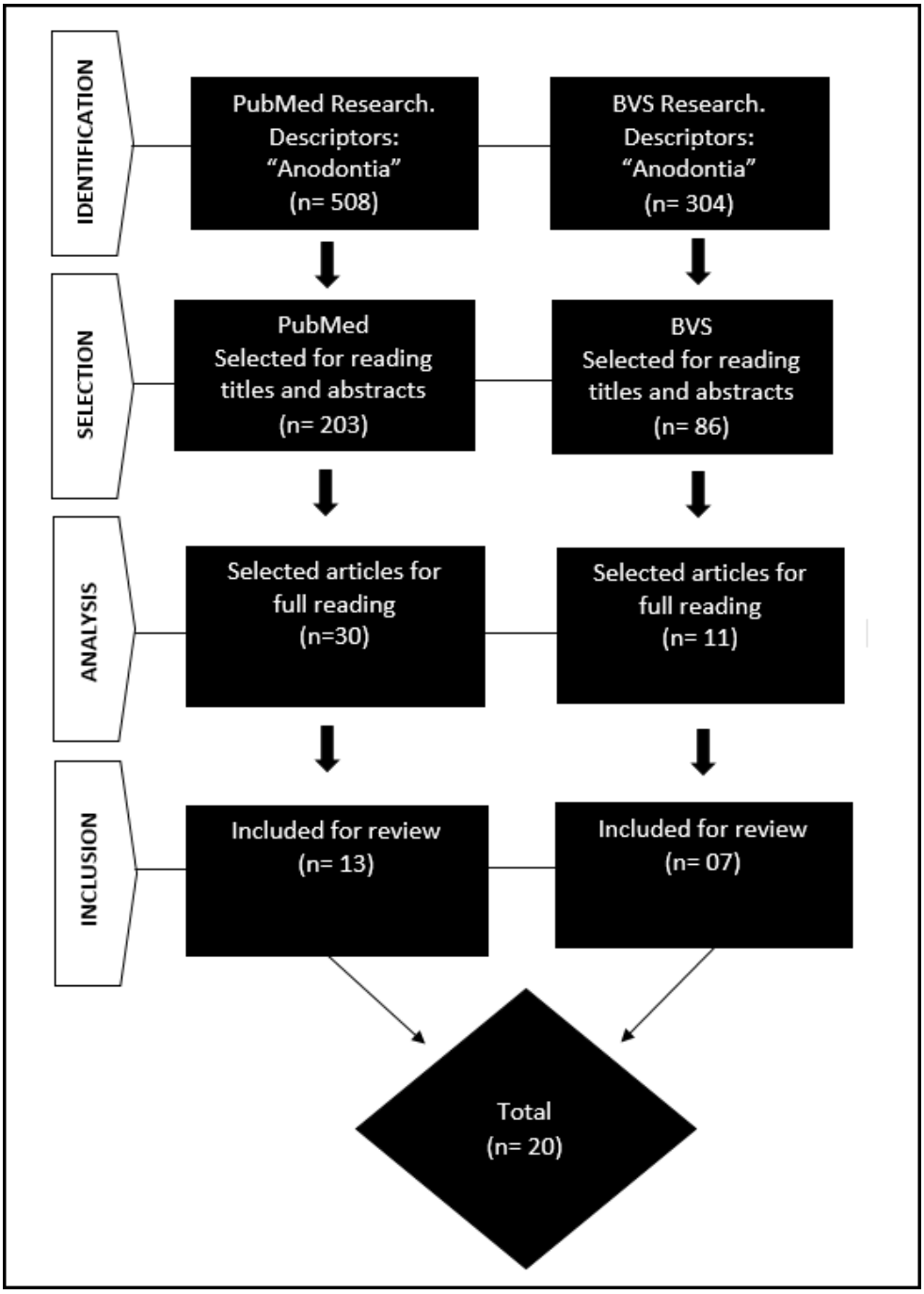
2. Methodology

For the study, an advanced search was carried out in the electronic databases PubMed and Virtual Health Library (BVS), in the period from 2010 to 2020, using the term "Anodontia" indexed in the Medical Subject Heading Terms (Mesh Terms – MeSH) for PubMed and the same term indexed in the "Descriptors in Health Sciences" (DeCs) for BVS platform. The methodology used for the choice of articles was qualitative as specified in (Pereira, et al., 2018).

