Aetiology of Oral Diseases and their Association with Systemic Diseases

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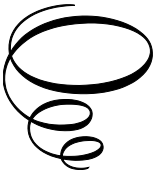

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CHAPTER 1

GENETIC AND EPIGENETIC INFLUENCE ON DENTAL AGENESIS

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List of Abbreviations

AXIN2: Axis inhibition protein 2
BMP4: Bone morphogenetic protein 4
EDA: Ectodysplasin-A
EDAR: Ectodysplasin-A receptor
EDARADD: EDAR associated death domain
GJB6: Gap Junction Protein β-6
IRF6: Interferon regulatory factor 6
LEF 1: Lymphoid enhancer-binding factor 1
MSX1: Msh homeobox 1
NEMO: NF-kB essential modulator
OMIM: Online Mendelian Inheritance in Man
***PAX9*:** Paired box gene 9
TBP: TATA box-binding protein
TNF: Tumour necrosis factor
TNS: Tooth and nail syndrome
WNT10A: Wingless integration 10A

Introduction

The normal dentition consists of 20 temporary teeth and 32 permanent teeth, but these numbers can vary in cases of supernumerary teeth and of dental agenesis. Agenesis is one of the most common dental anomalies found by dentists in their daily clinical practice (De Coster et al., 2009). Of notice is that agenesis always excludes the lack of the third molars.

Besides agenesis, other terms can be used to indicate the lack of development of dental follicles, such as anodontia, which is the total absence of teeth, oligodontia, which is a partial anodontia with the absence of six or more teeth, and hypodontia, the absence of less than 6 teeth (Vastardis, 2000).

The normal development of teeth results from a series of interactions that involve numerous genetic signalling pathways that are epigenetically influenced by extracellular factors (Townsend et al., 2012). More than 300 genes involved in the development of teeth have been identified (Thesleff, 2006).

The lack of teeth can be an isolated phenotype, as a non-syndromic symptom or occur as part of a syndrome. Isolated cases of missing teeth can be familiar or sporadic in nature. Familial dental agenesis can have several types of transmission: autosomal dominant, autosomal recessive or X-linked (Thesleff, 2000).

Agenesis of 1 or 2 teeth is frequent (80% of cases) and its consequences are quite different, depending on the type of tooth involved. On the other hand, multiple dental agenesis is a rare condition that leads to functional and/or aesthetic prejudice, being a public health issue that requires attention (Bergendal et al., 2009).

The goal of this chapter is to review the genetic and epigenetic influence on dental agenesis. For a dentist, it is important to understand the aetiology of failure in tooth development and to use that knowledge to improve clinical diagnosis and provide the most appropriate treatment to patients.

1.1. Dental agenesis

1.1.1. Frequency and risk factors

Dental agenesis is one of the most common dental anomalies present in humans, with an incidence of 1.6 to 9.6%, and can affect the maxilla and

mandible and be symmetrical or not (Poulet et al., 2014).

Agenesis of wisdom teeth has a higher incidence, affecting 20% of the population. In addition, the agenesis of temporary teeth is rarer than that of permanent teeth (0.1 and 0.9% respectively). The oligodontia rate is lower, having an estimated frequency between 0.08 and 0.16% (De Coster et al., 2009).

The prevalence of dental agenesis varies according to the type of tooth. The most affected teeth are the second lower premolars (corresponding to 34% of the agenesis), the upper lateral incisors (32.7%) and the second upper premolars (12.8%) (Nieminen, 2009). Dental agenesis rarely affects the first and second maxillary molars, the first mandibular molars, the maxillary central incisors, and the canines. No significant difference in agenesis incidence between the right and left sides for a particular tooth in both arches was observed (Al Jawad et al., 2015).

The agenesis can occur isolated, non-syndromic, or associated with syndromes (Klein et al., 2013). When it occurs in a non-syndromic manner, genetics is pointed as its main aetiologic factor.

In fact, congenitally missing teeth are those that fail to erupt in the oral cavity and remain invisible on a radiograph, which implies that they are caused by disturbances during the early stages of tooth development (Keerthana et al., 2020).

Some studies establish a correlation between the congenital absence of deciduous and permanent dentitions (Järvinen & Lehtinen, 1981; Fekonja, 2005; Jesudasan et al., 2015).

Gender and ethnicity are two risk factors for dental agenesis. In fact, this condition is more frequent in women than in men (Larmour et al., 2005; Al Jawad et al., 2015) with a 1.37 times higher prevalence in women than in men (Polder et al., 2004). The frequency of dental agenesis, as well as the type of missing teeth, varies with the population (Al Jawad et al., 2015). As an example, lower mandibular second premolars and maxillary lateral incisors were more often recorded as absent in the Caucasian population, while in Asian studies the mandibular incisors were the most frequently absent (Larmour et al., 2005; Keerthana et al., 2020).

