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Chapter

Failure of Tooth Development: Prevalence, Genetic Causes and Clinical Features

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Abstract

In dental practice may be encountered a wide variability in the clinical dental phenotype of tooth number. Failure of tooth development at the bud stage causes tooth agenesis and reduction in tooth number in the dental arch which involves various complications. Tooth agenesis is one of the most common developmental anomalies of human permanent dentition and tends to run in families, may aggregate within families, suggesting a genetic cause. Tooth agenesis can occur in association with a variety of craniofacial syndromes, but it is also found as an isolated trait (familial or sporadic). Other tooth anomalies, such as tooth shape and size, delayed eruption of teeth, malposition, short roots or taurodontism, have been noted in association with non-syndromic tooth agenesis as well. Both the deciduous and permanent dentitions may be affected by missing teeth. Variations in the number of missing teeth can be determined by a mutation in one gene, by mutations in multiple genes, induced by local or systemically acting environmental factor, caused by a combination of gene mutations and environmental factors acting together, or by damage to chromosomes. As the number of missing teeth increases, so does the severity of clinical consequences and the impact on oral health–related quality of life.

Keywords: abnormalities in the tooth number, tooth agenesis, missing teeth, hypodontia, oligodontia

1. Introduction

The craniofacial growth and its harmonization with the dental apparatus take place according to a genetic program that acts in a coordinated manner, in both embryo foetal and postnatal stages. In addition to the structural pattern of development, the genetic program also ensures the control of each stage of ontogenesis, both in space and time, which eliminates the risk of developmental errors. During odontogenesis intricate genetic, molecular and cellular regulations establish accurate tooth number and precise location, size, morphology, and composition of each tooth.

However, deviations from usual structure, or function are possible. Any deviation, qualitative and/or quantitative, from usual pattern of development may be called developmental abnormality or anomaly. Developmental anomalies are also

known as congenital anomalies or birth defects. Congenital anomalies are defined by the World Health Organization (WHO)"as structural or functional anomalies". They can occur during antenatal life and can be detected"prenatally, at birth, or later in infancy" [1].

Development failure of one or more teeth is a result of specific disturbances (failure in the initiation of tooth formation, reduced odontogenic potential of the dental lamina, or premature arrest of tooth development) during the early stages (tooth initiation or morphogenesis stage) of odontogenesis affecting reciprocal interactions between the dental epithelium and mesenchyme and leading to absence of tooth germ [2]. Therefore, the usual number of deciduous and permanent dentitions, in both jaws, decrease and the condition is known as tooth agenesis. Family, twin, adoption and tooth development at molecular levels studies provide evidence-based interpretation of genetics as the predominant factors in the etiology of tooth agenesis. Frequently association of tooth agenesis with inherited monogenic syndromes supports the role of genetics in the etiology of missing teeth.

Absence of tooth developmental has direct clinical implications causing physical appearance, emotional, and functional impact on the affected individual. Most affected individuals lack only one or two permanent teeth, but patients who experience agenesis of more teeth are frequently encountered in dental practice as well. Severe forms of missing teeth lead to greater oral impairments. The lack of teeth, especially anterior teeth, malocclusion, drifting of teeth, diastemas between present teeth have negative impact on the oral health-related quality of life of the patients. Tooth agenesis poses medical problems due to ddysmorphic features that may only require cosmetic concern, or major anomalies that require clinical or cosmetic attention. Multidisciplinary teams[1] will manage therapeutic options, such as retaining the primary tooth, orthodontic treatment to close the edentulous spaces, dental surgical implants, and fixed or removable dental prosthetic appliances. The proper treatment may be tailored to the individual. It not only improves speech and masticatory function but also psychosocial distress that may help to restore self-confidence.

2. Terminology and classifications

There are several terms used to describe tooth agenesis: congenital absence of teeth, congenitally missing teeth, lack of teeth, or aplasia of teeth. Some suggest that the term" congenitally missing" teeth could be misleading because teeth are not visible at birth in the oral cavity and tooth development is completed after birth, or teeth may be lost by dental disease, or trauma, or extracted on clinical grounds. In the case of teeth, the development and differentiation continue long after birth, and instead of congenital many anomalies could rather be called developmental anomalies [3]. For the purpose of this chapter the term tooth agenesis will be used throughout. In the literature are used, most commonly, other descriptive terms mainly defined according to the number of missing teeth:

- Hypodontia is the lack of one to six teeth missing (excluding the third molars) with mild to moderate levels of severity.

[1] Clinical management of tooth agenesis requires careful multidisciplinary planning. Multidisciplinary team should include general dental practitioners, dental nurses, orthodontists, pedodontics, prosthodontists, oral and maxillofacial surgeons, specialist laboratory technicians, clinical psychologists, clinical geneticists, dermatologists, speech and language therapists.

- Oligodontia is the failure of development of more than six teeth missing (excluding the third molars) with severe level of severity.

- Anodontia means the lack of all teeth without any associated abnormalities causing an extremely severe dental phenotype.

The terms hypodontia and oligodontia are sometimes used interchangeably being considered as a unique clinical entity. As stated by Nieminen [3] and Vastardis [4], this classification of tooth agenesis may not properly reflect the severity of the phenotype as the third molars are excluded. Wherefore tooth agenesis based on dental phenotype severity may be partial or selective, or hypodontia (mild forms of agenesis), severe forms of agenesis or oligodontia, and very rare cases of agenesis of whole the dentition or anodontia. According to OMIM [5], selective tooth agenesis (STHAG) with no other associated systemic features or isolated tooth agenesis has been separated into two entities. The first entity refers to oligodontia characterized by the developmental absence of six or more permanent teeth. The second one refers to hypodontia characterized by the developmental failure of fewer than six teeth. The number of missing teeth in both cases excludes agenesis of third molars, commonly called wisdom teeth.

Incisor-premolar hypodontia (IPH) is a term also used in the literature based on the high frequency of incisors and premolars missing teeth [6]. For the purpose of this chapter the term tooth agenesis will be used throughout.

3. Clinical epidemiology

3.1 Prevalence of tooth agenesis

Prevalence of tooth agenesis is an important information to be of use not only for the clinician and patients but also for policy makers, given the implication for treatment protocols. Many published studies reported large variation in the prevalence of tooth agenesis across the world due to differences between methods of sampling, sample size, age of subjects, orthodontic or non-orthodontic enrolled subjects, number of males and females, the third molars included or excluded, or ethnic population groups. Moreover, it has been claimed that agenesis of permanent teeth has increased over the years. Mattheeuws et al. [7] considered that the period of time was too short and the available data too limited to describe a possible trend in the human dentition. Their meta-analysis seems to confirm that tooth agenesis has been diagnosed more often in recent studies.

Both the primary and permanent dentitions may be affected by variations in the number of teeth, but the prevalence is different. A prevalence of less than 1% in the primary dentition has been reported in the European population ranging from 0.4 to 0.9%, and it has been reported to be 2.4% in Japanese population [6, 8, 9].

Prevalence of permanent dentition has been studied extensively because it is no doubt more affected than primary dentition. Prevalence of tooth agenesis in permanent dentition also differs among studies of orthodontic/non-orthodontic subjects. Non-orthodontic population prevalence across the world varies between 1.6 and 9.6 per cent (most often-cited) [10–21] and calculated overall prevalence of tooth agenesis was estimated to be 6.53% ± 3.3% [22]. So far, some systematic reviews compare and evaluate prevalence studies on non-syndromic permanent teeth agenesis in various populations showing the prevalence varying from 0.3% in Indian population [16] to 15.7% in Hungarian population [17]. Polder et al. [11] reported the prevalence of non-syndromic agenesis in permanent teeth of European

population (third molars excluded) varying between 3.4% in Switzerland to 10.1% in Norway. The wide range of prevalence values observed in population studies has suggested geographic differences. Published data reviewed by Pemberton et al. [23] reported that people of Scandinavian descent are the most susceptible to tooth agenesis in the permanent dentition whilst those of Asian or Arabic descent are the most susceptible in the primary dentition.

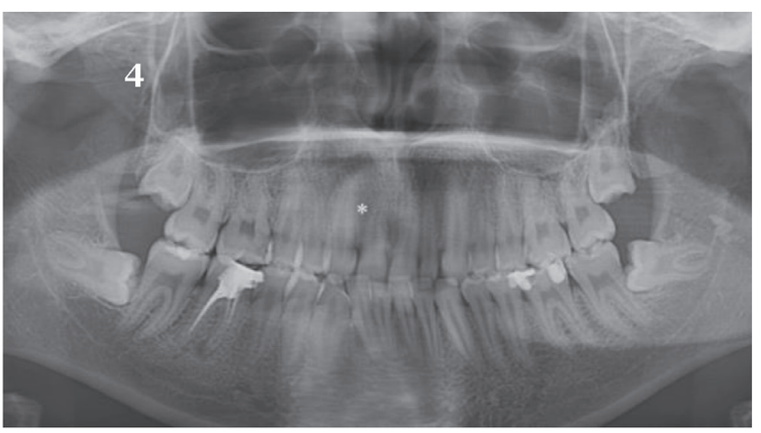
3.2 Distribution of tooth agenesis by gender

Gender predominance in tooth agenesis has been reported (**Table 1**) suggesting gender as a risk factor. Tooth agenesis show prevalence rates higher in females

Type of dentition	Prevalence %		Prevalence %	
	Minimum	Maximum	Male	Females
Primary	0.4	0.9	No significant differences	
Permanent	3.4	10.1	4.6	6.3

Table 1.
The prevalence of non-syndromic agenesis in permanent teeth (third molars excluded) in European population (summarized data).





	Right quadrants	Left quadrants
Upper teeth (maxillary)	8 7 6 5 4 3 2* 1	1 2 3 4 5 6 7 8
Lower teeth (mandibular)	8 7 6 5 4 3 2 1	1 2 3 4 5 6 7 8

Figure 1.
*Female patient, 22 years old with non-syndromic tooth agenesis. (1,2,3) intraoral photos showing the missing upper right lateral incisor and the microdontia of the contralateral tooth. (4) panoramic radiograph confirming the agenesis of the maxillary right lateral incisor. * position of the missing tooth.*

compared to males [11, 12, 24]. However, other studies reported no significant difference between the prevalence of tooth agenesis in males and females [19, 20].

3.3 Number of missing teeth

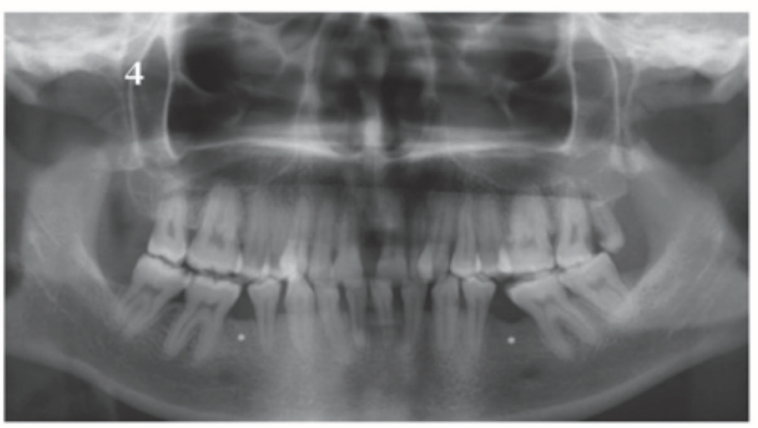
In most patients, dental agenesis involved only one (47.8%) (**Figure 1**) or two teeth (35.1%) (**Figure 2**) [11]. Absence of one or two permanent teeth was reported in 83% - 87.9% of the subjects with tooth agenesis [11, 19, 20]. Thus, most of the affected individuals suffer only a mild form of tooth agenesis.