The search on PubMed platform was performed with filter for full texts in english, portuguese and spanish, in the period from 2010 to 2020. As an exclusion factor, dissertations, theses and book chapters were discarded. A number of 508 articles were found. A total of 203 articles were selected for title and abstract reading. As an inclusion factor, only articles related to genetics associated with non-syndromic agenesis were selected for full-text reading, totaling 30 articles. Of these, only 13 dealt specifically with the proposed theme.

In the BVS platform was also used the filter for full texts in english, portuguese and spanish, from 2010 to 2020, and discarding dissertations, theses and book chapters. A total of 304 articles were found, which 86 were selected for title and abstract reading. Of these, 07 were selected for full text reading and inclusion, because they dealt specifically with the proposed theme. Thus, a total of 20 studies that bet corresponded better to the objectives proposed by this study, were included to review (Figure 1).

Figure 1 - Flowchart descriptor of the selection process of the studies for review.



Source: authors.

3. Results and Discussion

3.1 Epidemiological studies

Regarding the prevalence and distribution of non-syndromic dental agenesis, Gomes, et al., (2010) found in a study in the Brazilian population the prevalence of agenesis of 6.3%,

39.4% in men and 60.6% in women. About the most affected teeth, the upper lateral incisor was the most frequently absent tooth, followed by the second lower premolar. Tallón-Walton, et al., (2010) found in Spain a prevalence of agenesis of 9.48% (7.25% excluding third molars) and 0.39% for oligodontia. Alsoleihat & Khraisat, (2014) found a prevalence of 11.8% (11.1% for men, 12.5% for women) in a study in the Druze population (Middle East). 90% of the individuals exhibited mild hypodontia (one or two missing teeth) and the most commonly absent teeth were the upper lateral incisors and the canines, followed by the lower and upper second premolars. Gracco, et al., (2017) found in Italy a prevalence of 9% (9.1% for women and 8.7% for men). The most common absent teeth were the second lower premolars (20.3 and 18.1%), followed by the upper lateral incisors (17.8 and 17.7%) and second upper premolars (7.4 and 6.3%). The absence of one tooth for five teeth was observed in 344 patients (8.6%), and 15 patients had six to nine missing teeth (0.4%).

The incidence of agenesis in deciduous dentition is considerably lower than in permanent dentition. Studies report 0.4 to 0.9% of individuals from the European Union and Brazil, in addition to 2.4% in Japan (Salama & Abdel-Megid, 1994; Daugaard-Jensen, et al., 1997; Yonezu, et al., 1997; Kramer, et al., 2008; Chung, et al., 2008). (Lai &Seow, 1989) Furthermore, Daugaard-Jensen, et al., (1997) reported in their studies that the most absent deciduous tooth was the lateral incisor.

Some studies state that the prevalence rates of agenesis in both deciduous or permanent teeth are significantly higher in women, compared with men, respectively at a ratio of 3:2 (Brook, 1974; Vastardis, 2000; Mattheeuws, et al., 2004; Polder, et al., 2004; Kirzioglu, et al., 2005; Alshahrani, et al., 2013). In addition to sex, race seems to influence the prevalence of agenesis, where there is a lower prevalence in melanoderm patients, when compared to leucoderm patients (Polder, et al., 2004; Harris & Clark, 2008).

3.2 More frequently genes involved in human dental agenesis

3.2.1 PAX9

The gene is present on chromosome 14q13.3. It belongs to the PAX gene family, which encompasses a group of pairedbox transcription factors, acting during the beginning of embryo development. It is expressed in the mesenchyma derived from the neural crest of the mandibular and maxillary arch, contributing to the formation of the stratified squamous epithelium, palate

and teeth. The expression occurs before the first morphological manifestations of odontogenesis (Peters & Balling, 1999; Klein, et al., 2005; Faber, 2006; Ribeiro, et al., 2011).

Individuals who have mutations in coding regions of the PAX9 gene are more subject to absences from the first and second upper molars and lower second molars (Figure 2) (Kim, et al., 2006; Faber, 2006). In addition to dental absence, affected individuals tend to present microdontia of some tooth. Therefore, the mutation in this gene seems to be related to the development, positioning and morphogenesis of dentition (Gene, 2010; Suda, et al., 2011).

Current mutations reported in PAX 9

Šerý, et al., (2015) developed a study aiming to identify polymorphisms or mutations in the PAX9 and MSX1 genes. They used the capillary sequencing method in a test group of 270 individuals and in a control group of 30 individuals. Screening revealed a previously unknown g.9527G> T heterozygous mutation in the PAX9 gene in monozygotic twins with oligodontia and three more affected members of this family. The same variant was not found in healthy relatives. This mutation is located at intron 2, in the region recognized as the splice site between exon 2 and intron 2. The authors' hypothesis is that the error in pre-mRNA splicing may lead to a lower expression of pax9-encoded proteins contributing to the development of agenesis.

