Genetic Causes of Congenital Tooth Agenesis

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Abstract

Differential gene expression and mutations have significant ramifications on dental development, especially regarding odontoblast development in both the primary and permanent dentition. One of the most significant effects is tooth agenesis, a condition where an individual has one or more missing teeth. This paper will expound the prevalence, major symptoms, genetic precursors, associated conditions, and health implications of congenital tooth agenesis. Although many genetic factors, external influences, and inheritance patterns contribute to the development of tooth agenesis in an individual, the three primary genes involved are MSH Homeobox 1 (MSX1), Paired Box Protein 9 (PAX9), and Axis Inhibition Protein 2 (AXIN2). The expression of these genes have a significant impact on the growth of the functional form of teeth, and this paper will investigate the connection between gene expression and its molecular impact during various stages of odontoblast development.

Introduction

Tooth agenesis, or conditions of missing teeth, is a relatively common condition in some populations, affecting anywhere from 3-11% of European/Asian populations (1). It is characterized as the developmental absence of 1 or more teeth and can be caused by multiple factors or conditions. It is diagnosed by either a clinical evaluation or radiographic finding. Tooth agenesis can present in three forms: hypodontia, missing one to six teeth, oligodontia, which represents a lack of more than 6 teeth, and anodontia which is the complete lack of dentition. According to Rolling et al, 1980, the prevalence of tooth agenesis in females was 1.01-1.68 times higher than in males (2). The prevalence of hypodontia in Caucasians is 3.9-6.3%, in Chinese the prevalence is approximately 6.1-7.7% (3), 13.4% in African populations, and 4.4% in Latin Americans (4). In contrast, the prevalence of tooth agenesis in the deciduous dentition is less than 1% (5).

Tooth agenesis can take various forms based on the amount of missing dentition. The types of teeth most significantly affected by this condition are the mandibular second premolars and maxillary lateral incisors. Some basic symptoms are deeper bites, smaller occlusal table, poor gingival contours, overeruption of opposing teeth, and nonworking interferences, such as class II and III skeletal relationships, all of which contribute to reduced chewing ability and pronunciation (6). Tooth agenesis can affect a wide variety of ages, affecting both the primary dentition and the permanent dentition. A child's primary dentition consists of 20 teeth, with 10 per arch. Primary dentition has a thinner layer of enamel, or outer hydroxyapatite covering, as well as thinner dentin, or inner tissue, compared to permanent dentition. Primary teeth usually exfoliate and permanent teeth, which contain 32 teeth with 16 per arch, begin to erupt at age 6 (7). Additionally, untreated cavities in primary teeth typically affect the amount of caries in erupting permanent teeth (8).

Tooth agenesis may be caused by various systematic diseases or other associated medical conditions. A significant cause of tooth agenesis is thalidomide embryopathy, a series of anomalies present in infants due to early exposure to thalidomide. Thalidomide is a sedative used to treat morning sickness and leprosy (10). Another condition that may contribute to congenital tooth agenesis is Down Syndrome, as it affects the mouth and its related oral functions. In one study of 46 Down syndrome patients examined, 65% of patients experienced tooth agenesis of at least one tooth (11). Orofacial clefting, often expressed through Van der Woude syndrome, which includes cleft lip, cleft palate, small mounds of tissue on the lower lip, or pits on the lower lip also occurred (12). Various external causes, like chemo/radiotherapy or infections, can also be factors that cause tooth agenesis. 66.7% of children under age 4 who endured conventional chemotherapy developed tooth agenesis, whereas 18.2% of subjects age 4 or older later experienced some form of agenesis (13). Infections, such as maternal rubella virus infection, during odontogenesis in infancy can lead to dental abnormalities and tooth agenesis (12).

These associated conditions, or tooth agenesis itself, may be caused by evolution or changes in genetic factors that contribute to oral health. According to Oeschger, 2022, having missing teeth is correlated with a shorter face and a less convex facial profile. This was the same for males and females (14). Furthermore, Oeshger demonstrated the number of missing teeth had a strong effect on craniofacial configuration. In females, the number of missing teeth predicted 14.3% of variation on craniofacial configuration, and in males, 19.2% of variation was predicted. Overall, the amount of missing teeth represented more than 85% of facial shape variation (14).

