Tooth agenesis: genes and syndromic diseases – literature review

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INTRODUCTION AND OBJECTIVE

Tooth developmental disorders are a common abnormality expressed in quantitative and qualitative changes. Congenital lack of tooth buds is one of the most common dental malformation and occurs with a frequency of 1.6% – 9.6% in various geographical areas and among races [1], most often concerning the permanent dentition. The least common anomaly includes the canines and central incisors of the jaws [2], as well as the deciduous dentition, where it was found with a frequency of 0.4% – 0.9% [3], an anomaly affecting more women than men. Depending on the number of missing buds, it can be classified into: hypodontia – missing one or several teeth (not counting the third molars), oligodontia – at least 6 teeth missing, and anodontia – all teeth missing. The development of primary teeth begins in the 4th week in utero, while the development of permanent teeth around 24 weeks of age. Proper development of dental tissues that form during embryogenesis depends on a series of epithelial-mesenchymal interactions mediated by signaling pathways. Many growth factors, receptors and transcription factors are shown to play key roles during odontogenesis [4].

Over the years, numerous theories of agenesis have been developed, of which the most popular seems to be genetic, phyllogenetic, environmental, neurogenic and premature ossification of the Turkish saddle [5]. However, the main causes of dental agenesis are genetic mutations. The gene or group of genes, as well as the environmental factors that change during the formation of tooth buds, lead to a qualitative, quantitative or change in the function of the formed protein. Mutations cause disturbances at the level of molecular interaction, leading to tooth anomalies that may concern the colour, shape or number of teeth [4, 5].

In recent years, the genetic code has been analyzed using modern techniques, such as DNA sequencing and experimental research on animals, which allowed identification of some genes responsible for the inhibition of tooth development [4]. Numerous genes have been found to be involved in the formation of tooth buds, the main ones including AXIN2, TGFA, MSXI, PAX9, IRF6, and FGFR1, which code signals, receptors, signalling mediators, and the expression of a given gene in the cell nucleus. Chromosomal defects and mutations within the above-mentioned genes responsible for the development of teeth and disorders in their signal pathway, may lead to various forms of agenesis in deciduous and permanent teeth [4].

OBJECTIVE AND REVIEW METHODS

The aim of this study was to present a review of the literature on the etiology of dental agenesis, with particular emphasis...
on the genetic background and associated congenital abnormalities. 32 articles from the last 18 years from the following databases were qualified for the study: Pubmed, GoogleScholar and Scopus. Inclusion criteria: congenital disorders, syndromic disease, children, with missing teeth, tooth agenesis.

**DESCRIPTION OF THE STATE OF KNOWLEDGE**

Formation of tooth buds – characteristics of the best-known genes in the process of odontogenesis. Many genes are involved in both isolated and syndromic tooth agenesis. The most studied and involved in the development of this anomaly are: MSX1, PAX9, AXIN2, WNT10A, EDA, TGF, SHH.

**FGF.** The FGF family consists of 19 different growth factors active in facial and mesenchymal epithelial cells, and are involved in cell proliferation. The genes of the FGF family are essential in the process of osteogenesis and chondrogenesis. Mutations within this growth factor lead to disorders such as craniosynostosis, cleft palate. Fgf13 and Fgf10 ligands are derived from the mesenchyme and are responsible for the multiplication of incisal epithelial stem cells, thus disturbances within them lead to inhibition of incisor growth, while inactivation of the Fgf2 ligand stops the development of the tooth at the budding stage [4].

**MSX1.** The MSX1 gene plays an important role in craniofacial development, particularly in odontogenesis. There is evidence that mutations in the MSX1 gene may be associated with cleft lip and palate pathogenesis. MSX1 became the first gene identified in human non-syndromic tooth agenesis. The most distinguishing feature of tooth hypodontia associated with MSX1 is the frequent absence of the second premolars and third molars (75%). Mutations in MSX1, encoding a transcriptional repressor in the loop of both Wnt and BMP4 pathways, have been repeatedly found to cause no-syndromic tooth agenesis, and are most often associated with isolated tooth deficiencies. Patients with MSX1 mutations showed isolated tooth agenesis (62.02%), oral clefts (21.25%), Wiktop syndrome (10%) or Wolf-Hirschhorn syndrome (6.25%) [1, 6, 7].