Although tooth agenesis is a common development anomaly, the prevalence becomes progressively smaller as the number of missing teeth increases. For example, isolated agenesis of at least six teeth is relatively rare, affecting 0.08% of the Dutch population [25] and 0.16% of the Danish population [26]. Polder et al. [11] reported an overall prevalence of 0.14% in affected patients with six or more teeth. In addition, lack of all teeth without associated abnormalities is extremely rare, and prevalence is unknown [19].

3.4 Tooth agenesis and type of teeth affected

Apparently, any tooth in the arch can be missing, but tooth agenesis tends to affect distinct tooth classes differentially. Some tooth types were more often





	Right quadrants	Left quadrants
Upper teeth (maxillary)	8 7 6 5 4 3 2 1	1 2 3 4 5 6 7 8
Lower teeth (mandibular)	8 7 6 5 4 3 2 1 *	1 2 3 4 5 6 7 8 *

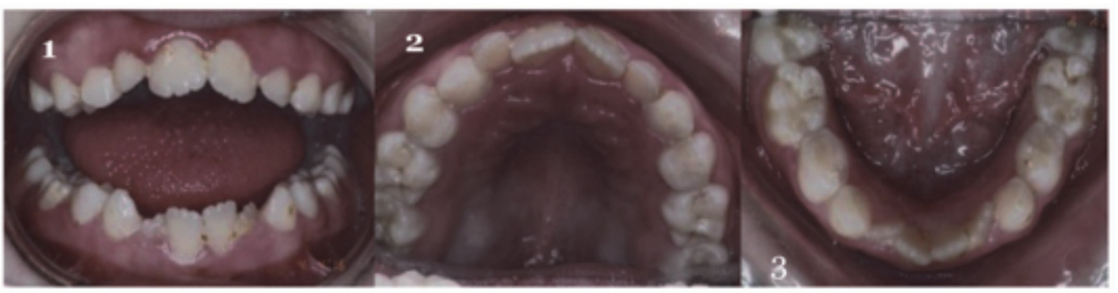
Figure 2.
*A 28-year-old female patient with trisomy 21 presenting lower second premolars agenesis. Several dental anomalies are observed on the intraoral photos (1,2,3): Upper diastema, maxillary lateral incisors microdontia, ectopic canines and spaced lower teeth. (4) panoramic radiograph shows the absence of the lower second premolars and an agenesis diagnosis can be confirmed. * position of the missing tooth.*

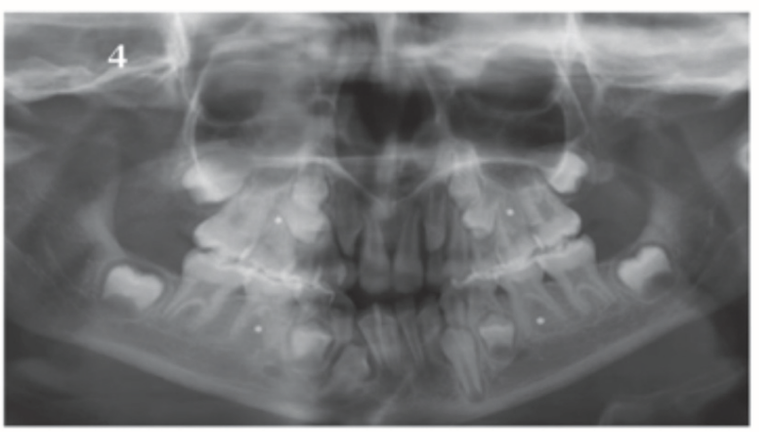
missing than other ones. Thus, the frequency of the individual teeth involved varies [11].

In the deciduous dentition, the upper lateral incisors account for more than 50% and together with lower incisors for 90% of all affected teeth [27]. Nieminen highlighted that there is an obvious association between the agenesis of the temporary teeth and the permanent teeth; a temporary tooth affected by agenesis is almost every time followed by missing of the corresponding permanent tooth [3, 27].

The third molars are the most prevalent missing teeth in all reports. Up to 70% of the population experience problems with their third molars, whether it is failure of proper eruption (impaction) or not erupting at all (agenesis). Up to 25% of the population may lose at least one third molar [10] and therefore, usually, third molar is excluded from the classification. The lowest prevalence of third molar agenesis reported so far was 10.1% for African American population [28] and the highest prevalence was 41% for the Korean population [29]. Excluding the third molars, in European population, the most frequently missing tooth is mandibular second premolar (2.91%–3.22%), followed by maxillary lateral incisor (1.55%–1.78%) or second premolar (1.39%–1.61%), as reviewed by Gracco et al. [19].

Other data support the conclusion that the most commonly missing tooth was the maxillary lateral incisor, followed by mandibular and maxillary second premolars [22]. **Figure 3** illustrates the bilateral absence of second lower premolars. Agenesis of lower central incisors is common in Asian populations in both primary and permanent dentitions [9].





	Right quadrants	Left quadrants
Upper teeth (maxillary)	* 8 7 6 5 4 3 2 1	* 1 2 3 4 5 6 7 8
Lower teeth (mandibular)	8 7 6 5 4 3 2 1 *	1 2 3 4 5 6 7 8 *

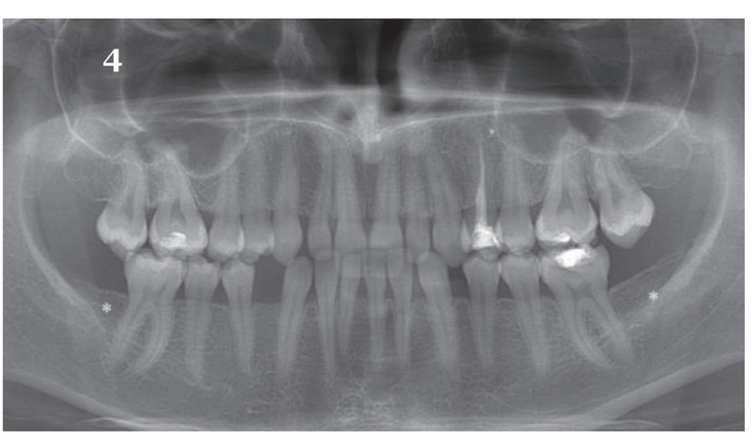
Figure 3.
*Female patient aged 7 years old with confirmed trisomy 21 presenting all four second premolars agenesis. Intraoral photos (1,2,3) emphasize a mixed dentition with lack of space for the alignment of the permanent teeth. (4) panoramic radiograph shows the congenital absence of the second premolars in both dental arches. * position of the missing tooth.*

Less commonly affected teeth are, in order, lower incisors, maxillary first premolars, mandibular first premolars, maxillary canines and mandibular second molars (**Figure 4**). Patients who experience agenesis of these teeth (e.g., canine or maxillary central incisor) more often present with many missing teeth [11].

The most stable teeth are maxillary central incisors (prevalence of agenesis 0.016%) and mandibular first molars and canines (prevalence of agenesis about 0.03%) [3]. Recently, Eshgian et al. [21] concluded that hypodontia affected specific type of teeth. In their study, the most commonly missing teeth were maxillary premolars, lateral incisors and mandibular premolars. Comparing their results with other data from previous studies, they explained the differences in patterns and prevalence of tooth agenesis between different population groups by ethnic diversity in the distributions of mutant genes. The explanation was supported by the prevalence of people with missing permanent teeth which was significantly lower in blacks than in whites in U.S.A. [28], and different type of affected tooth, mandibular incisor in Hong Kong children population [30] and mandibular second premolars among Italians [19]. Polder et al. [11] considered that difference in the ethnic groups is not the explanation of differences in prevalence between populations due to the small number of reported hypodontia cases and the difficulty of detecting the anomaly without appropriate evidence.

Distinct patterns of permanent teeth agenesis have been reported but, as a general rule, if only one or a few teeth are missing, the absent tooth will be the most distal tooth of any given morphological class [3, 15, 24, 31].

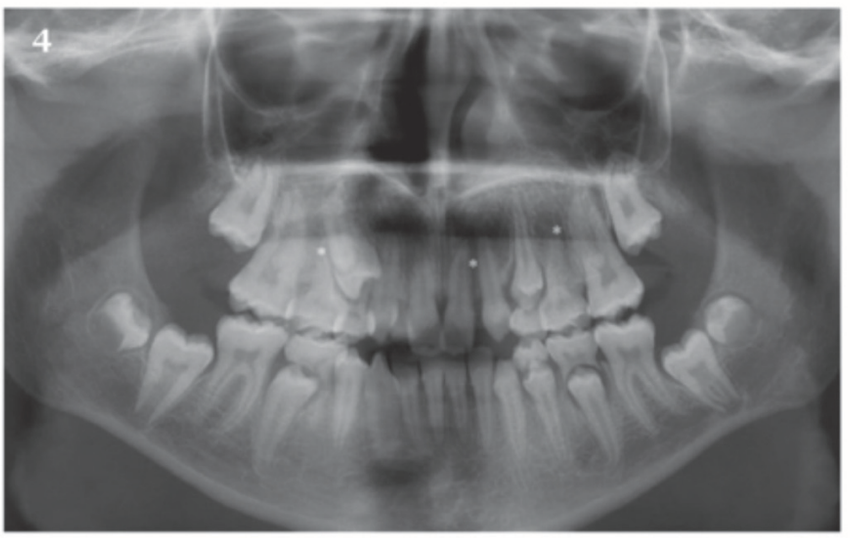




	Right quadrants	Left quadrants
Upper teeth (maxillary)	8 7 6 5 4 3 2 1	1 2 3 4 5 6 7 8
Lower teeth (mandibular)	8 7 6 5 4 3 2 1 *	1 2 3 4 5 6 7 8 *

Figure 4.
*Tooth agenesis in a non-syndromic 21-year-old female patient. Intraoral photos (1,2,3) emphasizing a generalized microdontia and as a result, teeth are spaced with larger gaps in the lower arch. (4) Anamnesis and the examination of the panoramic x-ray reveal the congenital absence of the lower second molars, both in the right and in the left quadrant. * position of the missing teeth.*





	Right quadrants	Left quadrants
Upper teeth (maxillary)	* 8 7 6 5 4 3 2 1	* * 1 2 3 4 5 6 7 8
Lower teeth (mandibular)	8 7 6 5 4 3 2 1	1 2 3 4 5 6 7 8

Figure 5.
*A 13-year-old male with confirmed Down syndrome presenting different dental anomalies. Intraoral photos (1–3) show mixed dentition with delayed eruption of permanent teeth, remarking the absence of the upper left lateral incisor. (4) Examination of the panoramic radiograph reveals the absence of the upper second premolars and of the maxillary left lateral incisor. * position of the missing teeth.*

It is known that upper lateral incisors, second premolars, and third molars are the last forming teeth in their tooth family, are in the embryonic fusion of the maxilla and the medial nasal processes and erupt in the critical terminal area of the dental lamina. For these reasons, the last forming teeth are more vulnerable to the critical actions of both genetic and environmental factors during odontogenesis and fail to develop. This can explain why tooth agenesis most frequently affects premolars, lateral incisors, and molars (**Figure 5**). The anomaly was called 'end-of-series [31, 32]. In 2017, it has been assumed by Juuri and Balic that tooth agenesis most frequently affects the last tooth to develop within the tooth family due to a gradual decrease of the odontogenic potential of the dental lamina [33].