Materials and Methods

This systematic review focused on the following question: What is the epidemiologic background, factors of cause, and possible ways of treating patients with tooth agenesis?

Search strategies

For the literature review, databases such as PubMed, Science Direct, Google Scholar, and Wiley Online Library were utilized. Keywords that were used in our search included: “inheritance of tooth agenesis,” “agenesis genes,” “gene expression,” and “case study,” which narrowed and focused the range of research papers to published works that would precisely answer the research question. These four keywords established essential aspects of the research paper that effectively analyzed the holistic genetic basis of tooth agenesis, supported by specific case studies of relevant research that demonstrated how certain genes associated with tooth development can affect agenesis based on their differential expression and mutations, which expanded upon the concept of genetic inheritance.

Results/Discussion

Tooth agenesis is typically inherited in an autosomal dominant pattern, whereas autosomal recessive or X-linked inheritance patterns are less common (12). Vastardis, 2000, has suggested that tooth agenesis is typically transmitted with incomplete penetrance. Incomplete penetrance occurs when some individuals with the mutant genotype express the condition, whereas others with the genotype do not inherit the condition (27). The primary genes that affect tooth agenesis are MSH Homeobox 1 (MSX1), Paired Box Protein 9 (PAX9), and Axis Inhibition Protein 2 (AXIN2) (12). Mutations in these genes are most likely to affect tooth agenesis due to their interactions in teeth development during odontogenesis. Autosomal dominant and recessive mutations in MSX1 cause hypodontia, and only autosomal dominant mutations lead to oligodontia. In PAX9, autosomal dominant mutations lead to molar hypodontia, oligodontia, and peg shaped laterals. However, while agenesis in anterior teeth, like maxillary lateral incisors, tends to rely on genetic transmission, it is suggested that agenesis in posterior teeth, such as second molars and premolars, could be sporadic. In families with a history of tooth agenesis, other dental abnormalities, such as supernumerary teeth, microdontia, and anomalous teeth, were demonstrated (22).

The MSX1 gene is involved in nonsyndromic tooth agenesis, especially oligodontia and hypodontia formed during epithelial-mesenchymal interactions in early odontogenesis (12). The agenesis of the second mandibular premolars and third molars is most likely to occur when MSX1 is mutated (15). According to Satokata, 1994, mice deficient of Msx1 displayed a cleft secondary palate, insufficient alveolar mandible and maxilla, tooth agenesis, and defective facial bone development (16). Mutations that affect different locations of the MSX1 gene engender various phenotypic outcomes, which are polymorphic variants (17). A variation in the MSX1 gene can also lead to agenesis in maxillary lateral incisors (17). Currently, five point mutations in MSX1 have been discovered, including two substitution mutations and three forming a premature stop codon. The M61K and S105X mutations fall within the region before the protein's homeodomain while Q187X, R196P, and S202X occur within the homeodomain itself (22). Different mutations disrupt different functions of the MSX1 transcription factor. For instance, the M61K mutation occurs outside of the homeodomain and interrupts protein interactions. On the contrary, the R196P mutation is within the homeodomain, obstructing the protein's function and stability (22). One recently discovered example of a mutation in MSX1 gene caused autosomal dominant nonsyndromic oligodontia. Xin et al., 2018, found that this specific mutation prevented the odontogenesis of dental pulp stem cells (DPSCs), which are mesenchymal stem cells that allow for proliferative cell differentiation, through inhibition of the ERK signaling pathway (18). Interactions between epithelial and dental papilla cells induce the differentiation of DPSCs into odontoblasts and primary and reparative dentin, but mutant DPSCs could not differentiate because MSX1 lost its homeodomain structure. As a transcription factor, MSX1 cannot stimulate differentiation without a homeodomain polypeptide structure because it cannot bind or interact with DNA when the homeodomain is mutated (22). Due to the mutation, the translation of MSX1 ended abruptly before its homeodomain. Mutant DPSCs that were transfected with a mutant MSX1 plasmid had nuclear localization in the cytoplasm of DPSCs,

instead of the nucleus, demonstrating that nuclear translocation of MSX1 was inhibited. Consequently, cell proliferation in mutant DPSCs was less than that of the control group as there were less mutant DPSCs than the wild-type at the end of the study. Differentiation was also reduced in the mutant group, because mutant transfection resulted in less expression of dentin sialophosphoprotein (DSPP) and bone sialoprotein (BSP), which are precursor proteins for other dental structure development (18). DSPP fosters the mineralization of the dentin and strengthens the enamel, which allows for the proper development of teeth at birth (19). BSP includes a recognition sequence that induces osteoblasts to attach to bone surfaces where they facilitate bone synthesis (28).