3.2.2 MSX1

The MSX1 gene is located on chromosome 4p16.2. This gene is a member of the homeobox family, being called msh homeobox 1. The protein encoded by this gene acts as a transcriptional repressor during embryogenesis, through interactions with the components of the nuclear transcription complex and other homoproteins. These genes play a relevant role in epithelium-mesenchyma interactions during vertebrate embryogenesis, contributing to the formation of limbs and craniofacial development, especially in dentistry. (Perry, et al., 2006; Faber, 2006; Ribeiro, et al., 2011).

Individuals with mutations in the MSX1 gene more often have the absence of the first and second upper premolars, in addition to the second lower premolars (Figure 2) (Kim, et al., 2006; Faber, 2006). Mutations in the MSX1 gene generally do not affect deciduous dentition. It was observed that, in addition to developing the agenesis of certain dental groups, mutations of this gene were also related to the occurrence of cleft lip and/or palate (Gene, 2010).

Current mutations reported in the MSX1

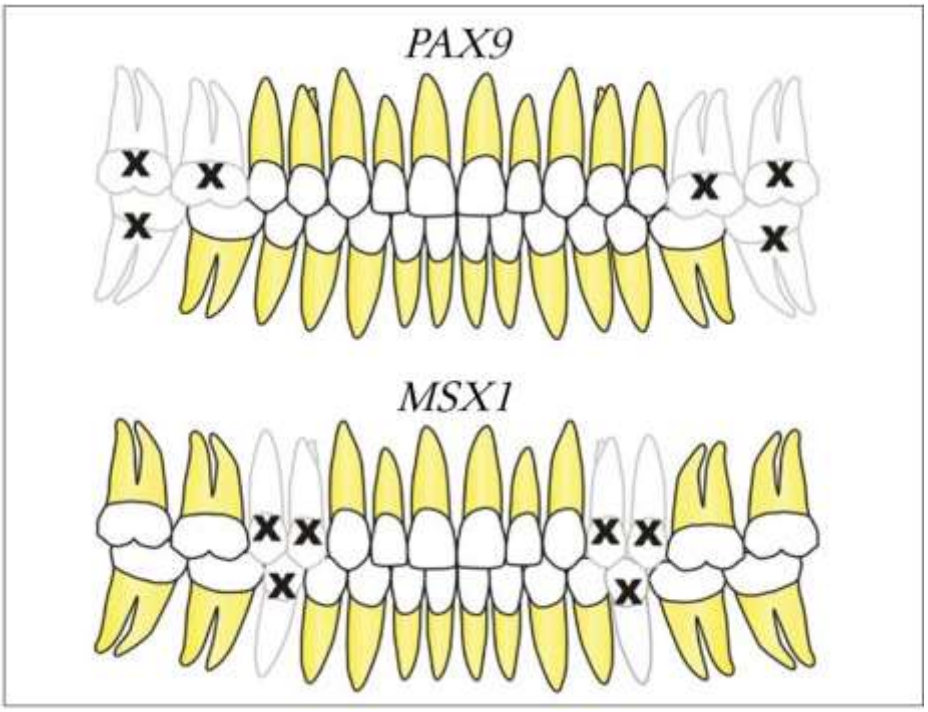
Reddy, et at., (2013) aimed to evaluate whether the msx1 671 T> C gene variant was involved in the etiology of non-syndromic dental agenesis in Raichur patients. Blood samples were collected from 50 affected individuals (test group) and 50 patients without agenesis (control group). Genomic DNA was extracted from blood samples and polymerase chain reaction (PCR) and restriction fragment polymorphism (RFLP) were performed for the digestion products that were evaluated. Their results showed a positive correlation between the MSX1671 T> C gene variant and non-syndromic dental agenesis, thus, being a good screening marker for agenesis.

Zhang, et al., (2014) conducted a meta-analysis of 4 case-control studies to explore the association between MSX1 polymorphisms and transform-β1 growth factor (TGF-β1) genes in relation to hypodontia. A group of 643 patients with agenesis (test group) and 733 healthy patients (control group) were part of the experiment. The results of the meta-analysis showed that polymorphisms in the rs1095 region of the MSX1 gene may influence the transcriptional activity of this gene, and are also associated with hypodontia. However, the association between TGF-β1 and sporadic dental agenesis has not yet been well understood.