3.5 Bilateral versus unilateral tooth agenesis

Tooth agenesis may be either bilateral or unilateral. Pinho et al. [32] hypothesized that if the etiology of hypodontia is primarily genetic, then bilateral missing teeth phenotype would be expected to be more commonly observed. Unilateral

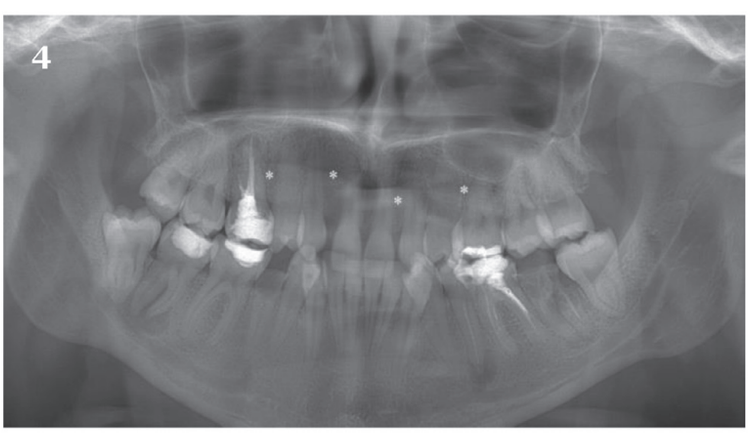
hypodontia might be a variation in severity of a genetic trait showing a microdont or peg-shaped contralateral tooth.

Most studies reported predominance of bilateral missing teeth, as reviewed by Rakhshan [15]. Goya et al. [34] found that symmetry of congenitally missing teeth was predominant (74.6%), Kirzioglu et al. [35] observed that bilaterally missing teeth was 73.2%, and Endo et al. [36] reported that 89% of the patients presented bilaterally missing teeth. Other researchers have found unilateral tooth agenesis more common [37]. Polder et al. [11] compared (based on nine studies) the occurrence of bilateral and unilateral agenesis for the most four affected teeth showing that only for maxillary lateral incisors prevalence of unilateral agenesis was lower than bilateral agenesis.

- Bilateral agenesis of maxillary lateral incisors occurred more often.
- Unilateral agenesis involving mandibular second premolars occurred more common.
- Unilateral agenesis affecting maxillary second premolars was more frequently.
- Unilateral agenesis of mandibular central incisors occurred more often.

Medina [38] stated that while symmetrical dental missing affects the maxilla (**Figure 6**), the mandible shows mostly unilateral agenesis. In the opinion of other





	Right quadrants	Left quadrants
Upper teeth (maxillary)	* * 8 7 6 5 4 3 2 1	* * 1 2 3 4 5 6 7 8
Lower teeth (mandibular)	8 7 6 5 4 3 2 1	1 2 3 4 5 6 7 8

Figure 6.
*Non-syndromic tooth agenesis in a 26-year-old female patient. Clinical intraoral appearance (1,2,3) emphasizing multiple dental problems, accentuated by the bilateral absence of the upper lateral incisors and of the second premolars. (4) panoramic radiograph confirming the agenesis of the four upper teeth. * position of the missing teeth.*

researchers, the most common symmetric missing tooth could be the mandibular second premolar agenesis, followed by the absence of the maxillary second premolar or maxillary lateral incisor, as reviewed by Rakhshan [15].

3.6 Distribution of missing teeth over maxilla/mandible

No overall difference in tooth agenesis has been reported between maxilla and mandible for permanent dentition [11]. However, Gomes et al. [20] found maxillary hypodontia in 59.2% of patients and in the mandible of 40.8% with an overall ratio of 1.45:1 in orthodontic patients. Several reports mentioned a small but not always significant predominance of missing teeth in the maxilla [19, 20, 24] whilst other reported more missing teeth in the mandible than in the maxilla [36].

For the primary teeth, agenesis is more common in the maxilla [27].

3.7 Distribution of missing teeth over left/right sides

No significant difference between left and right sides of the jaw has been reported. Nevertheless, predominance of tooth agenesis on the left side has been reported in some Scandinavian studies, as reviewed by Arte S. [18] and Fekonja A. [24] have found the missing teeth were more commonly absent on the right side.

3.8 Distribution of missing teeth across anterior/posterior regions

No clear difference in tooth agenesis has been found between the anterior and posterior regions. Most studies showed higher prevalence in the anterior segment [15] and the few remaining analyses found no significant differences [36]. Endo et al. [36] suggested that in mild cases of tooth agenesis, the anterior segment might be more involved while the posterior segment might be predominant in severe cases.

3.9 Age of detectability

Polder et al. considered the age of detectability as an important issue. A meta-analysis study made by Polder et al. revealed that the visibility of tooth germs by X-ray examination hangs on their degree of mineralization. Subjects at the same chronological age can show significant differences in mineralization stages and dental age. The major differences in mineralization can be found especially in mandibular second premolar buds or third molar buds which present a late onset of mineralization. Therefore, radiographic examination may show a false-positive result and a misdiagnosis of tooth agenesis [11].

All primary teeth have erupted by the age of three and all permanent teeth except the third molars between the age of 12 and 14. Therefore, three to four years of age children are suitable for diagnosis of missing primary teeth by clinical examination, and 12 to 14-year-old children (the precise determination of teeth mineralization stages), for diagnosis of permanent teeth [22, 39]. While some studies reported age of detectability after eight years of age for the permanent dentition, and failure for the third molar to form is detectable by age 11.

4. Genetic causes of tooth agenesis

Investigations so far show that several heterogenous factors may be involved in tooth agenesis. Tooth development is a complex process which involves a

combination of genetic, epigenetic, and environmental factors. Thus, there is no single etiology of tooth agenesis. Family, twin, and adoption studies[2] are the primary exploration by which the genetic basis of a condition may be established. In addition, observed prevalence differences between populations, and association with heritable syndromes supplied evidence for strong genetic influences on tooth agenesis [8]. These findings provided the reasoning for recent efforts to identify the relevant susceptibility genes and the molecular mechanisms by which they interact with environmental influences, and to correlate tooth agenesis phenotypes with their causative factors. Furthermore, genetic studies on mouse models with dental agenesis have identified a few transcription factors and signaling molecules, such as WNTs (wingless-related integration site), BMPs (bone morphogenetic proteins), FGFs (fibroblast growth factor), and NF–κB (nuclear factor kappa B) as candidate genes in human isolated and syndromic agenesis [40].

More than 300 genes are expressed and control odontogenesis and, apparently, any of these gene mutations may cause tooth agenesis. Among these genes, PAX9 (paired box gene 9), MSX1 (muscle segment homeobox 1), EDA (ectodysplasin A), WNT10A (wingless-type MMTV integration site family, member 10A), and AXIN2 (axis inhibitor 2) are the most frequently reported mutations associated with non-syndromic tooth agenesis (hypodontia/oligodontia), as reviewed by Al-Ani et al. [41] and Liu et al. [42]. (**Table 2**) These all genes have roles in both signaling pathways and in mediating the signal transduction cascades.

Normal expression of these genes is important for the tooth development. MSX1 is a transcription factors active in regions of condensing ectomesenchyme in the tooth germ. PAX9 is a transcription factor as well, it is expressed in the tooth mesenchyme, playing a significant role during odontogenesis in the progressive and reciprocal signal transduction pathways that normally occur in epithelial–mesenchymal cells. Both Msx1 and Pax9 are involved in the Bmp and Fgf pathways and interact during the tooth-bud-to-cap transition. Their expression profiles during early tooth development are largely overlapping, and Pax9 is known to activate transcription of *Msx1* at the bud stage. AXIN2 plays an important role in the regulation of the stability of beta-catenin in the Wnt signaling pathway. EDA is involved in epithelial-mesenchymal signaling during morphogenesis of ectodermal organs, including teeth, hairs, feathers, and mammary glands. WNT10A is strongly expressed in the dental epithelium at the initiation stage and plays a role in tooth development beyond the bud stage [31].

Studying 34 unrelated patients with isolated tooth agenesis, van den Boogaard et al. [43] reported that 19 patients, representing 56% of them, had mutations in the WNT10A gene. Of 34 patients, 3% presented mutations in the MSX1 gene, 9% and 3% had mutations in the PAX9 and AXIN2 genes, respectively. It was concluded that WNT10A is a significant gene in the etiology of isolated hypodontia.

Frameshift and nonsense mutations are highly likely all causative because they involve profound alteration of the protein primary structure, but missense mutations in these genes are found to cause tooth agenesis phenotypes characteristic in terms of severity and affected teeth as well [44].

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[2] If a tooth agenesis is caused by genetic factors, then individuals who are genetically related should share similar risks for the condition. Family studies look for genes that cause familial aggregation of a heritable trait. Twin studies compare the rate of tooth agenesis between monozygotic and dizygotic twins as a test for genetic contributions. Monozygotic twins have been concordant and have shown variation due to epigenetic factors, environmental modifiers, or interactions. Studies of adoption can help distinguish the relative influence of genes and environment.

Gene symbol/ locus	Gene name	Cytogenetic location	Gene / locus OMIM number	Description of tooth agenesis clinical features	Inheritance	Phenotype OMIM Number
AXIN2	axis inhibitor 2	17q24.1	604025	Oligodontia – severe permanent teeth agenesis	Autosomal DOMINANT	608615
EDA	ectodysplasin A	Xq13.1	300451	Tooth agenesis, selective, X-linked 1 (STHAGX1)	X-linked DOMINANT	313500
GREM2	GREMLIN-2 homolog, cystine knot superfamily gene	1q43	608832	Tooth agenesis, selective,9 (STHAG9)	Autosomal DOMINANT	617275
LRP6	low density lipoprotein receptor-related protein-6	12p13.2	603507	Tooth agenesis, selective,7 (STHAG7)	Autosomal DOMINANT	616724
MSX1	muscle segment homeobox 1	4p16.2	142983	Tooth agenesis, selective,1, with or without orofacial cleft (STHAG1)	Autosomal DOMINANT	106600
PAX9	paired box gene 9	14q13.3	167416	Tooth agenesis, selective,3 (STHAG3) Hypodontia/ Oligodontia 3	Autosomal DOMINANT	604625
STHAG2		16q12.1* (*the disorder was placed on the map by statistical methods)	602639	Tooth agenesis, selective, (STHAG2)	Autosomal recessive	602639
STHAG5		10q11.2-q21* (*the disorder was placed on the map by statistical methods)	610926	Tooth agenesis, selective,5 (STHAG5) Hypodontia/ Oligodontia 5 (He-Zhao deficiency)		610926
WNT10A	wingless-type MMTV integration site family, member 10A	2q35	606268	Tooth agenesis, selective,4 (STHAG4) with or without ectodermal dysplasia	Autosomal DOMINANT or recessive	150400
WNT10B	wingless-type MMTV integration site family, member-10B	12q13.12	601906	Tooth agenesis, selective,8 (STHAG8)	Autosomal DOMINANT	617073

Online Mendelian Inheritance in Man (OMIM™) is a comprehensive, authoritative and timely knowledgebase of human genes and genetic phenotype compiled to support research and education in human genomics and the practice of clinical genetics. It is freely available and updated daily.