**WNT.** A group of molecules that contribute to the regulation of growth processes within the orofacial tissues and the development of teeth. These molecules are expressed during the initiation of the tooth development process. In mice, inactivation of Wnt leads to reduced facial growth, cleft lip with or without cleft palate, and decreased expression of the Wnt factor in the mesenchyme during tooth bud formation leads to a reduction in tooth size. Research shows that mutations within WNT10A are the most common cause of isolated hypodontia and oligodontia. Bi-allelic WNT10A mutations are usually associated with a larger number of missing teeth, compared to mono-allelic mutations. They also cause other dental disorders: abnormal shape of roots and crowns, molar taurodontism, and are associated with odonto-onycho-dermal dysplasia and Schöpf-Schultze-Passarge syndrome [2, 4].

**TGF.** A family involved in all stages of tooth development, which also include BMP and Activins. TGF-ß regulates craniofacial development in mice. Inactivation of TGF-ß, or mutations in the receptor, lead to lip and palate clefts. BMP act as bi-directional signalling agents between the epithelium and the mesenchyme. BMP2 and BMP4 are present in the epithelium of the nose and jaw. Inhibition and over-expression within the signalling pathways of BMP molecules lead to cleft lip. The BMP signal is important in tooth bud formation as it controls the cells and molecules involved in it. Abnormalities in the signalling pathways of BMP molecules in mice lead to changes in the shape and size of the face, as well as the absence of mandibular molars, reduced size of maxillary molars, changes in the shape of the crown or reduced number of roots [4].

**PAX.** PAX9 is the most common gene for non-syndromic dental agenesis. In PAX9-deficient mice, the development of teeth and taste buds is arrested and a cleft palate can be noted. The PAX9 gene appears to be at the top of the hierarchy of the odontogenic pathways as it induces activation of both Wnt and TGF-ß / BMP signalling for organogenesis. In patients with PAX9 mutations, hypodontia occurred in 8.33% and oligodontia in 91.67% of cases [1, 6].

**SHH.** Is the most important growth factor, and mutations within this factor are associated with the abnormal development of the face and teeth, leading to such anomalies as lip and palate clefts, and changes in the size and shape of the face. SHH is a factor present during important phases of tooth development: initiation of tooth formation, formation of the morphology of the tooth crown, and tooth size. Disruption of the SHH signalling pathway is responsible for defective jaw growth and development, and for premature fusion of left and right parts of the dental lamina, leading to the fusion of incisor buds. Mice with SHH defect exhibit delayed tooth eruption and delayed root development [4].

**Tooth agenesis in congenital disorders.** Dental agenesis may present as an isolated defect or may be associated with more than 60 different congenital syndromes (Tab. I).

Down syndrome (DS) is one of the most common chromosomal abnormalities worldwide, occurring with a frequency of 1 in 600 – 1,000 live births. Dental agenesis in people with DS occurs with a frequency of about 54.6 – 58.5%, not including third molars. The most common missing teeth are the maxillary lateral incisors (27%), the second – mandibular premolars (21%) and the second maxillary premolars (18%). People with DS are particularly vulnerable to periodontal disease. Other disorders include macroglossia, taurodontism, mouth breathing, bruxism, microdontia and malocclusion [8,9].