Tatematsu, et al., (2015) demonstrated from a study in a Japanese family with non-syndromic dental agenesis that its etiology came from a new mutation by replacing nucleotides in the intronic region between exons 1 and 2 of the MSX1 gene. As the mutation was located at 9 bp before exon 2 (c.452-9G> A), the authors speculated that nucleotide substitution would generate an abnormal splice site, leading to dental agenesis.

In the study by Xin, et al., (2018) the authors demonstrated a new mutation in the MSX1 gene (frameshift, with the deletein of twenty nucleotides, c.128_147del20, p.Met43Serfsx125, in exon 1 of this gene) a fact that causes non-syndromic oligodonia in affected families. In addition, it was noted that mechanically MSX1 regulates odontogenesis through the ERK signaling pathway in dental pulp stem cells.

Figure 2 - Representation of the pattern of dental absence due to mutations in the PAX9 and MSX1 genes.



Source: Faber (2006).

3.2.3 AXIN2

The AXIN2 gene is located on chromosome 17q23-q24. It performs an important role in regulating the stability of beta-catenin in the Wnt signaling pathway (Sarkar & Sharpe, 1999; Ribeiro, et al., 2011). The Wnt family of proteins is part of a large family of signaling molecules that have a wide-ranging role during embryonic development and demonstrate regionally restricted expression in the tooth (Sarkar & Sharpe, 1999).

It is observed that individuals with an AXIN2 mutation exhibit a mixed pattern of dental agenesis (Noor, et al., 2009). Therefore, the mutations that affect the AXIN2 gene are related to the development of dental agenesis and colorectal cancer. In patients with the mutation there is an absence of 8 to 27 permanent teeth and alterations in deciduous dentition were observed in only one patient (Gene, 2010).

Current mutations reported in the AXIN 2

Liu, et al., (2015) identified a Chinese individual with non-syndromic oligodontia presenting a new missense mutation in AXIN2 (c.314T> G). This mutation results in the

substitution of Val in residue 105 by Gly (p.Val105Gly). The residue 105 is located in the highly conserved regulatory site of the G protein signaling domain (RGS) of the AXIN2 gene, this being the first study that indicates a mutation in the RGS domain of AXIN2.

Current mutations reported in the Wnt

Mostowska, et al., (2015) studied the agenesis of upper lateral incisors. In their study, they aimed to determine the contribution of nucleotide variants in wingless MMTV integration sites in members of family 10A (WNT10A), MSX1 and PAX9 for the risk of agenesis in a Polish population. Mutation screening showed four mutations by non-synonymous substitution located in the WNT10A coding sequence in 25% of the patients selected for the sample, p.Arg113Cys, p.Phe228Ile and the newly identified Arg171Leu. No potentially etiological mutation scans were identified in MSX1 and PAX9.

Zhang & Wu, (2016) conducted a case-control study involving 129 individuals with non-syndromic agenesis (test group) and 218 healthy individuals (control group). The DNA of the sample was obtained from the patients' blood and the ligase detection method was used to analyze two single nucleotide polymorphisms (SNPs) of the WNT10A gene. A significant difference between the cases of the test group and the cases of the control group was observed in the frequencies of alleles and genotypes of both SNPs (rs116998555 and rs147680216), and this study was the first case-control evidence in which the risk of hypodontia may be related to wnt10A gene polymorphism.

In the study by Salvi, et al., (2016) complete exome sequencing (WES) was performed in members of 5 families to identify new or previously described causation gene mutations. Three individuals were carriers of a known homozygosis mutation in the Wnt family member gene 10A (WNT10A) (rs121908120) and curiously, two of these individuals were siblings and also carried a heterozygous functional variant in the death domain associated with EDAR (EDARADD) (rs114632254), another gene causing agenesis, generating a combination of genetic variants. Overall this study confirmed the main role played by WNT10A in dental agenesis and the genetic heterogeneity of this anomaly. In addition, WES analysis can be an effective approach to researching non-syndromic genetic variants.

Dinckan, et al., (2017) identified in 10 Turkish families new variations. Among them, homozygotic and heterozygotic variants in LRP6, DKK1, LAMA3 and in the COL17A1 gene, in addition to variants known in WNT10A, which have already been identified as probably pathogenic for isolated dental agenesis. New variants in KREMEN1 have been identified as

probably pathogenic in 2 families with suspected syndromic dental agenesis. Variants in more than 1 gene were identified by segregating with dental agenesis in 2 families, suggesting oligogenic inheritance. Thus, the results of the study play an important role for WNT pathways genes in the etiology of dental agenesis when revealing new candidate genes.