Table 2.
Gene mutations involved in NON-SYNDROMIC tooth agenesis are passed on to the next generation following different Mendelian patterns of inheritance (according to OMIM database).

As a rule, homozygous (identical mutation on both alleles of a specific gene) or compound heterozygous (both alleles of a gene are mutant, but the mutations are different) carriers of gene mutations exhibit more severe phenotype of tooth agenesis than heterozygous carriers (two different alleles, but only one is mutant).

Besides the single-gene mutations, Michon [45] reported the functional role of miRNAs in proliferation and differentiation of cells and tissues during odontogenesis and possible dental defects development. His results support the view of complex genetic etiology of tooth agenesis.

Attention should be turned to the expression of a mutation in a family. In families with a probable dominant or recessive Mendelian inheritance, there seems to be a variable missing teeth phenotype. In other words, tooth agenesis patterns are different in expressivity among the affected members within a family having the same molecular cause. Vastardis studied incisor agenesis in families with dominant pattern of inheritance. Autosomal dominant disorders express variability in clinical manifestation caused by reduced penetrance and variable expressivity of mutant gene. Consequently, individuals in the same family who carry an identical mutation can vary in the severity of their incisor agenesis. Variable expressivity determines developmental alteration of lateral incisor shape (peg-shaped) or rudimentary third molars and unilateral agenesis may be the result of incomplete penetrance [46].

Mostowska et al. described a three-generation family with severe autosomal dominant oligodontia. Those affected lacked all permanent molars, second premolars, and mandibular central incisors. The authors found a novel mutation of MSX1. Mutation occurs in exon 2, at nucleotide 581 a cytosine is changed to a thymine (c.581C → T transition), and disrupts the homeobox domain, which is highly conserved. The new mutation causes non-syndromic oligodontia (absence of 14 permanent teeth) in their proband. Two healthy members from the proband's family carry the same missense mutation [47]. To date, many studies provide evidence for great intra- and inter-familial clinical variability in families with isolated tooth agenesis [3, 13, 41].

There are several possible genetic mechanisms to explain these major differences in expressivity of the phenotype with the same molecular cause. One of them lies in the concepts of penetrance and expressivity. Reduced (incomplete) penetrance and variable expressivity are factors that influence the effects of particular genetic changes and are commonly seen with Mendelian dominant traits. Tooth agenesis shows incomplete penetrance, since pedigree studies demonstrate individuals who must carry the mutation but who do not appear to be affected themselves. Reduced penetrance probably occurs when final effect of a gene mutation can be indirectly influenced by modifier genes, epigenetic factors, or miRNAs. Potential modifier genes may act in the same or in different development pathways altering (exacerbate or attenuate the effect of the gene mutation) the clinical phenotype.

Epigenetic factors do not change the gene sequence. Epigenetic alterations may be induced spontaneously, in response to environmental factors, or may be part of a person's make up (allele dosage, copy number variants, allele variants). Identical twins are ideal subjects for studying the effects of epigenetic modifications. Monozygotic co-twins sharing sex, age, and identical genomes display discordant phenotypes for missing teeth which may be explained by epigenetic differences. In their twin study, Townsend et al. supported the view that, even though there is a relatively strong genetic basis to missing teeth, the number or position of affected teeth can be influenced by epigenetic factors. Epigenetic alteration activities, such as DNA methylation and histone modification, at each stage, at the local level during the odontogenesis process, may account for distinct phenotypic differences in the final appearance of teeth of the identical twins. During tooth development,

odontogenetic cells reply differently to epigenetic variation in spatiotemporal expression of local signaling molecules passing between cells. [48]

miRNAs play an important role in controlling gene activity by regulating translation during tooth development. Changes in miRNAs levels have been linked to several dental defects [45]. Thus, in a population, the missing teeth phenotype might not occur so often as the abnormal genotype. On the other hand, individuals with the same genetic condition may have more missing teeth than another having only one missing tooth. Thus, expressivity describes individual variability. Variable expressivity is probably caused by a combination of genetic, environmental, and lifestyle factors, most of which have not been identified.

Dreesen et al. analyzed hypo−/oligodontia phenotype variations in nine families at individual, intrafamilial and interfamilial levels aiming to evaluate whether the different agenesis patterns in the pedigrees are predictive of mutations in specific genes based on reported genotype–phenotype associations. Familial aggregation was noted but the tooth agenesis patterns were variable between family members, in terms of number of missing teeth. Therefore, tooth agenesis is not (always) a simple monogenic disorder. The authors proposed a multifactorial aetiological model with many genes and environmental factors modulating the clinical expression [49].

4.1 Genetic heterogeneity of selective tooth agenesis (STHAG) and clinical features

Genetic heterogeneity describes different gene mutations or genetic mechanisms that produce the same or similar clinical phenotype. Heterogeneity can be recognized by subtle differences in clinical phenotype or evidence of different patterns of inheritance. Genetic testing can confirm the gene mutation responsible for a certain clinical phenotype. Usually, genetic heterogeneity complicates the risk estimation in genetic counseling and genetic prognoses.

Two types of genetic heterogeneity are recognized: locus heterogeneity (clinical phenotype is caused by mutations at two or more different loci), and allelic heterogeneity (clinical phenotype is caused by more than one mutation within the same gene, same locus).

Locus heterogeneity is well documented in selective tooth agenesis (STHAG).

There are ten loci associated with STHAG. Nine of them are autosomal loci (STHAG1 to STHAG9) and one STHAGX1 is sex-linked locus as it follows the X-linked dominant pattern of inheritance. The corresponding gene located at **STAHG1** is MSX1 on chromosome 4p16. The genes for the following loci are PAX9-**STHAG3** on chromosome 14q12, WNT10A-**STHAG4** on chromosome 2q35, formerly LTB3-**STHAG6** on chromosome 11q13.1, LRP6-**STHAG7** on chromosome 12p13, WNT10B-**STHAG8** on chromosome 12q13, GREM2-**STHAG9** on chromosome 1q43, and EDA-**STHAGX1** on chromosome Xq13. The molecular basis of STHAG is known for STHAG1,3,4,7,9 and STHAHX1. For STHAG2 and 5, the disorder was placed on the map by statistical methods. (**Table 2**).

In 1998, Ahmad et al. [50] reported an autosomal recessive form of hypodontia in a large consanguineous Pakistani family. This was the first report of hypodontia associated with other dental anomalies, such as enamel hypoplasia and failure of teeth eruption, leading to the edentulous state prematurely. The locus was named **STHAG2** which is located on chromosome 16p12, but the gene for this locus has not been described so far.

In 2000, Wang et al. [51] described a rare, heritable, form of agenesis of permanent teeth. The tooth number anomaly was named He-Zhao deficiency. The only clinical feature of affected individuals was oligodontia. It was transmitted in an

autosomal dominant manner with reduced penetrance in a large six successive generation family coming from a small village in China. The number of missing teeth ranged from "a few teeth to the entire set of teeth". Some of the patients were more likely to have first and second molars. This distinct form of permanent tooth agenesis is associated with **STHAG5** locus on chromosome 10q11.2.

In 2015, Huckert et al. [52] reported mutations in LTBP3 (latent transforming growth factor-beta-binding protein 3) gene causing different dental phenotypes and brachyolmia (short trunk, mild short stature with platyspondyly and scoliosis). The association of oligodontia with hypoplastic amelogenesis imperfecta, taurodontic molars and short stature has been designed as a distinct entity named DASS (dental anomalies and short stature) (OMIM 601216). So, STHAG6 was incorporated into DASS.

Another example of locus heterogeneity is provided by mutations in EDA, EDAR and EDARADD genes which express the similar phenotype of hypohidrotic ectodermal dysplasia (**Table 3**).

Allelic heterogeneity is illustrated by the different mutations in the MSX1 and PAX9 genes. For example, MSX1 mutations show overlapping and non-overlapping phenotypes. Almost all mutations are responsible for autosomal dominant STHAG1 involving second premolars, first molars and third molars. Few MSX1 mutations are associated with combinations of tooth agenesis with oral clefting (cleft palate only and cleft lip and cleft palate) and nail abnormalities (Witkop syndrome) [49] (**Table 3**).

4.2 Genotype–phenotype correlations

Genotype–phenotype correlations refer to the association between specific germline mutations, meaning genotype, and the resulting spectrum of disease expression of that mutation in the affected individual, meaning phenotype. Usually, such correlations are made for monogenic disorders which follow Mendelian inheritance patterns. Moreover, the correlations can clarify which characteristics of a mutation affect the severity of dental anomaly with a genetic background. On the other hand, the pattern of tooth agenesis provides useful information about how gene mutation might affect an individual and other member of the family. Tooth agenesis runs in families and hypodontia/oligodontia patients have one or more affected family members [48]. So, the family members can be appropriately counseled by a geneticist, and predictive/pre-symptomatic genetic testing should be considered for early diagnosis and early intervention, especially for children.

Research studies have linked non-syndromic hypodontia/oligodontia phenotype with specific gene mutations. For example, among identified mutations, MSX1 and PAX9 genes can cause variation in clinical phenotype of tooth agenesis. Kim et al. [53] studied the pattern of missing teeth in families with certain MSX1 and PAX9 mutations. The missing teeth pattern associated with MSX1 mutants was different from that associated with mutations in PAX9. MSX1-associated tooth agenesis involved bilaterally symmetrical absence of maxillary and mandibular second premolars and maxillary first premolars. PAX9-associated tooth agenesis involved also bilaterally symmetrical missing teeth, usually maxillary and mandibular second molars were affected. Yu et al. [54] stated that WNTB10B-associated oligodontia affected most lateral incisors. In contrast, genotype–phenotype analysis of oligodontia pattern associated with WNT10A mutations revealed that premolars were the most frequently missing teeth.