**Hypohydrotic ectodermal dysplasia (HED).** A group of genetic developmental disorders manifested by improperly developed structures of ectodermal origin: teeth, hair, nails, and skin glands. The disease affects 1 in 100,000 children and is more common in boys. The symptoms of this craniofacial disease include agenesis of the teeth, variability in size and shape of the teeth (e.g. conical teeth), problems with tooth eruption, and decreased salivation. The most common type of HED inheritance is the gender-linked form. The literature also describes an autosomal dominant inheritance associated with a mutation in the EDAR gene. Mutations in the WNT10A, AXIN2, MSX1 and PAX9 genes play an important role in tooth agenesis in people with HED [9–13].
Table 1. Syndromes associated with tooth agenesis

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Inheritance pattern</th>
<th>Prevalence rate</th>
<th>Tooth agenesis</th>
<th>Genes responsible for tooth agenesis</th>
<th>Range of dental abnormalities</th>
<th>Cleft lip / palate</th>
<th>Anomalies of the maxilla / mandible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Down syndrome</td>
<td>Not inherited</td>
<td>1:600-1000</td>
<td>Yes</td>
<td>TRISOMY 21</td>
<td>Taurodontism, Bruxism, Microdontia</td>
<td>Yes</td>
<td>Micrognathia</td>
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<td>Palaska et al., 2016 [8]; Shimizu et al., 2009 [9]</td>
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<tr>
<td>Hypohydrotic ectodermal dysplasia</td>
<td>Autosomal-dominant</td>
<td>1:100,000</td>
<td>Yes</td>
<td>EDA, WNT10A, AXIN2, MSX1 PAX9</td>
<td>Size/shape abnormalities – conical-peg shaped teeth, delayed eruption</td>
<td>Yes</td>
<td>Reduction in the height of alveolar crest in maxillary and mandibular arches</td>
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<td>Shimizu et al., 2009 [9]</td>
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<td>Mues et al., 2014 [10]</td>
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<td>Kishore et al., 2014 [12]</td>
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<td>Turner syndrome</td>
<td>Not inherited</td>
<td>1:2500</td>
<td>Yes</td>
<td>WNT10A</td>
<td>Short, narrow roots, premature eruption, size/shape abnormalities</td>
<td>Yes</td>
<td>Retrognathia, retrognathia</td>
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<td>Pasaday et al., 2020 [14]; Thiesen et al., 2015 [15]</td>
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<td>Apert’s Syndrome</td>
<td>Autosomal dominant</td>
<td>1:65,000–100,000</td>
<td>Yes</td>
<td>MSX, FGFR2</td>
<td>Crowding, delayed eruption, ectopic eruption, supernumerary teeth, enamel defects</td>
<td>Yes</td>
<td>Maxillary hypoplasia</td>
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<tr>
<td>Syndrome</td>
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<td>Reitsma et al., 2014 [16]; Fekonja, 2005 [17]; Vtdiati Saberi et al., 2011 [18]; de La Dure-Molla et al., 2019 [19]; Jędryszek et al., 2009 [20]</td>
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<td>Pierre Robin syndrome</td>
<td>Not known-multifactorial</td>
<td>1:8500</td>
<td>Yes</td>
<td>MSX1</td>
<td>Microdontia, supernumerary teeth, taurodontism, dwarf roots</td>
<td>Yes</td>
<td>Micrognathia, retrognathia</td>
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<td>Jędryszek et al., 2009 [20]; Pedraza et al., 2022 [21]</td>
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**Turner syndrome.** A genetically-determined congenital anomaly caused by the complete or partial absence of one of the X chromosomes. The incidence is estimated at 1:2,500 female births. The phenotype of this disease entity consists of: short stature, webbed neck, and most often – sterility. Additionally, premature tooth eruption, retrognathia and Gothic palate may appear [14,15].

**Apert’s syndrome.** A genetically-determined congenital anomaly, occurring with a frequency of about 1 in 65,000 – 1 in 100,000 births. The features of this disease include cranial deformities caused by premature fusion of cranial sutures, syndactyly, cleft palate, and intellectual disability. The frequency of agenesis of at least 1 tooth is estimated at 46.4%. The most frequently missing teeth are the lateral incisors of the maxilla and the second premolars of the mandible [16–20].