Ruiz-Heiland, et al., (2018) studied mutations in the WNT10A gene that could possibly be present in families affected by non-syndromic oligodontics. Thus, they selected a sample of 20 patients with oligodontia in Germany between 1986 and 2013. Mutation screening was positive in 50% of the 20 patients. Thus several phenotypes have been found in individuals presenting mutations in the WNT10A gene. Among them, the stop codon p.C107*, as well as the biallelic variants of p.F228I, correlated with the most severe oligodontia phenotypes.

3.2.4 Current mutations related to PAX9, MSX1, AXIN2, EDA, WNT10A, WNT10B, BMP4, LRP6, DKK1, EDAR, EDARADD, GREM2, KREMEN1, LTBP3 and SMOC2 genes.

Paixão-Cortez, et al., (2011) evaluated a sample of 360 patients who sought orthodontic treatment, of which 33% had dental agenesis. 35 of the patients were part of the test group and 15 patients were part of the control group. Both groups had their DNAs studied in the exons 2, 3 and 4 region of the PAX9 gene and also in adjacent regions (totaling 1,476 base pairs, bp) in addition to exon 2 of the MSX1 gene (698 bp). A trio (probing and its parents) was also studied. As results, six polymorphic sites were found; Three in PAX9 exon 3 and three in MSX1 exon 2. The MSX1 allele rs1095 occurred in individuals with agenesis, and two other mutations in this gene were previously associated with dental agenesis. Homozygous for PAX9 Ala240Pro mutation was studied in a family (probing and its parents), suggesting a recessive inheritance with variable expressiveness for agenesis. They concluded that common variants located outside the PAX9 and MSX1 DNA binding domain may also be related to dental agenesis.

Wang, et al., (2011) have shown that the PAX9 gene can transactivate a Bmp4 (which is a key signaling factor for the switch from bud phase to cap phase in tooth development), which causes most dental agenesis. The authors also demonstrated that the MSX1 gene alone suppresses the transcription of this promoter Bmp4, and that, in combination with the PAX9 gene, it acts as a potentiator of Bmp4 transactivation. In this 2011 study, the authors investigated the 5 known causes of dental agenesis, where MSX1 missense mutations can disrupt the potentiation effect of PAX9, or whether they lead to deficiencies in protein stability, protein-protein interactions, nuclear translocation, and DNA binding. However, none of the

molecular mechanisms studied produced a satisfactory explanation for the pathogenic effects of MSX1 mutations, requiring a totally different approach to the investigation of this stage of odontogenesis at the molecular level.

Chhabra, et al., (2014) schematizes the signaling factors involved in each stage of dental development, where some failure in these factors may result in defects in the development pattern (Figure 3).

Figure 3 - Representation of dental development stages and signaling factors.

Stage of tooth development	Protein factors involved in signaling from epithelium	Protein factors involved in signaling from mesenchyme
Initiation Stage	Fgfs, Bmps, Shh, Pitx2 and Wnts	Pax9, Ptc, Msx1, Msx2, Bmp4, Lhx6, Lhx7, Lef1, Dlx1, Dlx2,Gli1,Gli2, Gli3 and Barx1
Bud Stage	Bmp, Fgf, Wnts, Shh, Pdgf, p21, Msx2, Lef1 and Tgf-β	Pax9, Bmp, Dlx1, Dlx2, Lhx6, Lhx7, Msx1, Lef1, Gli1,Gli2, Gli3, Barx1 and Fgfs
Cap Stage	Bmp, Fgf, Wnts, Shh, Pdgf, p21, Msx2, Lef1 and Tgf-β	Pax9, Bmp, Dlx1, Dlx2, Lhx6, Lhx7, Msx1, Lef1, Gli1,Gli2, Gli3, Barx1, Bmp4, Msx2 and Fgfs
Bell Stage		

Source: Chhabra et al, (2014).