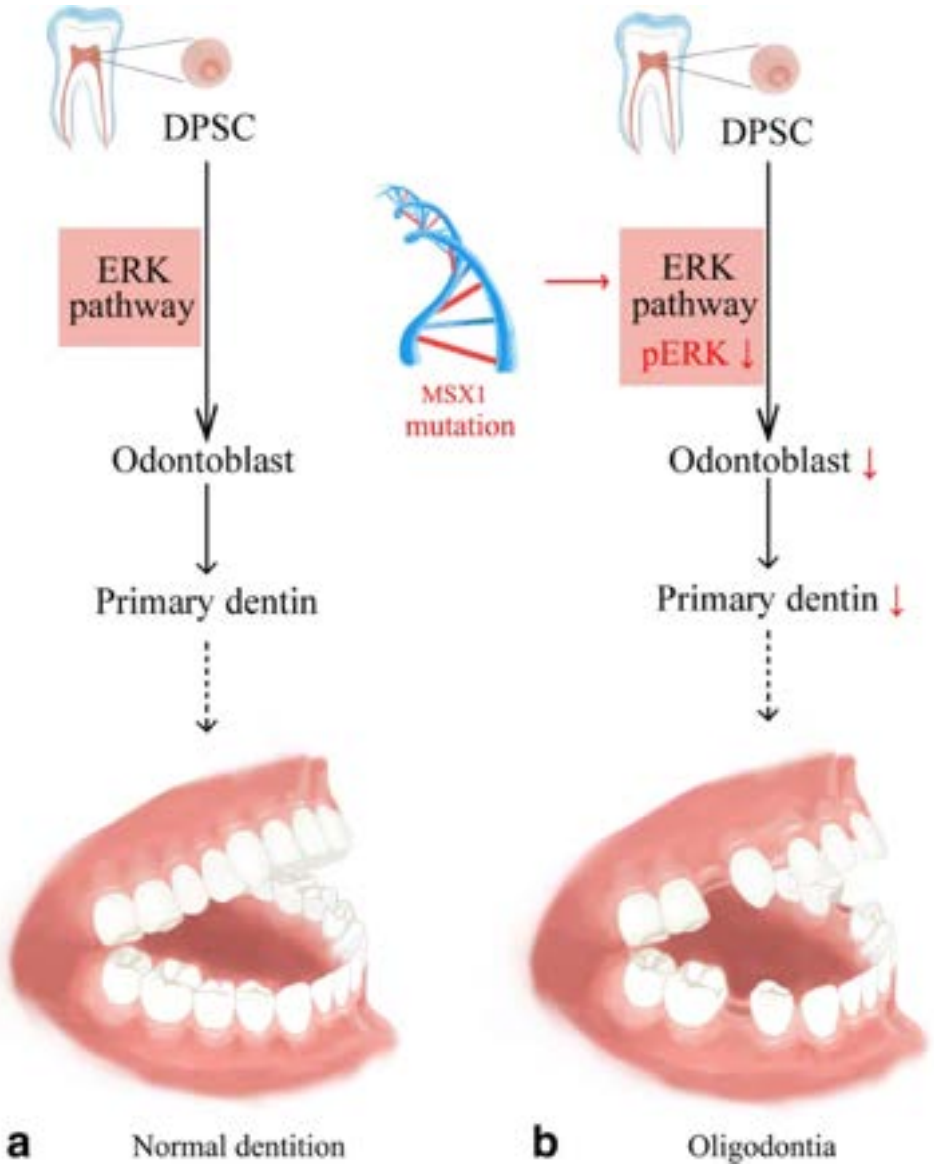

Figure 1: When DPSCs normally express the Msx1 gene, the ERK pathway is triggered and allows the growth of the primary dentin. However, mutant DPSCs do not facilitate odontoblast development due to the Msx1 mutation, which reduces the amount of primary dentin in the dentition (18).