**Pierre Robin syndrome.** A rare congenital anomaly with a prevalence estimated at 1 in 8,500 births. The most important symptoms of this syndrome include micrognathia, cleft palate and respiratory system obstruction. Tooth agenesis occurs in 3.2–7.6% of patients with this syndrome. Bilateral agenesis of mandibular second premolars is the most common [20–22].

**Tooth agenesis and rare syndromic diseases.** Multiple tooth bud agenesis also occur in rare syndromes, ranked by frequency: Rieger, Williams, Wolf-Hirschhorn, Kabuki, Van der Woude, Ellis Van Creveld, Bloch and Sulzberger, Laurence-Moon-Bied-Bardet, Goltz, Schopf-Schulz-Passarge, Franceschetti-Jadassohn, and Rapp-Hodgkin. The characteristics of these syndromes are revealed already in the prenatal or neonatal period. Among the syndromes described below, the agenesis of a large number of dental buds is a significant feature, and is directly related to the diagnosis of a given syndrome [20].

**Axenfeld-Rieger syndrome.** A syndrome associated with mutations in the PITX2 or FOXC1 genes. It is characterized by defects in the front part of the eye associated with dental abnormalities, such as microdontia, hypodontia, anodontia and maxillary hypoplasia [23,24].

**Wolf-Hirschhorn syndrome.** Caused by a deletion of the short arm of chromosome 4. The phenotypic features of this disorder include craniofacial abnormalities and intellectual disability. The size of the deletion usually determines the severity of the symptoms, and usually depends on the loss of specific genes in the terminal section of the chromosome. The loss of the MSX1 gene, which is responsible for odontogenesis and development of the facial cranium, will result in a cleft lip and/or palate, as well as dental abnormalities, including tooth agenesis [25].

**van der Woude syndrome.** Another congenital malformation. The clinical picture includes lip and palate clefts, hypodontia, and lower lip pits [26,27].

**Schopf-Schulz-Passarge syndrome.** Also known as palmar plantar keratosis, is an autosomal recessive condition associated with a mutation in the WNT10A gene. Apart from hyperkeratosis, other symptoms of this disorder include hypodontia, eyelid cysts and hair loss [28].

**Franceschetti-Jadassohn syndrome.** A rare disease with autosomal dominant inheritance caused by a specific defect in keratin protein. Patients with this syndrome have reticulated skin pigmentation, missing teeth, impaired sweat gland function, and lack of fingerprints, which is the most characteristic feature of this disease [29].

**CLINICAL MANAGEMENT**

Patients with rare syndromes require interdisciplinary treatment. Usually, the primary care physician who makes the diagnosis is a neonatologist or paediatrician, because the main clinical symptoms of a given disease entity appear in the
neonatal or infancy period. Later, patients with hypodontia should be given special dental care, as they suffer from many functional and aesthetic problems. Clinical diagnosis of dental agenesis always requires X-ray confirmation. It is recommended to perform a pantomographic X-ray, which allows exclusion of possible impaction of the teeth, and is decisive for the final diagnosis [30]. Children diagnosed with missing tooth buds should undergo comprehensive treatment which will include dentists of such specialties as: maxillofacial surgeon, dental surgeon, orthodontist or prosthodontist. Treatment in a dentist’s office may consist of an intensive prophylactic programme, making partial dentures adjusted to the age, orthodontic and conservative treatment [31].

The absence of one or several teeth seriously disrupts the proper development of a child, as tooth agenesis affects the craniofacial development and psychosomatic development of a patient at developmental age. It leads to malocclusion, speech and aesthetic disorders. This is important for our understanding of the impact of dental agenesis on the quality of life of children and their parents, and may help increase patient satisfaction from the dental aspect [1, 4, 32].

CONCLUSIONS

The review reveals that the interaction between genes, their signaling pathways and molecules are responsible for oral health, and in the case of a mutation leads to various oral pathologies. Although dental agenesis can be an isolated abnormality, there are many syndromes with manifestations of hypodontia complicated by other oral anomalies. The identification of craniofacial anomalies at an early age is of great importance for planning appropriate dental care.

REFERENCES