Recently, a study found sex-associated differences in non-syndromic tooth agenesis. The prevalence of single tooth agenesis was higher in males, while agenesis of two or more teeth was higher in females. Moreover, this study

demonstrated different patterns of lateral incisor agenesis between males and females (Kanchanasevee et al., 2023).

1.1.2. Aetiology

Several different theories explaining the aetiology of dental agenesis have been published.

Phylogenetic aetiology

Is dental agenesis a consequence of evolution? In fact, it is often mentioned that soon, the dental formula will consist of 28 teeth, with wisdom teeth tending to disappear. However, there are opposing opinions in the literature, and one is that dental agenesis is a characteristic of the phylogenetic evolution of the human species. Thus, a reduction in morphology and dental formula would accompany a reduction in the size of the jaws (Brace, 1964). Two theories have been described to explain the aetiology of dental agenesis.

Theory of reduction of the dental system

Many authors claim that our teeth are less useful nowadays. Teeth no longer serve as weapons or tools since the diet is smoother. Therefore, the selection pressure to maintain a stable dental system is reduced, resulting in a decrease in the size and number of teeth (Poulet et al., 2014). These authors base their theory on the fact that human premolars and molars are approximately 50% less bulky than those of Australopithecus. Another argument supporting this theory is that agenesis, particularly of wisdom teeth, would represent an adaptive advantage. In the difficult conditions in which our ancestors lived, a tooth eruption accident could cause a serious infection and lead to death. Therefore, natural selection would have favoured individuals with dental agenesis (Calcagno & Gibson, 1988). Most currently, there is a theory that evolutionary change is working to reduce the human dentition by the loss of an incisor, premolar, and molar in each quadrant (Al-Ani et al., 2017). As humans evolve, the size of the jaws and the number of teeth appear to be decreasing (Vastardis, 2000).

Theory of bone base decrease

To explain this theory that states that the size of the jaw decreased during evolution, some authors mention that softer types of food are a possible cause. In fact, this type of diet puts less pressure on the masticatory muscles and therefore reduces the stimulation of mandibular growth. In addition,

human ancestors had an occlusion that did not include overbite or overjet, a labidodontia. The evolution towards an overjet and overbite occlusion, a psalidodontia, is allowed thanks to a removal of the lower alveolar tooth block that reduces the distal space of the wisdom tooth. All of this leads to a situation in which the bone bases become too small for the correct morphogenesis of some teeth, causing more and more dental agenesis (Sofaer, 1973).

On the other hand, other researchers claim that there is no change in the size of the jaw during evolution and no proven connection between the size of the bone bases and the prevalence of dental agenesis (Chapelle, 1990).

Genetic aetiology

In 1996, a team of researchers discovered a mutation in the *MSX1* gene in individuals of a family who did not have all wisdom teeth and second premolars (Vastardis et al., 1996). This work highlighted genetic mutations that affect the dental development of people with dental agenesis. Although this genetic aetiology is the main subject of this work, it should be noted that, for most of the mild dental agenesis (1 or 2 teeth), no aetiology was found. In fact, most human characteristics and anomalies are determined by several factors (Carels, 2006) that invalidate the dogma of all genetics, that is, “a gene, a disease”.

The expression of a gene can be modulated according to the genetic network or the environment in which it is expressed. Each risk factor, whether genetic, environmental, or epigenetic (discussed below), alone is not enough to cause the anomaly, but it can contribute to the predisposition to develop this phenotype. Therefore, the interaction of several predisposing factors is more likely to cause dental agenesis (De Coster et al., 2008; Shimizu & Maeda, 2009). The aetiology of this condition is, therefore, multifactorial and the set of mechanisms that cause its development has yet to be discovered. Therefore, it is more appropriate to talk about influence instead of aetiology when linking the words genetics and dental agenesis.

1.2. Genetic influence on dental agenesis

1.2.1. Normal development of teeth (odontogenesis)

Odontogenesis includes two successive dentitions: the temporary and the following permanent dentition. It starts between the sixth and seventh week of embryonic development, concomitantly with the establishment of

craniofacial structures. Temporary teeth develop as epithelial sketches of the embryonic ectoderm that will cover the fronto-nasal, maxillary and mandibular processes. The teeth are supposed to be formed successively from a single dental blade (Klein et al., 2013; Dosedělová et al., 2015).