Another gene that affects tooth agenesis is PAX9, which ensures that the mesenchyme condenses around the tooth bud epithelium during odontogenesis. Peters et al in 1998 illustrated that PAX9 transcription factor expression is required for the transition from the bud stage to the cap stage in tooth development. Tooth development starts with an initiation stage at approximately 6 weeks of human gestation. At this stage, thickening of the epithelial bands occurs. The bud stage starts at 7-9 weeks of human gestation and it involves the epithelial invagination into the oral ectomesenchyme. Peters, in his mice model, showed that tooth development is initiated normally in mutant PAX9 groups and control (no mutation) groups. Additionally, both groups form epithelial buds at the bud stage but the condensation of mesenchymal cells around the bud is significantly less prominent. His study further illustrates that in mutant groups, the development is arrested at the bud stage and does not continue to the cap stage. This shows that PAX9 function is required in all developing teeth at or before the bud stage. Peters also illustrates that PAX9 leads to the expression of transcription factors BMP4, MSX1, and LEF1 for tooth development. The study analyzed the expression of these genes in mutant embryos. In PAX9 mutant embryos, BMP4 was barely detectable while MSX1 and LEF1 were found to be substantially down regulated. Mutations in PAX9 most likely cause second molar, second premolar, and mandibular incisor hypodontia (21). Peters et al also found that in both the maxilla and the mandible, PAX9 mutant mice have missing alveolar ridges which normally surround molars and incisors. Other than its activity in dental development, PAX9 is also involved in cell proliferation, resistance against apoptosis, and cell migration (21).