4.3 Familial non-syndromic severe tooth agenesis (oligodontia)

Mutations in nine genes (MSX1, PAX9, AXIN2, WNT10A, EDA, EDAR, EDARADD, NEMO and KRT17) have been associated with non-syndromic

Gene symbol	Gene name	Cytogenetic location	Gene/locus OMIM number	Name of disorder associated with tooth agenesis	Inheritance	Phenotype OMIM Number
AXIN2	axis inhibitor 2	17q24.1	604025	Oligodontia-colorectal cancer syndrome	Autosomal DOMINANT	608615
EDA	ectodysplasin A	Xq13.1	300451	Hypohidrotic ectodermal dysplasia 1 (HED)	X-linked reccessive	305100
EDAR	ectodysplasin A receptor	2q13	604095	Ectodermal dysplasia 10A, hypohidrotic/hair/nail type Ectodermal dysplasia 10B, hypohidrotic/hair/nail type	Autosomal DOMINANT Autosomal recessive	129490 224900
EDARADD	edar-associated death domain	1q42-q43	606603	Ectodermal dysplasia 11A, hypohidrotic/hair/tooth type Ectodermal dysplasia 11B, hypohidrotic/hair/tooth type	Autosomal DOMINANT Autosomal recessive	614940 614941
LTBP3	latent transforming growth factor-beta-binding protein 3	11q13.1	602090	Dental anomalies and short stature	Autosomal recessive	601216
MSX1	muscle segment homeobox 1	4p16.2	142983	Ectodermal dysplasia 3, Witkop type Orofacial cleft 5 Wolf-Hirschhorn syndrome* (*a contiguous gene deletion syndrome in which multiple genes are involved)	Autosomal DOMINANT Autosomal DOMINANT Isolated cases	189500 608874 194190
NEMO (IKBKG)	inhibitor of nuclear factor kappa-b kinase, regulatory subunit gamma	xq28	300248	Incontinentia pigmenti	X-linked DOMINANT	308300
PITX2	paired-like homeodomain transcription factor 2	4q25	601542	Axenfeld-Rieger syndrome, type 1	Autosomal DOMINANT	180500
WNT10A	wingless-type MMTV integration site family, member 10A	2q35	606268	Schopf-Schulz-Passarge syndrome Odontoonychodermal dysplasia	Autosomal recessive Autosomal recessive	224750 257980

Table 3.
Gene mutations frequently associated with SYNDROMIC tooth agenesis.

oligodontia, as reviewed by Liu et al. [42] Oligodontia phenotype is caused by haploinsufficiency. Mutations produce a reduction in functional gene product below a threshold required for normal dental development [8].

Apparently, reduced quantities of a gene product should equally affect the formation of all teeth. Oligodontia caused by defects in MSX1 and PAX9 yields typical, although variable and overlapping patterns of tooth agenesis [8]. Mutations of MSX1 result in the absence of all permanent third molars, all second premolars, maxillary first premolars and variably other teeth, whereas defects in PAX9 cause mainly agenesis of molars, typically of all permanent maxillary and the second and third mandibular molars as well as variably of other teeth [55]. Regarding AXIN2 gene, five mutations were reported to be associated with non-syndromic tooth agenesis: four missense and one frameshift mutations. The phenotype is variable in expression and involved at least seven teeth. One study reported that a mutation in EDARADD gene led to non-syndromic oligodontia [41].

4.4 Tooth agenesis as a complex (multifactorial) trait

Not all of the tooth agenesis forms can be linked to precis genetic mutations, at a single gene locus. Tooth agenesis is a common developmental anomaly and has a definite familial tendency. However, the proportion of affected near relatives is less than what expected for a monogenic trait. One way to recognize a complex trait is through unpredictable inheritance patterns in successive generations. Tooth agenesis is probably caused by several independent defective genes, acting alone or in combination with other genes, and interacting with environmental factors, leading to a specific clinical phenotypic pattern. Being produced by multiple genes, a multifactorial trait seems to be more susceptible to environmental/stochastic or nongenetic factors.

Incomplete penetrance, genetic background, and variable expression levels did not explain all major differences in the expressivity of the phenotype with the same molecular cause. For these reasons, some authors based on evidence from genetic studies, animal models, and environmental correlates suggested an oligogenic or polygenic inheritance of tooth agenesis [42, 45–48].

For instance, Vastardis [45] stated that tooth development is a very complex process and involves many" players". Thus, third molar agenesis cannot be explained in most cases with a simple model of autosomal dominant transmission. Fekonja et al. [24] suggested that genes could be the dominant factor for the agenesis in the anterior region, while the posterior teeth could be missing sporadically. Townsend et al. [56] proposed a multifactorial aetiological model, with possibly many genes, and also environmental and epigenetic factors contributing to tooth development based on lack of complete concordance for missing teeth in monozygotic twins.

It has been documented by various statistical analyses using single locus and polygenic patterns that both approaches are possible. From genetical point of view, multifactorial inheritance of tooth agenesis is troublesome to analyze. It is difficult to state whether hypodontia is a result of a polygenic or single gene defect. It arrives at a diagnosis of multifactorial inheritance for tooth agenesis only after the monogenic forms of inheritance have been considered and found unlikely.

4.5 Familial non-syndromic permanent teeth anodontia

Molecular basis or locus of isolated anodontia (OMIM 206780) are unknown. Gorlin et al. [57] described complete absence of the permanent dentition with the entire primary dentition present and erupted at a normal time. Anodontia presented

evidence of autosomal recessive inheritance, including multiple affected sibs and consanguineous parents. Based on three family studies, it was documented that anodontia of permanent teeth is a homozygous state of the gene responsible for pegged or missing maxillary lateral incisors [5].

Pseudoanodontia should not be confused with anodontia. Pseudoanodontia or false anodontia occurs, when teeth are absent clinically because of impaction, delayed eruption, exfoliation or extraction. In GAPO syndrome (GAPO syndrome is the acronymic designation for a complex of growth retardation, alopecia, pseudoanodontia, and progressive optic atrophy - OMIM 230740) is described pseudoanodontia, failure of tooth eruption. The syndrome is caused by mutations of ANTXR1 gene (anthrax toxin receptor 1) located on 2p13.3, and the pattern of inheritance is autosomal recessive [58].

4.6 Syndromic tooth agenesis

Tooth agenesis is usually isolated, but gene mutations have been identified that either cause tooth agenesis as a sole isolated agenesis, or tooth agenesis in association with a wide variety of multiorgan malformation syndromes. **(Table 3 and Appendix 1 – Table A1)**) The London dysmorphology database reported 150 syndromes as being associated with hypodontia [18].

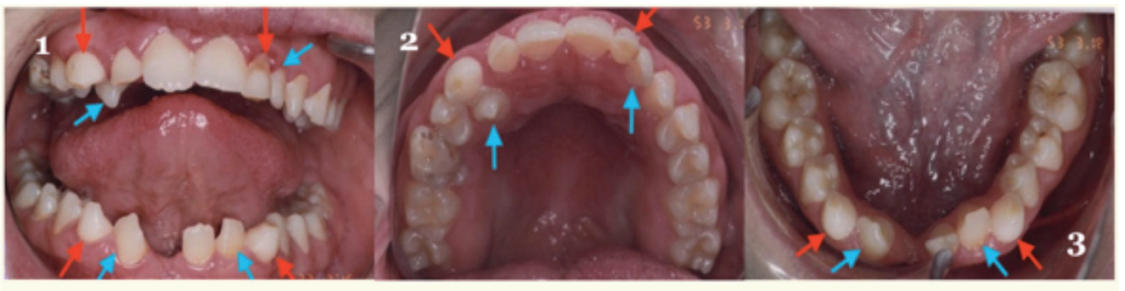
Thus, tooth agenesis is a primary feature of many single-gene Mendelian syndromes that affect not only teeth but also several other ectodermal derivatives indicating that the development of teeth and certain tissues/organs are under the control of the same gene molecular functions and common molecular mechanisms are responsible for tooth and other organ development. A pleiotropic mutation may influence several, apparently unrelated, traits simultaneously, due to the gene coding for a product used by a myriad of cells or different targets that have the same signaling function. For instance, two AXIN2 nonsense mutations caused syndromic tooth agenesis, such as oligodontia and predispose to colorectal cancer, or oligodontia and variable other findings, including colonic polyposis, gastric polyps, a mild ectodermal dysplasia phenotype with sparse hair and eyebrows, and early onset colorectal and breast cancers [42].

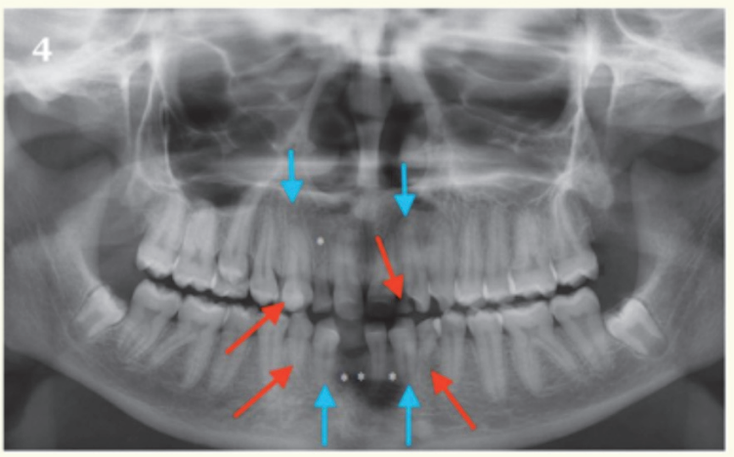
Adventitious chromosomal abnormalities cause tooth agenesis in association with other clinical features and recognizable patterns of malformations known as chromosomal syndromes.

- Down syndrome and tooth agenesis (OMIM 190685)

  Down syndrome (DS), a common and well-known syndrome, is caused by an autosomal aneuploid defect called trisomy involving the human chromosome 21 (Ts21). The extra chromosome 21 or part of its long arm (including many genes) may come in distinct genetic ways, such as full trisomy 21, mosaic trisomy 21 or unbalanced translocation trisomy 21 causing DS distinctive facial features. The difference between DS people could be made by chromosome analysis because craniofacial features are similar. So, cytogenetic analysis is not relevant for predicting the severity of oro-dental features in DS [59].

  Missing teeth were reported in 23–47% of cases (**Figure 7**). Third molars, second premolars, and lateral incisors are most frequently absent in the permanent dentition. Peg-shaped maxillary lateral incisors have been observed in 10%. In 12–17% of cases, deciduous lateral incisors are missing. Extreme hypodontia and anodontia have been noted occasionally [60]. There is a higher incidence of dental anomalies, such as taurodontism, fusion of deciduous lower lateral incisor with a canine, morphologic crown alterations,





	Right quadrants	Left quadrants
Upper teeth (maxillary)	* 8 7 6 5 4 3 2 1	1 2 3 4 5 6 7 8
Lower teeth (mandibular)	8 7 6 5 4 3 2 1 **	1 2 3 4 5 6 7 8 *

Figure 7.
*Multiple tooth agenesis in a 14-year-old female patient with trisomy 21. (1–3) intraoral photos reveal a mixed dentition. It is important to note that the prolonged retention of several primary teeth, either due to the congenital absence of the permanent successor tooth (which is the case of the missing maxillary right lateral incisor) or the deviation in the eruptive path of the permanent successor which determinate the concomitant presence of both the deciduous and the permanent teeth on the arch (in the figures, the deciduous teeth are marked with red arrows while the permanent ones are labeled by blue arrows). The degree of complexity involved in this case is increased not only by the agenesis of the upper right lateral incisor, but its association with another three missing incisors in the lower arch. (4) based on the anamnesis and the examination of the panoramic radiograph, it was confirmed the agenesis of the upper right lateral incisor, lower lateral incisors, and the lower right central incisor. Moreover, left second molars in both arches present an elongated pulp chamber and apically displaced furcations, which are specific for the diagnosis of taurodontism. * position of the missing teeth.*

enamel hypoplasia and hypocalcification. Irregular alignment is common as well. Tooth eruption of both deciduous and permanent teeth is delayed in 75% of cases and irregular sequence of eruption is common [60]. DS children with missing teeth have a more obvious tendency in developing a Class III relationship of the jaws than DS children without tooth agenesis. This must be taken into account when treating a DS patient [61].