Permanent teeth are formed from the germ epithelium in temporary teeth and bud formation occurs at an early stage of temporary tooth development. Tooth development occurs over a long period of time: the formation of the dental lamina is the first step and the end of the root construction of the permanent third molar (between 18 and 25 years old) is the last. The correct dental development or its failure depends on a series of interactions involving numerous signalling pathways that are epigenetically influenced by extracellular factors (Townsend et al., 2012).

1.2.2. Genes influencing dental agenesis

Dental agenesis can appear as isolated characteristic, in non-syndromic forms or in association with genetic diseases in the context of a recognized clinical syndrome. Non-syndromic is by far the most common form of congenital tooth absence and can involve different numbers of teeth. It is more common in permanent dentition, being rare in primary dentition (Burzynski & Escobar, 1983). Non-syndromic hypodontia may occur sporadically or may have family aggregation, it may be isolated or associated with other syndromic or non-syndromic dental abnormalities, being its clinical phenotype very varied (Swinnen et al., 2008; Williams & Letra, 2018).

Isolated cases may be familiar or sporadic and their mode of transmission is autosomal dominant, autosomal recessive or have an X-linked transmission (Dure-Molla & Berdal, 2008). Different sub-phenotypes of dental agenesis could probably be caused by different genes since there is a great variation in the expressiveness of genes. Several of them have been identified for their implications on dental morphogenesis and their regulatory roles throughout the development of the dental organ (initiation, morphogenesis, differentiation, determination of the location, size and shape of the tooth) (Shimizu & Maeda, 2009).

Nevertheless, still, nowadays, there is no consensus on whether hypodontia is a result of a polygenetic or single gene defect, although the former appears to be largely supported in the literature (Vastardis, 2000; Larmour et al., 2005).

1.2.3. Non-syndromic dental agenesis

Studies reveal the involvement of several main genes in isolated dental agenesis, particularly *PAX9*, *MSX1*, *AXIN2*, *EDA* and *WNT10A*.

Dental agenesis linked to the *PAX9* gene

The *PAX9* gene is a divergent homeobox gene and belongs to a family of transcription factors, including nine genes that play a role in establishing the embryonic pattern (Shimizu & Maeda, 2009).

In dental development, this gene is expressed early before any other morphogenetic signal, which certainly gives it an inducing role in the *MSX1*, *BMP4* and *LEF1* genes, and, therefore, an important role in the condensation of the mesenchyme in the budding stage that allows the passage to the canopy stage. In fact, studies in *PAX9* deficient homozygous mice have shown a halt in dental development at an early stage (Dure-Molla & Berdal, 2008; Shimizu & Maeda, 2009).

Isolated hypodontia and oligodontia are associated with mutations in this gene, being transmitted with an autosomal dominant pattern. In some families, these mutations cause oligodontia of permanent molars (Nieminen et al., 2001; Mostowska et al., 2006). Mutations in the *PAX9* gene lead to the absence of most permanent molars. Dental agenesis of deciduous teeth has only been reported in rare cases (Nieminen et al., 2001).

Eleven distinct disease-causing mutations in the *PAX9* gene have been identified, including missense and frameshift mutations (Abu-Hussein et al., 2015). These mutations include seven missense, six substitutions and a premature termination mutation (Peters & Balling, 1999). Only five of the mentioned substitutions lead to a change in the protein amino acid sequence (Peters & Balling, 1999). As an example, a patient with oligodontia had a missense mutation with the replacement of an arginine by a tryptophan in the paired domain of the *PAX9* gene and showed dramatically reduced DNA-binding activity (Ogawa et al., 2005). As these mutations occur in the paired DNA-binding domain of the *PAX9* gene, they result in disturbed regulation of tooth formation.

Of the three frameshift mutations, two are caused by the insertion of a single nucleotide and one by the exclusion of eight nucleotides and the insertion of 288 foreign nucleotides (Peters & Balling, 1999).

A genotype-phenotype correlation is observed at the level of *PAX9* mutations: missense mutations give rise to a less pronounced phenotype than nonsense mutations or those that involve a change in the reading frame (Bailleul-Forestier et al., 2008).

Dental agenesis linked to the *MSX1* gene

MSX1 is a homeobox gene located on chromosome 4 whose main function is to interact with the TATA box-binding protein (TBP) and some transcription factors to increase the rate of the transcription process (Vastardis, 2000).