Bock, et al., (2017) worked with 20 patients from the Department of Orthodontics of the University of Giessen in Germany from 1986 to 2013. They applied the Tooth Agenesis Code (TAC) to see which MSX1, AXIN2, EDA, or PAX9 gene would likely show mutation. Based on TAC scores and sons, genetic mutations were predicted for the MXS1 gene in 11 patients, presenting variants in 4 cases, but not being considered pathogenic (when the mutation does not alter protein function). The EDA gene appeared in 6 cases, where pathogenic mutations of exon-7 were performed in 2 patients, both were siblings with different TAC scores, which represents a new missense mutation. The evaluation of the AXIN2 gene was observed in 3 patients, which presented variants, however, none were considered pathogenic. Evaluation of the PAX9 gene was not presented with mutations in any of the patients. Thus, the study reveals that patients with non-syndromic oligodontia did not present any clinical relevance of association of TAC phenotypes for specific causation mutations.

Yu, et al., (2019) mention that an extensive analysis of databases revealed 15 genes responsible for developing non-syndromic dental agenesis, along with their signaling pathways in Wnt/β-catenin, TGF-β/BMP and Eda/Edar/NF-κB. However, genotype-phenotype correlation analysis shows that most causalist genes are also responsible for syndromic agenesis or other conditions. In a total of 198 mutations different from the 15 genes responsible for non-syndromic agenesis, 182 mutations (91.9%) are derived from seven genes (AXIN2, EDA, LRP6, MSX1, PAX9, WNT10A and WNT10B) compared to the remaining 16 mutations (8.1%) identified in the remaining eight genes (BMP4, DKK1, EDAR, EDARADD, GREM2, KREMEN1, LTBP3 and SMOC2).

Chhabra, et al., (2014) schematizes the types of genes involved in dental agenesis, the type of defect and the form of hereditary transmission (Figure 4).

Figure 4 - Genes associated with human agenesis.

Gene involved	Mutations of Genes associated with agenesis	Defect	Mode of transmission
MSX1	M61K, S105X, Q187X, R196P & S202X	Hypodontia Hypodontia Oligodontia	Autosomal dominant Autosomal recessive Autosomal dominant
PAX9	K114X, L21P, R26W, R28P, G51S, K91E, G73fsX316, V265fsX316 & R59fsX177	Molar hypodontia Oligodontia Peg shaped laterals	Autosomal dominant Autosomal dominant Autosomal dominant
AXIN2	Arg656Stop, 1994-1995insG	Incisor agenesis	Uncertain
LTBP3	Y774X	Oligodontia	Autosomal recessive
EDA	Thr338Met	Hypodontia	X linked recessive

Source: Chhabra et al, (2014).

Safari, et al., (2020) conducted a study to investigate mutations in the PAX9, MSX1 and WNT10A genes in 4 Iranian families with non-syndromic dental agenesis. From the blood cells of the affected patients, they performed DNA extractions using the Salting Out method, and the candidate genes were amplified and followed by the Sanger sequencing method. A missense variant (rs4904210) and 4 single nucleotide polymorphisms (SNPs) (rs2236007, rs12883298, rs12882923 and rs12883049) were found in the PAX9 gene. Five variants (rs149370601, rs8670, rs186861426 and rs774949973) including a missense variant (rs36059701) were detected in the MSX1 gene and no variant was found in the WNT10A gene. Thus, these genes may not play a role in non-syndromic dental agenesis among cases of Iranian patients.

4. Final Consideration

Studies have shown that mutations have occurred between intron and exon 2 of the PAX9 gene, as well as missense mutations in this gene. In addition, mutant variants were presented outside the PAX9 domain, being in its exon 3. Furthermore, the occurrence of mutations by nucleotide subitus between exons 1 and 2 of the MSX1 gene was demonstrated, additionally to mutations by frameshift deletein exon 1 of MSX1, or nonsense and missense mutations in MSX1. In the case of other genes, nucleotide substitution mutation occurred in WNT and missense mutation in EDA and its exon 7.

Epidemiological studies of dental agenesis showed that women were slightly more affected than men, and in relation to dental involvement, the upper lateral incisor followed by the second lower premolar, second upper premolar and canine, were the most absent teeth. Knowledge of the genotype-phenotype correlation between mutations and dental agenesis is important for the Dentist, as they assist in the diagnosis, referral for genetic counseling, treatment and prognosis.

Future studies in dental genetics are necessary, because its may bring to light the treatment or control of genes that cause dental agenesis, using the advantage of tissue development, coming from dental stem cells.

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Percentage of contribution of each author in the manuscript

Iago Demétrio da Silva – 60%

Caio Cesar Santos Patron Luiz – 5%

Andressa Bolognesi Bachesk– 30%

Brenda da Silva Balassa– 5%