- Wolf-Hirschhorn syndrome and missing teeth (OMIM 194190)

  The deletion of the distal short arm of human chromosome 4 causes del(4p) syndrome known as Wolf-Hirschhorn syndrome. The critical region is 4p16.3 (WHSCR) and lies approximately 2 Mb from the telomere, so that multiple genes are deleted. Most important genes, playing a major role in early development, are NDS2 (nuclear receptor binding SET domain protein 2), LETM1 (leucine zipper and EF-hand containing transmembrane protein 1),

and MSX1 (muscle segment homeo box homolog 1) cause the typical signs and symptoms of this disorder, such as characteristic facial appearance (microcephaly, high forehead, prominent glabella," Greek warrior helmet" facies, broad and/or beaked nose, hypertelorism, short philtrum, micrognathia, downturned corners of the mouth, short upper lip, dysplastic ears, preauricular tags), delayed growth and development, intellectual disability, and seizures. Agenesis of many permanent teeth has been reported [60].

About 10% of the patients have cleft lip and palate, 25% present cleft palate, and 50% with micrognathia and high arched palate.

Although, MSX1 gene is outside the WHSCR, in people with Wolf-Hirschhorn syndrome it is frequently deleted. Previous studies reported the critical role of MSX1 in dental, lip, and palate development [62, 63]. Some people with Wolf-Hirschhorn syndrome present mutations of MSX1 gene. It is expected that deletion of MSX1 gene might disrupt the formation of oral structures in early development, causing missing teeth and other dental abnormalities associated with an opening in the roof of the mouth (cleft palate) and/or a split in the upper lip (cleft lip). Nieminen et al. considered that haploinsufficiency of MSX1 gene is a possible mechanism for selective tooth agenesis 1 but a single copy of the gene is not sufficient to produce the oral cleft phenotype [64].

4.7 Sporadic tooth agenesis

Tooth agenesis cases are either familial or sporadic. Sporadic cases are commonly considered to be nonhereditary, with low risk for relatives or offspring.

By definition, a sporadic disorder arises in the absence of evidence for a heritable or environmental etiology. Affected individuals occur occasionally in families with no reported medical history of tooth agenesis. Consequently, apparently sporadic tooth agenesis may be not inherited from parents but may arise from different aetiologies. Fisher et al. considered that apparently sporadic disorders imply genetic or environmental factors. Sporadic cases can arise from new mutations in germs cells or somatic cells, as well as disorders with an environmental cause [65].

Usually, environmental factors may cause arrested tooth development. Different kinds of trauma in the dental region, such as fractures, surgical procedures on the jaw, and extraction of the preceding primary tooth are mentioned in the literature, as reviewed by Arte [18]. Furthermore, Vastardis H. [46] reported that dental agenesis in association with other developmental abnormalities may occur because of syphilis, scarlet fever, rickets or nutritional disorders during pregnancy or childhood that act in the early stages of a developmental process. Besides, the authors emphasized the effects of cranial irradiation on endocrine function and tooth development.

5. Genetic testing and diagnosis

Tooth agenesis is diagnosed by intraoral examination (teeth did not erupt), radiographic assessment of oral cavity (no visible mineralization), and a detailed dental history to rule out extractions and trauma. Unusual spacing in a child's dentition should lead the parent or dentist to suspect tooth agenesis. Occasionally, tooth agenesis could be a clinical sign of a possible underlying syndrome and not only an isolated disease. Referrals to genetic specialists should be considered if a dentist suspects a patient is affected with tooth agenesis.

Using genetic testing, it is possible to screen or diagnose a patient and make a precise etiological diagnosis. Tooth agenesis may occur without a family history, although it is often familial. Monogenic forms of tooth agenesis have a strong genetic component and genetic testing has usually a confirmatory role. The known mutations in some genes can be screened for early signs of developing problems and identification of the individuals at risk.

The analysis is available for genes involved in both syndromic and non-syndromic forms of tooth agenesis, but the test is expensive, and it is not always covered by health insurance.

Known genotype–phenotype correlations can be used for mutation detection. Clinical features in tooth agenesis might be predictive of underlying genotype. For example, if specific teeth are missing, such as maxillary first premolars associated with MSX1 mutations or lateral incisors associated with WNT10B mutations, tooth agenesis pattern gives clue to the most appropriate genetic tests to follow. Genetic testing panel for selective tooth agenesis analyses changes in nine genes at once. Looking for tooth agenesis-associated gene mutations, MSX1, PAX9, WNT10A, LRP6, EDA, WNT10B cause non-syndromic selective tooth agenesis, AXIN2 causes oligodontia-colorectal cancer syndrome, LTBP3 causes dental anomalies and short stature, and PTH1R causes primary failure of tooth eruption.

http://ctgt.net/panel/oligodontia-selective-tooth-agenesis-ngs-panel

Combining the clinical features with genetic data is possible to increase precision in diagnosis, assess prognosis, and prediction of treatment response, provide information for healthcare management and family planning. Genetic counseling is indicated if an individual has a positive family history. For example, Boogaard et al. [43] consider that by including WNTA10A in the DNA diagnostics of isolated tooth agenesis, the yield of molecular testing in this condition was significantly increased from 15% to 71%.

6. Tooth agenesis associated with other clinical features

Several dental anomalies have been reported in association with congenitally missing teeth. Tooth number reduction is frequently associated with a reduction in tooth size of (microdontia), altered crown morphology (molars with fewer cusps), short-rooted teeth, and enlarged tooth body and pulp chamber (taurodontic molar). The fusion of primary teeth is often followed by hypodontia in the permanent successors.

6.1 Clefting and tooth agenesis

Clefting, or an aberrant space between normally fused tissues, usually occurs as either cleft lip with or without cleft palate (CL/P) or cleft palate only (CPO). Whether cases of clefts with dental anomalies should be considered isolated or syndromic cleft can be debated. However, the co-occurrence of cleft lip/palate and tooth agenesis is sometimes described as CL/P-hypodontia syndrome. Arte [18] described hypodontia as a very common anomaly in patients with oral and facial clefts. More studies analyzed tooth agenesis patterns in unilateral/bilateral, complete/incomplete, CL, CL/P or CPO, inside or outside the cleft region.

Published data show that tooth agenesis is more frequently observed in patients with cleft lip and palate (CLP) or their unaffected sisters and brother than in the general population because of close relationship between tooth and cleft formation with respect to the critical time of development and anatomical position [66–69]. Bartzela et al. reported a higher prevalence of dental anomalies in people with cleft

lip and palate than in the non-cleft population, even outside of the cleft region. They studied tooth agenesia patterns in human unilateral and bilateral cleft lip and palate and identified more than 50 different patterns of missing teeth. The most common pattern involved maxillary lateral incisors, and maxillary and mandibular second premolars. The frequency of tooth anomalies seems to be related to the severity of the cleft type. The prevalence of missing teeth reaches 100% in patients with the most severe type of isolated cleft, such as complete bilateral mixed clefting phenotype.

The prevalence of tooth agenesis in people complete unilateral cleft lip and palate has been reported within a range of 48.8% to 75.9% inside the cleft area. The prevalence outside the cleft region was found to be between 27.2% and 48.8% [66]. when compared with the prevalence of tooth agenesis in general population, which ranges between 3.2% to 7.6%, the prevalence of tooth agenesis in non-affected siblings of cleft lip and palate patients was found to be 11.1% outside the cleft area [11, 70].

The high prevalence of missing teeth outside of cleft region suggests the common genetic background for both tooth agenesis and clefts. So, odontogenesis and palate formation are developmentally related events, and one gene or few genes, might be involved in both processes, in common genetic pathways. Other studies reported no absence of permanent teeth in the maxillary arch outside the cleft (distal to the canines) in unoperated patients with cleft, suggesting that the surgical procedure done to close palatal clefts disrupts the formation of the developing tooth buds, as reviewed by Slayton et al [68].

Slayton et al. provided an overview of published data related to similar genetic component for non-syndromic simultaneous presence of both orofacial clefts and hypodontia. The combined phenotype of tooth agenesis with orofacial clefts outside the cleft region was described in both humans and animal models and provide evidence to support a common genetic etiology. Mouse knockout models for deficiency of MSX1 and PAX9 failed to form teeth and had cleft palate [68].

Few monogenic disorders, such as Van der Woude syndrome (caused by mutation in the IRF6 gene - interferon regulatory factor 6), ectrodactyly-ectodermal dysplasia-clefting syndrome 3 (caused by mutation in the TP63 gene - tumor protein p63), and Kallmann's syndrome (caused by mutation in the FGFR1 gene - fibroblast growth factor receptor 1) have both clefting and hypodontia as typical phenotypic findings (**Table A1**). It should be pointed out that the same gene, IRF6 (interferon regulatory factor 6) may cause a disease as rare as Van der Woude syndrome and also to contribute to much more common defects, such as isolated cleft with or without cleft palate [71].

6.2 Disturbances of teeth eruption and tooth agenesis

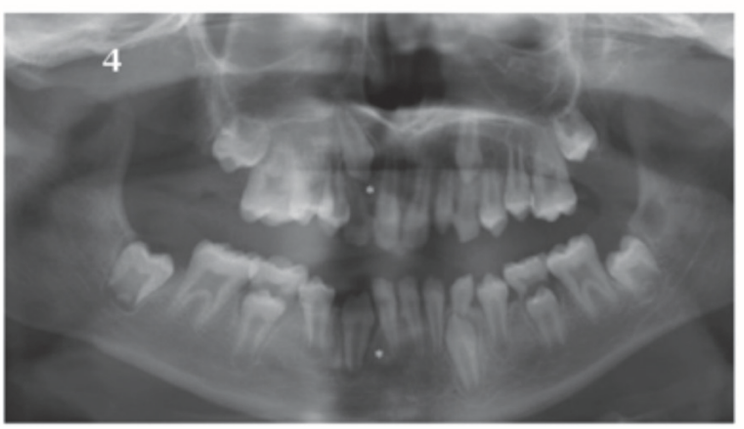
Primary failure of tooth eruption (OMIM 125350) was reported in association with hypodontia. The most affected teeth are first, and second molars and involvement can be unilateral or bilateral. Based on family studies, the reported pattern of inheritance was consistent with autosomal dominant ones and molecular cause involved mutation of PTHR1 gene (parathyroid hormone 1 receptor) located on 3p21.31 [72]. Regarding permanent dentition, delayed development of posterior permanent teeth in association with the third molar agenesis was reported in the literature, as reviewed by Nieminen [3]. An average delay of two years was observed, with great variation, in a group of 85 patients with agenesis of on the average seven permanent teeth. It was also reported excessive retardation of development of teeth contralateral to missing teeth. Schalk-van der Weide [25] reported a tendency of early developing teeth of males to be retarded in association with

severe agenesis, and in females with severe agenesis second mandibular molars to be significantly delayed in development (only mandibular teeth were studied). The delay correlated with the extent of agenesis was most prominent in positions next to the teeth that had failed to develop.