The coded protein plays a mediating role between the epithelium and the mesenchyme during dental and craniofacial development (Shimizu & Maeda, 2009) and helps to determine the position and shape of the teeth. It enters the process from the early stages of ecto-mesenchymal interactions, which explains why *MSX1* gene mutations can prevent the development of dental germs and lead to dental agenesis (Dure-Molla & Berdal, 2008).

To date, many mutations have been described, being transmitted in an autosomal dominant manner. These changes cause agenesis of the posterior teeth and may or may not be associated with syndromes (Kapadia et al., 2007; Dure-Molla & Berdal, 2008; Liang et al., 2016).

For example, a mutation in this gene (substitution of arginine for proline in the homeodomain of the protein) is associated with the absence of second premolars and third molars (Vastardis et al., 1996) and a meaningless mutation will result in a TNS (tooth and nail syndrome) also called Witkop syndrome (Jumlongras et al., 2001). The main characteristics of this syndrome, which is an ectodermal dysplasia, are missing or tapered teeth in both dentitions, absence of fingernails and toenails at birth, slow growth, and thin and brittle hair (Devadas et al., 2005).

Relationship between the *PAX9* and *MSX1* genes

The *MSX1* and *PAX9* genes are involved in the genetic networks that regulate odontogenesis and interact at the gene and protein level. The PAX9 protein forms an interaction with MSX1, leading to the formation of a heterodimeric protein complex. This complex helps the PAX9 protein in the simultaneous activation of both *MSX1* and mesenchymal *BMP4* gene expression during tooth development. This interaction ultimately drives morphogenesis of the dental organ, in particular the transition from bud to cap stage and enamel knot induction (Ogawa et al., 2005). In addition to

Bmp4 downregulation, *PAX9* mutations can result in a selective reduction in PAX9 protein binding to sites that regulate *MSX1* gene expression levels. Mutations in either *PAX9* or *MSX1* genes can also lead to defective protein-protein interactions, both at the gene and protein levels that disrupt normal downstream functions important for dental morphogenesis (Ogawa et al., 2005).

Studies have shown that mutations in these two genes are also associated with reduced root dimensions (Jumlongras et al., 2001; Jumlongras et al., 2004), as well as tooth size (Kirac et al., 2016). No significant association between mutations and type of congenitally missing teeth was observed (Kirac et al., 2016).

Dental agenesis linked to the *AXIN2* gene

After excluding *MSX1* and *PAX9* gene mutations, a genotype study of a Finnish family with severe but variable dental agenesis allowed the identification of a nonsense mutation in the *AXIN2* gene located on chromosome 17, causing loss of function (Lammi et al., 2004).

The *AXIN2* gene is induced by Wnt signalling, suggesting that its expression serves as a negative feedback regulator of Wnt signalling (Jho et al., 2002; Leung et al., 2002). The Wnt family of proteins is part of a large family of signalling molecules that play a wide role during embryonic development and demonstrate regionally restricted expression in the tooth (Sarkar & Sharpe, 1999). Overactivation of this pathway can lead to the formation of supernumerary teeth and a loss of activation, in the case of the *AXIN2* gene mutation, to dental agenesis (Andl et al., 2002).

This is not the only possible change resulting from a defect in this gene. The predisposition to cancer is another possible change that depends on the intracellular level of β-catenin (Giles et al., 2003). One of the objectives of Wnt signals is to regulate the stability of β-catenin. When cells receive a Wnt signal, β-catenin is stabilized and binds to transcription factors of the TCF family that regulate the expression of Wnt target genes. In the absence of the Wnt signal, β-catenin will be phosphorylated and subsequently degraded by the action of a multiprotein complex (Seidensticker & Behrens, 2000).

Hereditary colorectal cancer is particularly underlined by a study of a family affected by several cases of oligodontia, presenting colorectal neoplasms when members without dental agenesis did not present them (Lammi et al., 2004). Olfactory neuroblastoma and gastric adenoma might also be

associated with the phenotype of pathogenic germline *AXIN2* variants (Macklin-Mantia et al., 2020).

Dental agenesis linked to the *EDA* gene

Isolated dental agenesis has also been found in individuals carrying mutations in the *EDA* gene present on the X chromosome. In 2006, Tao et al. (2006) found a point mutation in the *EDA* gene in a Mongolian family with hypodontia as the only feature present in male individuals (females are carriers). In 2008, cases of non-syndromic hypodontia in two Chinese families with two nonsense mutations in this gene were described (Li et al., 2008).

EDA, which has been identified as the mutated gene in X-linked anhidrotic forms of ectodermal dysplasia, encodes the TNF-like signalling molecule, which plays an important role in the development of the epithelium **(**Kere et al., 1996).

Song et al. (2009) described three new mutations (p.Ala259Glu, p.Arg289Cys, and p.Arg334His) in four individuals of 15 unrelated males with non-syndromic oligodontia. Another study by Khabour et al. (2010) identified a missense mutation (replacement of arginine with cysteine) causing this dysplasia that is characterized by speech problems, reduced sweating (anhidrosis), heat intolerance and absence of teeth.

A meta-analysis of Fournier et al. (2018) observed that only 30% of patients having mutations in the *EDA* gene, had third molar agenesis.

Dental agenesis linked to the *WNT10A* gene

Although the first mutations in the *WNT10A* gene have been identified in patients with recessive odonto-onycho-dermal dysplasia and in the Schöpf-Schulz-Passarge syndrome (Bohring et al., 2009; Castori et al., 2011), in 2011, a first case of isolated autosomal dominant hypodontia has been described (Kantaputra & Sripathomsawat, 2011).

Van Den Boogaard et al. (2012) looked for mutations in the *WNT10A* gene in 58 patients with dental agenesis. This study observed that 19 of 34 patients with non-syndromic oligodontia carried mutations in the *WNT10A* gene. Of these cases, 12 had biallelic mutations (9 had two missense mutations, 3 were heterozygotes for a missense mutation and a nonsense mutation). Seventeen of these patients had at least one associated sign of ectodermal dysplasia. The patient with the highest number of dental

agenesis was the carrier of a nonsense (c.321C> A) mutation (p.Cys107Ter) in the homozygous state in the *WNT10A* gene.

Several studies have concluded that monoallelic or biallelic mutations in the *WNT10A* gene are associated with a wide range of pathologies leading to phenotypes ranging from isolated dental agenesis of variable number to well-recognizable ectodermal dysplasia (Arte et al., 2013; Song et al., 2013).

Zeng et al. (2021) studied the functional effects of *WNT10A* gene mutations that were associated with agenesis. These researchers observed that most of these variants potentially destabilized or prevented the formation of the disulphide bond essential for correct protein function. This would lead to decreased Wnt signalling.

1.2.4. Syndromic dental agenesis

The genes that regulate dental development are also involved in the development of other tissues and, therefore, mutations in these genes can affect areas other than tooth structures. Online Mendelian Inheritance in Man (OMIM) lists more than 60 different syndromes in which associations are found between dental problems and other organs.

It is important to know the anomalies in the different body structures to guide the search for a syndrome and, possibly, refer the patient to more in-depth examinations. Only some of the most well-known syndromic dental agenesis will be discussed here.

Ectodermal dysplasia

In 1994, Freire-Maia and Pinheiro were the first to classify 160 distinct hereditary ectodermal dysplasia, genetically and clinically, a heterogeneous group of diseases characterized by dystrophies in the development of ectodermal structures. These researchers established that, to belong to this category of disease, at least two of the four following structures must be affected: nails, hair, sweat glands and dentition. In fact, the same developmental mechanism includes teeth and other organs of ectodermal origin, such as the mammary glands (Mikkola & Millar, 2006).

According to the type of hereditary transmission, this disorder can be classified in hypohidrotic ectodermal dysplasia and hidrotic ectodermal dysplasia.

Hypohidrotic ectodermal dysplasia is associated with the X chromosome and can assume a recessive or a dominant form. The recessive type is also called Christ-Siemens-Touraine syndrome and represents 60% of ectodermal dysplasia. It is the result of a mutation of the *EDA1* gene located in Xq12-q13.1, which encodes a transmembrane protein, expressed in the sweat and sebaceous glands, keratinocytes, and dander. The *EDAR* and *EDARADD* genes may also be involved. However, these 3 genes still do not explain all known cases (Allali et al., 2007). Women are generally more affected than men, with a ratio of 17.3/100,000 individuals to 1/100,000. The main features include hypotrichosis (thin and rare hair), hypohidrosis (compromised sweat glands) with pigmentation and dryness of the skin around the eyes, as well as saddle nose, prominent forehead, protruding lips, and hoarse voice. Dental anomalies can be hypodontia and malformations, such as tapered and canine incisors, reduced mesio-distal dimension, and appearance of wedge-shaped roots (Barberia et al., 2006). The most well-known dominant type associated with the X chromosome is Incontinentia pigmenti, that results from a mutation in the *NEMO* gene (Xq28) and has a prevalence of 1-9/1,000,000. Anomalies can be present in nails, hair, or skin, but can also include intellectual deficit, atrophy, or cerebral oedema, in addition to microcephaly. The dental consequences can be a delayed eruption of permanent teeth, severe hypodontia (6 or more teeth), taurodontism, microdontia and macrodontia (Aquino et al., 2012). Sawaya de Castro et al. (2021) reported a case of a patient with hypohidrotic ectodermal dysplasia having complete anodontia.