6.3 Reduction in tooth size and shape

In population studies the relationship of tooth agenesis and microdontia has been shown to be statistically significant. Microdont teeth is small enough to be outside the usual limit of variation and along with the reduction in size, these teeth often exhibit a change in shape. Microdont teeth may be either usual form or with tapering (peg or conical) crowns (**Figure 8**). The most common form of microdontia is localized type, affecting maxillary incisors. Peg maxillary lateral incisors are seen in 1.2 to 3.2% of general population. This is a genetic trait which is manifest as either peg or missing maxillary lateral incisors. The microdont teeth show an autosomal dominant inheritance pattern and variable expressivity. Some studies reported families in which both genitors have pegged permanent maxillary lateral incisors. Their children had severe tooth agenesis involving primarily agenesis of succedaneous permanent teeth. It was suggested that children expressed the gene mutation in homozygous status. Some studies reported a 2:1 preference for the left side. In addition, reduced tooth sizes have also been observed within the healthy





	Right quadrants	Left quadrants
Upper teeth (maxillary)	8 7 6 5 4 3 2 1 *	* 1 2 3 4 5 6 7 8
Lower teeth (mandibular)	8 7 6 5 4 3 2 1 *	1 2 3 4 5 6 7 8 *

Figure 8.
*Tooth agenesis in a down syndrome male patient, aged 8 years old. (1–3) intraoral evaluation shows the absence of the right lateral incisors both in the upper and lower arches. (4) the panoramic radiograph confirms the agenesis of maxillary right lateral incisor which is associated to a peg-shaped in the contralateral quadrant. Moreover, agenesis of the lower right lateral incisor is also revealed together with a hypotaurodontism in all four first molars. * position of the missing teeth.*

relatives of patients with severe tooth agenesis [3]. Baccetti [73] reported a significant reciprocal association between agenesis of second premolars and reduced upper lateral incisors. Third molar agenesis was associated with reduction in the cusp number of the molars, as reviewed by Arte [18]. The association of microdontia and tooth agenesis is frequently observed in Down syndrome and various types of ectodermal dysplasia. Generalized microdontia of all teeth is extremely rare in people without some sort of syndrome.

6.4 Malposition of teeth

Abnormal positions, or ectopic placement, of teeth (OMIM 189490) are believed to result from a disturbance of the tooth developmental structure. Various forms of the position or eruption disturbance of teeth tend to be associated with tooth agenesis. Differences in frequencies of the abnormal trait between population groups have been observed, as well as differences in the pattern of associations among displaced maxillary canines (a typical type of malposition of canines) and tooth agenesis.

Pirinen et al. [74] studied the palatal displacement of the canine in regard to congenital absence of permanent teeth in 106 Finnish probands and their first- and second-degree relatives. All the probands had had surgical and orthodontic treatment for displaced maxillary canines. Incisor-premolar hypodontia and peg-shaped incisors were found to be strongly associated with palatally displaced canines. The authors concluded that palatally displaced canine belongs to a spectrum of dental anomalies related to incisor-premolar hypodontia.

Peck et al. reported a strong association of displaced maxillary canines with third molar agenesis and second premolar agenesis, whereas upper lateral incisor agenesis was not significantly interrelated [75]. Garib et al. reported an increased occurrence of displaced maxillary canines associated with second premolars agenesis [76]. Lagana et al. concluded that only the agenesis of maxillary lateral incisors should be considered directly connected with displaced maxillary canine [77].

6.5 Taurodontism

Taurodontism (OMIM 272700) is characterized by large pulp chambers, with changes usually most striking in the molars. The taurodont tooth lies deep in alveolar bone. Taurodont teeth are associated with missing teeth in chromosome aneuploydies, such as Down syndrome (**Figure 9**). It occurs also in other syndromes, especially those having an ectodermal defect, e.g., otodental dysplasia. A family having affected sibs with a combination of sparse hair, oligodontia, and taurodontism was reported in the literature [78].

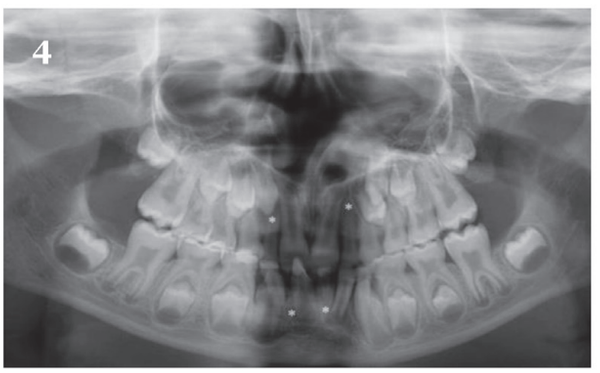
6.6 Rotation of premolars and/or maxillary lateral incisors

It has been documented by Baccetti T. [73] that rotation of premolars is significantly associated with missing upper lateral incisors. The author found a significant association between unilateral agenesis of upper lateral incisors and rotation of the lateral incisor on the other side of the dental arch, and between unilateral agenesia of premolars and rotation of premolars on the other side of the arch.

6.7 Enamel hypoplasia, hypocalcification

The finding that there is a significant association between enamel hypoplasia and hypodontia not involving systemic syndromes has been reported by Baccetti T. [73]





	Right quadrants	Left quadrants
Upper teeth (maxillary)	* 8 7 6 5 4 3 2 1	* 1 2 3 4 5 6 7 8
Lower teeth (mandibular)	8 7 6 5 4 3 2 1 *	1 2 3 4 5 6 7 8 *

Figure 9.
*Multiple tooth agenesis in an 8-year-old male patient with down syndrome. (1,2,3) examination of the dental arches reveals a mixed dentition, with a delayed tooth eruption pattern. (4) panoramic radiograph showing the absence of both the lateral incisors in the maxillary arch and the agenesis of the lower right lateral incisor and the left central incisor. Moreover, the agenesis is associated with mesotaurodont first molars in both upper and lower arches * position of the missing teeth.*

and Lai et al. [79] It may indicate a common genetic origin for both dental anomalies. However, it also is possible that a single or concurrent environmental factor may have been responsible for the etiology of both defects. Some authors have noted that local infection, as well as radiation, may cause both hypodontia and enamel hypoplasia, as review by Lai et al. [79]

6.8 Concomitant hypo-hyperdontia (CHH)

Concomitant hypo-hyperdontia (CHH) is a rare mixed numeric dental anomaly characterized by congenitally missing teeth and supernumerary teeth occurring in the same individual. These two conditions are considered as the opposite extremes in the development of the dentition [80]. The prevalence of CHH was found to range from 0.002 to 0.7%. Due to its rarity and sporadicity, the causes of CHH have been completely unknown. So far, only 80 cases have been reported in the literature. Wang et al. summarized prior research and concluded that more than two-thirds of cases had one supernumerary tooth, and the remaining, two or more teeth. The most commonly supernumerary tooth was mesiodens. Most frequently missing teeth were upper lateral incisors, lower incisors, and premolars. Only a few cases had canines and molars agenesis. Both jaws were affected, bimaxillary hypo-hyperdontia, in about three fourth of the cases. The remaining one-fourth presented maxillary hypo-hyperdontia, the only maxilla being involved [81]. In most cases,

CHH was diagnosed during a regular dental examination. Recently, Wang et al. [81] presented 21 cases of CHH, including 4 familial cases and a syndromic case, and scrutinized their dental phenotypes. Their study results indicated molar taurodontism as the most frequently (29%) observed concurrent dental anomaly of CHH. They also described the fusion of primary lower lateral incisors and canines followed by missing permanent lower laterals. More results described the central cusps of premolars identifiable from the panoramic radiograph of 3 cases. Only one case presented macrodontia of tooth number 9 (upper left central incisor), a premaxillary supernumerary toothand missing tooth number 10 (upper left lateral incisor). The authors concluded," these concurrent dental aberrations suggested that molecular and cellular mechanisms regulating tooth number also play significant roles in tooth morphogenesis".

7. Conclusions

Tooth agenesis has a high prevalence in human population. It was documented that missing tooth has a negative impact on daily quality of life causing significant complications, such as physical appearance problems, oral functional limitations, or psychosocial distress, and cost not only for the affected individual but also for the public health care system worldwide. Early diagnosis is still the best way to prevent complications of missing teeth but understanding the genetic make-up of affected individuals, the dentist must integrate the tools of genetics in the dental practice for prediction, prevention, and personalized dental therapy.

Conflict of interest

The authors declare no conflict of interest.

Appendix 1 – Table A1

Syndrome name and prevalence	Tooth agenesis - levels of severity	Associated phenotypic features by region	Genetic cause	Inheritance	OMIM Orpha-code
ADULT syndrome *acro-dermato-ungual-lacrimal-tooth* <1/1,000,000	**Hypodontia / Oligodontia** associated dental anomalies: small teeth, dysplastic teeth, premature loss of secondary teeth (<25 years)	*Eyes* • Lacrimal duct obstruction • Conjunctivitis *Breasts* • Breast hypoplasia • Mammary gland hypoplasia • Widely spaced nipples • Absent nipples • Hypoplastic nipples *Hands and feet* • Ectrodactyly • Syndactyly *Skin* • Ectodermal dysplasia • Atrophic skin • Thin skin • Dry skin • Freckling • Photosensitive skin • Dermatitis • Adermatoglyphia *Nails* • Dysplastic nails • Nail pits *Hair* • Blond hair • Thin scalp hair • Sparse axillary hair • Premature scalp hair loss (>30 years)	mutations of TP63 gene (tumor protein p63) 3q28	AD	103285 978

Syndrome name and prevalence	Tooth agenesis - levels of severity	Associated phenotypic features by region	Genetic cause	Inheritance	OMIM Orpha-code
Axenfeld-Rieger syndrome, type 1 1/200,000	**Hypodontia** (maxillary incisors)	*Face* • Maxillary hypoplasia • Short philtrum • Prominent supraorbital ridges *Eyes* • Iris dysplasia (goniodysgenesis) • Iris hypoplasia • Prominent Schwalbe line (posterior embryotoxon) • Glaucoma • Displaced pupils • Dyscoria • Polycoria • Aniridia • Microcornea • Megalocornea • Strabismus *Nose* • Broad nasal bridge *Mouth* • Thin upper lip **ABDOMEN** *External Features* • Umbilical defect (redundant periumbilical skin) *Gastrointestinal* • Imperforate anus • Anal stenosis **GENITOURINARY** *External Genitalia (Male)* • Hypospadias	mutations of PITX2 (paired-like homeodomain transcription factor 2) 4q25	AD Genetic heterogeneity Variable expressivity	180500 782