Hidrotic ectodermal dysplasia, also called Clouston's disease, results from a mutation in the Gap Junction Protein β-6 (*GJB6*) gene, which codes for connexin 30. This type of dysplasia has an autosomal dominant transmission, since the mentioned gene is present in chromosome 13 (13q12) (Allali et al., 2007; Shi et al., 2019). In addition to the classic damage to nails, hair and skin, some patients also develop hyperkeratosis and hyperpigmentation in the joints and bony protuberances. Teeth are generally unaffected, and sweating is normal (Allali et al., 2007).

In addition to ectodermal dysplasia, orofacial clefts are also conditions associated with hypodontia, 70% of which are isolated anomalies and 30% are part of 300 syndromes (Phan et al., 2016; Huda et al., 2021).

Van Der Woude syndrome

Van Der Woude syndrome has an incidence of 1/60,000 births, with a 70% prevalence of hypodontia having been reported. Mutations in the *IRF6* gene

(1q32-q41) have been identified in 50 not related families to Van Der Woude syndrome (Park et al., 2007). This gene encodes a transcription factor expressed in many embryonic craniofacial structures, including the medial edges of the fusing palatal processes and the dental buds (Kondo et al., 2002; Gagliardi & Lopes Cardoso, 2018).

This syndrome is one of the most common autosomal dominant human disorders associated with cleft lip and/or palate (1%), but also pitting of the lower lip mucosa and hypodontia (Pegelow et al., 2008; Gagliardi & Lopes Cardoso, 2018).

Pierre Robin syndrome

Pierre Robin syndrome has an incidence of 1/10,000 births and a prevalence of 50% of hypodontia, most often affecting the mandibular teeth. This syndrome has been described as an autosomal recessive human disorder associate with cleft palate, micrognathia and glossoptosis (Park et al., 2007).

It is important to note that dental agenesis may be present in cases of isolated labio-palatal clefts, with an increase in the number of missing teeth being observed with the severity of the cleft (Karsten et al., 2005). This hypodontia is the least present in the case of cleft lip (10%) and the mostly present in case of bilateral cleft lip-palate (60%). The lateral maxillary incisor is the tooth most frequently affected for clefts of this non-syndromic origin (Ribeiro et al., 2003).

Although several genes may be involved, according with the systematic review of Varadarajan et al. (2021), the most common gene associated with Pierre Robin syndrome is the *SOX9* gene. This gene codes for a transcription factor that regulates chondrocyte fate, essential for the development of the skeleton and cartilage (Perrine et al., 2020).

Down syndrome

Another relatively frequent syndrome is Down syndrome, also called Trisomy 21, characterized by the total or partial presence of a third copy of chromosome 21. Besides the well-known intellectual deficit, other morphological anomalies, such as poorly located palpebral slits, a round face or even a flat nape may appear.

Dental changes may also be present, as observed in a Danish population showing dental agenesis in 69.8% of women and 90.7% of men carrying the Down syndrome (Russell & Kjaer, 1995). These individuals may also

present dental anomalies such as rash, position, structures, as well as microdontia or taurodontism. Functional disorders and pathologies of the mucous membranes and periodontium can also be expected (Sixou, 2008; van der Linden et al., 2017).

1.3. Epigenetic influence on dental agenesis

Studies in homozygous twins were used to highlight how individuals with the same DNA could present a different dental phenotype. Martin et al. (1997) described several environmental influences to explain these differences, such as different nutrition or teratogenic transplacental effects. Another study led by Boraas et al. (1988) was able to assess the genetic factor by eliminating the environmental factor after separating the twins shortly after birth and raising them differently. This study was only able to attribute some observed similarities to the genes. But genetic and environmental factors are not the only ones responsible for the phenotype. Several studies have also highlighted a phenomenon called epigenetic.

Epigenetic is a term that, in its broad sense, refers to changes in gene expression without changes in the nucleotide sequence, that is, epigenetic factors are responsible for the way in which genes will be expressed (Townsend et al., 2005). This definition includes interactions between cells at the tissue level that occur during dental development, in addition to others that directly affect DNA. It is important to note that nowadays, molecular geneticists often use this term with a focus on specific examples of epigenetic events, such as DNA methylation and acetylation (Townsend et al., 2005).