Syndrome name and prevalence	**Tooth agenesis - levels of severity**	**Associated phenotypic features by region**	**Genetic cause**	**Inheritance**	**OMIM Orpha-code**
		ENDOCRINE FEATURES • Growth hormone deficiency			
Ectodermal dysplasia 3, Witkop type 1–2/10,000	Normal to small primary teeth Partial to total absence of permanent teeth (**anodontia**)	*Face* • Normal facies *Mouth* • Lip eversion *Skin* • Normal sweat glands *Nails* • Thin, small friable nails • Koilonychia • Longitudinal ridging • Nail pits • Toenails often more affected than fingernails • Nail changes improve with age *Hair* • Normal hair	mutations of MSX1 (muscle segment homeobox 1) 4p16.1	AD	189500 2228
Ectrodactyly, Ectodermal Dysplasia, and cleft lip/palate syndrome 3; EEC type 3 1–9/100.000	**Selective tooth agenesis** Microdontia Caries	*Face* • Maxillary hypoplasia • Malar hypoplasia *Ears* • Hearing loss • Small ears • Malformed auricles *Eyes* • Blue irides • Photophobia • Blepharophimosis • Blepharitis • Dacryocystitis	mutations of TP63 *(tumor protein p73-like; tp73l p53-related protein p63)* 3q28	AD	604292 1896

Syndrome name and prevalence	Tooth agenesis - levels of severity	Associated phenotypic features by region	Genetic cause	Inheritance	OMIM Orpha-code
		• Lacrimal duct abnormalities *Nose* • Flat nasal tip *Mouth* • Cleft lip • Cleft palate • Xerostomia • Absence of Stensen duct **ENDOCRINE FEATURES** • Growth hormone deficiency • Hypogonadotropic hypogonadism • Central diabetes insipidus			
Hypohidrotic ectodermal dysplasia 1 (XHED) or Christ-Siemens-Touraine syndrome 1/15,000 (1/50,000 to 1/100,000 male births)	**Hypodontia** **Adontia** Microdontia Conical teeth Taurodontism	*Head* • Small cranial length *Face* • Frontal bossing • Hypoplastic maxilla • Small chin • Small facial height • Prominent supraorbital ridges *Eyes* • Periorbital wrinkles • Periorbital hyperpigmentation • Absent tears • Absent miebomian glands • Scant-absent eyebrows • Scant-absent eyelashes *Nose* • Small nose • Hypoplastic alae nasi • Nasal mucosa atrophy	mutations of EDA (ectrodysplasin A) Xq13.1	X-linked recessive Xq13.1 Heterozygous females show variable expressivity (mild to severe manifestations) including hypodontia, conical teeth, reduction in scalp/body hair, and difficulty nursing	305100 238468

Syndrome name and prevalence	Tooth agenesis - levels of severity	Associated phenotypic features by region	Genetic cause	Inheritance	OMIM Orpha-code
		• Ozena • Depressed nasal root and bridge ('saddle nose') *Mouth* • Decreased palatal depth • Prominent lips **RESPIRATORY** • Respiratory difficulties *Nasopharynx* • Atrophic rhinitis • Atrophic pharyngeal mucosa • Hypoplastic or absent mucous glands which may lead to dried secretions and obstruction *Larynx* • Atrophic mucosa causing dysphonia **CHEST** *Breasts* • Hypoplastic-absent mammary glands • Hypoplastic-absent nipples **SKIN, NAILS, & HAIR** *Skin* • Hypohidrosis • Anhidrosis • Sweat pore aplasia • Soft, thin skin • Dry skin • Mild localized pigmentation abnormalities • Skin peeling/scaling (newborn)			

Syndrome name and prevalence	Tooth agenesis - levels of severity	Associated phenotypic features by region	Genetic cause	Inheritance	OMIM Orpha-code
		• Eczema • Periorbital wrinkling • Periorbital hyperpigmentation • Hypoplastic-absent sebaceous glands • Hypoplastic-absent eccrine sweat glands *Nails* • Spoon-shaped nails *Hair* • Hypotrichosis • Fine, brittle hair • Scanty hair • Absent or scanty eyelashes • Absent or scanty eyebrows • Blonde, fine scalp hair **VOICE** • Hoarse voice due to dry laryngeal mucosa **METABOLIC FEATURES** • Intolerance to heat and fevers • Susceptible to hyperthermia			
Kallmann syndrome 2 hypogonado-tropic hypogonadism 2 with or without anosmia; HH2 1/8,000 males and 1/40,000 females, but is probably underestimated.	**Tooth agenesis, variable in number** (in some patients)	**HEAD & NECK** *Ears* • Hearing loss, unilateral (rare) *Eyes* • Iris coloboma (rare) *Nose* • Hyposmia/anosmia (in some patients) • Absence of nasal cartilage, unilateral (rare)	mutation of FGFR1 (fibroblast growth factor receptor 1) 8p11.23	AD	147950 478

Syndrome name and prevalence	Tooth agenesis - levels of severity	Associated phenotypic features by region	Genetic cause	Inheritance	OMIM Orpha-code
		Mouth • Cleft lip • Cleft palate **SKELETAL** • Osteopenia (in some patients) *Hands* • Clinodactyly (rare) • Fusion of fourth and fifth metacarpal bones (rare) • Ectrodactyly (rare) *Feet* • Ectrodactyly (rare) **ENDOCRINE FEATURES** • Hypogonadotropic hypogonadism • Delayed or absent puberty • Low to undetectable gonadotropin levels • Low testosterone level • Low estradiol level **GENITOURINARY** *External Genitalia (Male)* • Micropenis • Cryptorchidism *Internal Genitalia (Female)* • Primary amenorrhea			
KBG syndrome *macrodontia, mental retardation, characteristic facies, short stature, and skeletal anomalies* unkown prevalence	**Oligodontia** Associated dental anomalies: macrodontia of the upper central incisors, wide upper central incisors, ridged teeth, fused incisors	*head* • microcephaly *face* • round face early in life • triangular face later in life • long philtrum	ankrd11 (ankyrin repeat-containing cofactor 1) 16q24.3	AD	148050 2332

Syndrome name and prevalence	Tooth agenesis - levels of severity	Associated phenotypic features by region	Genetic cause	Inheritance	OMIM Orpha-code
		ears • large prominent ears *eyes* • hypertelorism • telecanthus • long palpebral fissures • broad bushy eyebrows *nose* • anteverted nares • hypoplastic alae nasi **chest** *ribs sternum clavicles & scapulae* • cervical rib fusion • accessory cervical ribs **genitourinary** *internal genitalia (male)* • cryptorchidism **skeletal** • delayed bone maturation *spine* • vertebral body fusion • vertebral arch abnormalities • thoracic kyphosis *hands* • clinodactyly • decreased hand length • syndactyly **skin, nails, & hair** *skin* • simian crease *hair* • broad bushy eyebrows			

Syndrome name and prevalence	Tooth agenesis - levels of severity	Associated phenotypic features by region	Genetic cause	Inheritance	OMIM Orpha-code
		• low anterior hairline • low posterior hairline **neurologic** *central nervous system* • developmental delay • mental retardation • eeg anomalies (in some patients) • seizures (in some patients)			
Oral-facial-digital syndrome, type 1 *(*OFD1) 1/50,000 – 1/250,000	Dental caries Anomalous anterior teeth Enamel hypoplasia Supernumerary teeth **Missing teeth**	*Head* • Microcephaly *Face* • Frontal bossing • Facial asymmetry • Microretrognathia • Hypoplasia of the malar bones *Ears* • Low-set ears • Hearing loss *Eyes* • Epicanthus • Hypertelorism • Telecanthus • Downslanting palpebral fissures *Nose* • Broad nasal bridge • Hypoplastic alar cartilage *Mouth* • Hyperplastic oral frenuli • Buccal frenuli • Median cleft lip (in 45% of patients)	mutations of OFD1 gene Xp22.2	X-linked DOMINANT Xp22.2 (usually lethal in males)	311200 2750

Syndrome name and prevalence	Tooth agenesis - levels of severity	Associated phenotypic features by region	Genetic cause	Inheritance	OMIM Orpha-code
		• Pseudocleft of the upper lip • Lobulated tongue (30–45%) • Bifid tongue (30–45%) • Tongue nodule • Cleft palate • Tongue hamartoma (70%) • High-arched palate • Thickened alveolar ridges • Irregular margin of the lips **CARDIOVASCULAR** *Heart* • Cardiac anomalies **ABDOMEN** *Liver* • Fibrocystic liver (45%) • Dilatation and beading of the intrahepatic bile ducts • Hepatic fibrosis *Pancreas* • Pancreatic cysts (29%) **GENITOURINARY** *Internal Genitalia (Female)* • Ovarian cysts *Kidneys* • Adult onset polycystic kidney (50%) **SKELETAL** *Hands* • Abnormalities of the fingers (45%) • Clinodactyly • Syndactyly • Brachydactyly			

Syndrome name and prevalence	Tooth agenesis - levels of severity	Associated phenotypic features by region	Genetic cause	Inheritance	OMIM Orpha-code
		• Polydactyly, preaxial or postaxial (rare) • X-ray shows irregular pattern of radiolucency and/or spicule-like formation in metacarpals and phalanges *Feet* • Abnormalities of the toes (25%) • Duplication of the hallux • Polydactyly, preaxial or postaxial (rare) **SKIN, NAILS, & HAIR** *Skin* • Milia of upper face and ears (infancy) • Dry scalp *Hair* • Dry, rough, sparse hair • Alopecia **NEUROLOGIC** *Central Nervous System* • Variable mental retardation (40%) • Central nervous system malformations (40%) • Abnormal gyrations • Absence of corpus callosum • Gray matter heterotopias • Myelomeningocele (rare) • Stenosis of the aqueduct of Sylvius (rare) • Hydrocephalus • Arachnoid cysts			

Syndrome name and prevalence	Tooth agenesis - levels of severity	Associated phenotypic features by region	Genetic cause	Inheritance	OMIM Orpha-code
		• Cerebellar abnormalities • Seizures • Hypothalamic hamartoma • Porencephaly *Behavioral Psychiatric Manifestations* • Major depression (rare) **LABORATORY ABNORMALITIES** • Abnormal liver enzymes in those with hepatic cysts or fibrosis • Proteinuria in those with cystic kidneys			
Van der Woude syndrome 1 (VWS1) 1/35,000 – 1/100,000	**Hypodontia**	*Mouth* • Lower lip pits • Cleft lip • Cleft palate • Cleft uvula	mutations of IRF6 gene (interferon regulatory factor 6) 1q32.2	AD	119300 888

Table A1.
Tooth agenesis associated frequent in genetic syndromes based on OMIM database.

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