Therefore, epigenetics includes events that occur at the level of DNA in cells, as well as events that occur during development influenced by the spatial and temporal arrangements of cells (Townsend et al., 2012).

Townsend et al. (2009) showed that, excluding the environmental factor and if homozygous twins have similar genetics, these individuals could show different expressions of missing or reduced incisors. These twins have a genetic predisposition close to the threshold of agenesis, however, small variations in local epigenetic events during odontogenesis can lead to different phenotypic expressions of lateral incisors and premolars.

Mathematical models have also been developed to demonstrate how significant morphological changes can be produced by small epigenetic events (Salazar-Ciudad & Jernvall, 2002). Currently, it is known that

epigenetic regulation of genetic activity induced by the environment occurs by one of two methods, affecting the chromatin condensation (by DNA methylation and/or histone modification) or directly preventing protein synthesis (non-coding RNA) (Barros & Offenbacher, 2009).

Lin et al. (2018) presented a review of the epigenetic factors, such as DNA methylation and histone modification, that may interfere with tooth development. These factors affect cell proliferation, differentiation and apoptosis, roles that are crucial during odontogenesis, regulating the number, size and shape of teeth (Li et al., 2018). This knowledge will help in the development of tooth regeneration, probably making it possible in the future (Lin et al., 2018).

1.4. Treatment of dental agenesis

Dental agenesis is the most common dental anomaly. For this reason, it is necessary to know how to make the best possible diagnosis and provide the most appropriate treatment.

Non-eruption of the permanent tooth more than one year later than expected, or even after six months following the emergence of the contralateral tooth, warrants a high degree of suspicion (Sridhar et al., 2022).

A complete anamnesis, an exobucal and endobucal examination, a complete radiological examination, including, if possible due to economic reasons, a cone beam radiography, as well as other data, such as photos or orthodontic casts, will allow the choice of the appropriate treatment and will lead the patient to genetic tests, especially if this dental agenesis is just a symptom of a more significant syndrome, as described above (Fan, 2020; Drancourt et al., 2022).

In fact, radiographic evaluation by orthopantomography enables the diagnosis of tooth agenesis and must be always carefully analysed in addition to family historical anamnesis regarding absence of teeth.

Of clinical relevance, is the earlier recognition of dental agenesis as it, naturally, is an important issue when developing long-term and comprehensive interdisciplinary treatment to restore aesthetic and function.

The prevalence of agenesis has a direct consequence for the costs of tooth replacement. Those with more missing teeth require more replacement, which means higher costs (Hobkirk et al., 2011). On the assumption that every missing tooth needs replacement, it is clear that ‘rare’ patients with

multiple agenesis are far more expensive than ‘common’ patients with only one missing tooth. Many other factors, besides the economic one, are involved in the complex process of treatment planning. Not only the number but also the distribution of the missing teeth are important variables in the estimation of treatment need (Polder et al., 2004).

Dental agenesis, specially affecting anterior teeth is sought by parents or relatives of children/teenagers as social awareness of dental disease. This is of great aesthetic concern as young active people can experience social/work limitations in their daily life. A few studies concluded that hypodontia can have a negative impact on quality of life (Al-Ani et al., 2017).

Functionally, individuals with hypodontia tend to have deeper bites and spaces. Missing posterior teeth may not only result in further deepening of the bite, but the condition may also lead to nonworking interferences, poor gingival contours, and overeruption of the opposing teeth. Moreover, patients with hypodontia experience more difficulty in chewing due to a smaller occlusal region. In a cross-sectional study, carried out in 2010, it was found that hypodontia patients have more chewing difficulties if the deciduous teeth associated with the missing permanent teeth had been exfoliated (Laing et al., 2010). Of notice, recent research pointed out that dental agenesis has no effect on the total mandibular length and on the mandibular body length, but it may result in a shortening of the mandibular arch length and more retrusive position of the mandible (Jurek et al., 2021).

Treatment plans, which tend to be complex, must be faced by the patient and his family as by the multidisciplinary professionals as long-term, i.e., several years to achieve results as well as close maintenance post-treatment (Hobkirk et al., 2011). Of special relevance is the accurate assessment of the complaints of the patient and his parents (Al-Ani et al., 2017).

The treatment can be orthodontic, with the objective of closing open spaces, removable or fixed prosthetics with the design of a sealed bridge, but also to implant a less invasive solution than the bridge. Other possible solutions may be surgery, using a technique of auto-transplantation, conservative odontology or, in stable cases, just abstention (De Santis et al., 2019).

All these treatments are important considering the consequences that can arise from dental agenesis, at the functional level, as well as chewing, phonation, swallowing and ventilation disorders. Skeletal growth in the

transverse, sagittal and vertical directions can also be affected (De Santis et al., 2019).

As mentioned before, at the aesthetic and psychological level, the lack of the first can lead to a problem for the other, with loss of self-esteem or behavioural and communication disorders. Therefore, a multidisciplinary collaboration, including a psychologist, in addition to an orthodontist or geneticist, can be useful. In the end, each case is unique, from the aetiology of dental agenesis and its impact on the patient to possible treatments. It should be noted that other treatments are likely to be considered in the future, such as the storage of dental stem cells for autologous use (Thonat et al., 2011).

General Conclusions

In addition to environmental causes, genetic and epigenetic influences on dental agenesis have been identified, allowing us to conclude that this condition results from a complex interaction between these three factors. Each factor alone is not enough to cause the anomaly, but it can contribute to a predisposition. The accumulation of these predispositions would then be responsible for the appearance of dental agenesis.

The genetic influences on dental agenesis can be subdivided into non-syndromic, with the involvement of several independent defective genes, such as *MSX1* or *PAX9,* and syndromic, when agenesis is part of a disease with different phenotypic changes, such as typical ectodermal dysplasia. The type of phenotype and its severity depend on the affected gene, the type and location of the mutations. The epigenetic influence is responsible for the differential expression of our genetic material through the temporal and spatial fields. Therefore, it is essential to understand the genetic and epigenetic factors underlying dental agenesis to explain the susceptibility and origin of the malformation and to develop the treatment adapted to each patient.

In addition to a wide variety of genes, environmental and epigenetic factors involved in dental agenesis that have been discovered in recent years, it is still necessary to conduct research to understand all possible aetiologies and interactions between the etiological factors. Although there is no direct practical application of genetics or epigenetics to the dental clinician, the dentist should be aware of this due to its contribution to dental changes in the individual, in the future.

The treatment plan should be prepared according with the patient's complaints, dental development and age. Closing spaces by eruption guidance is a valid option in cases of congenital absence of maxillary incisor teeth. This method makes spontaneous closure of gaps belonging to congenitally missing teeth possible by erupting maxillary canines in place of maxillary lateral incisors and achieving a class II occlusion. Enamel reduction must be applied in maxillary 1st and 2nd deciduous molars on mesial and distal sides for this purpose. In case of congenital maxillary or mandibular 2nd premolars absence, then 1st deciduous molars should be reduced from distal side and 2nd deciduous molars should be reduced from mesial and distal sides, if it is aimed to close the spaces of missing teeth with eruption guidance. Alternatively, eruption guidance can be conducted with early removal of maxillary and mandibular 1st and 2nd deciduous molars (Ülgen, 2005).

Orthodontic mechanics intend to create a roominess (it means that, in some cases, it might be necessary to open or to close spaces in the jaw(s)) to apply the tooth rehabilitation needed either with removable prothesis, or resin bonded fixed partial dentures or conventional fixed partial dentures, or dentures supported by implants or build-up restorations of microdontic teeth (Bilgin & Kaya, 2018). Overjet, overbite and posterior occlusion must be evaluated carefully while deciding to open or close the spaces of congenitally missing teeth in alveolar bone. Spaces had better open if there is a favourable molar relationship, a decent overjet or a deep bite. Additionally, when a tooth is planned to substitute another tooth, then parameters like tooth size, shape, colour and eruption level have to be evaluated teeth (Hobkirk et al., 2011).

Another alternative treatment option is the transplantation of maxillary third molars to edentulous areas or premolar extraction in other quarters of jaws that shows crowding can be applied when dealing with congenital absence of second premolars (Bilgin & Kaya, 2018). It is ideal to have an open tooth apex that allows pulpal revascularization, and three quarters of root length should be developed. Root canal treatment may not be necessary in a tooth with an open apex, because revascularization may occur spontaneously. On the other hand, root canal treatment should be performed in an appropriate time when a tooth with a closed apex is transplanted. Orthodontic force should not be applied for the first 3-6 months after autotransplantation. Additionally, when applied, the amount and duration of force should be minimized. Orthodontic treatment can be initiated after the radiographic verification of lamina dura (Hobkirk et al., 2011).

Comprehensive treatment planning involving correction of skeletal discrepancies, elimination of deep bite, aligning and levelling of teeth and space arrangements is necessary for patients with hypodontia who require multidisciplinary treatment approaches. Future innovations in this field may bring up treatment of the genes causing tooth agenesis with gene therapies and development of tooth tissues from dental stem cells (Bilgin & Kaya, 2018).

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