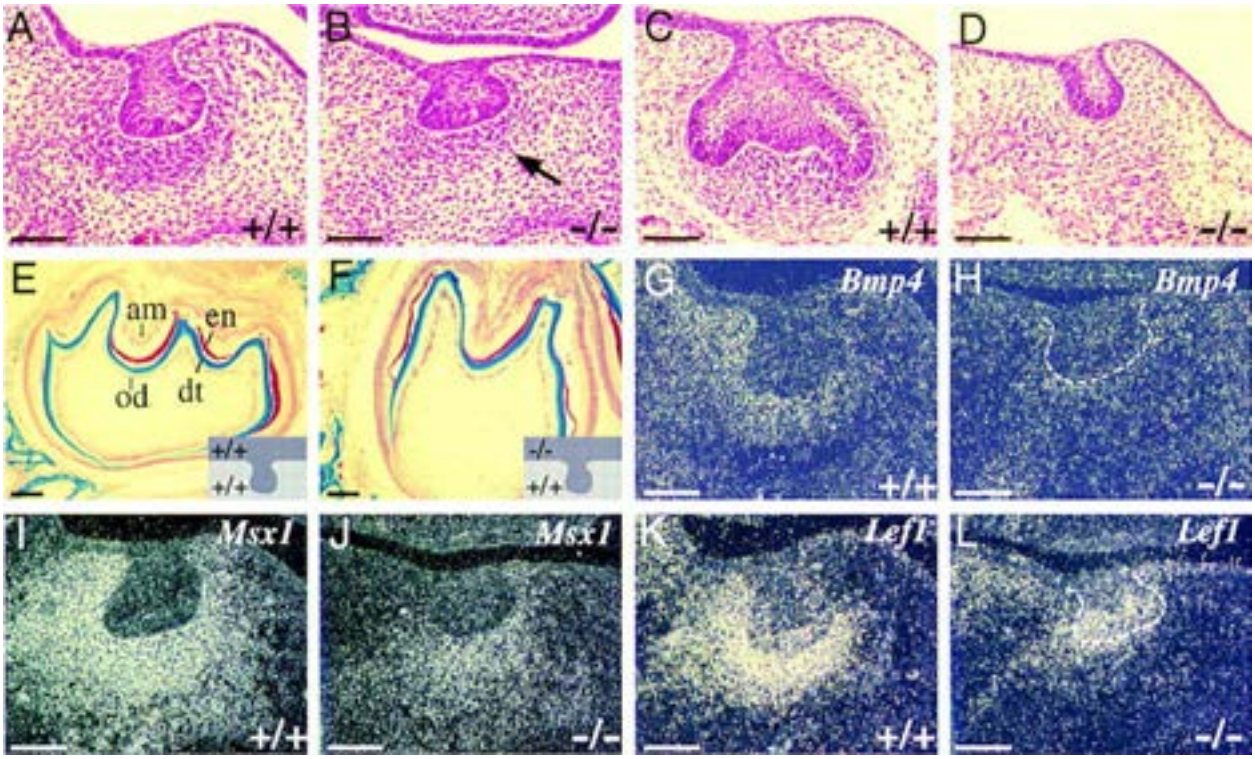

Figure 2: In the wild-type embryo (A), the mesenchymal cells condense normally during the bud stage, but in the mutant embryo (B), there is less condensation around the forming tooth bud. As a result, the embryo has reached the cap stage in wild-type (C), but only loose mesenchyme has formed around the tooth bud in mutant (D) (24).

AXIN2, a negative regulator of the catenin Wnt pathway, is involved in embryonic development, and mutations in this gene can lead to forms of sporadic incisor agenesis along with colorectal cancer (20). According to Hlouskova, 2017, the function of axis inhibitor protein 2, a protein coded by AXIN2 gene, is required for the proper differentiation and growth of stem cells during ontogeny. During the WNT pathway, the WNT protein activates the LEF1(lymphoid transcription factor which induces transgene molar expression of the LEF1 promoter. In molar development, this occurs during the thickening of the epithelial bands in the dental mesenchyme, whereas in incisor development, it persists after the cap stage of the tooth bud and causes cellular differentiation of ameloblast and odontoblast differentiation. The expression of the LEF1 promoter is also crucial for the formation of the initiation of enamel and dentin, or hard tissues of the tooth during the bell stage (24). Kratochwil, in a study of mutant LEF1 gene in mice, demonstrated that the mesenchyme of mutant teeth germs failed to transition into the cap stage because sufficient dental papilla, or the condensation of mesenchymal cells, did not form around the growing tooth bud (24). Several other mesenchymal genes involved in the Wnt signaling pathway, such as FGF3 or FGF10, are dependent on the expression of LEF1 and are

therefore not expressed, which prevents the formation of a proper enamel knot and proper odontoblast differentiation.

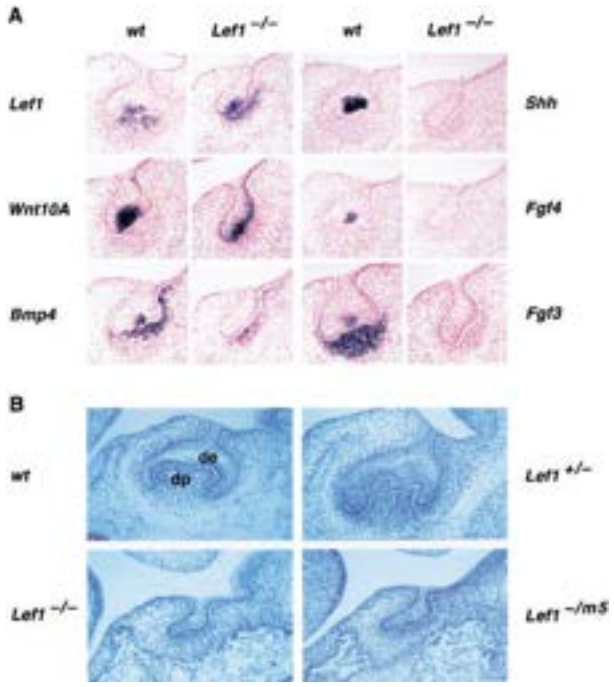

Figure 3: Wild-type mice (wt) express genes crucial for dental papilla development, whereas Lef1 mutant mice (Lef1-/-) fail to express these genes. The transcribed and translated protein products of these genes are indicated in the mesenchyme with dark probes.

Furthermore, the cause of tooth agenesis can also be attributed to associated symptoms, such as Down Syndrome. The majority, or 88% of patients with Down Syndrome experience third molar hypodontia (25). Due to abnormal nervous system growth, altered nerve fiber growth and patterning reduce the amount of interactions between the epithelial and mesenchymal cells, which prevents the proper formation of mesenchymal dental follicles around the tooth bud. Even if these interactions can occur, the abnormal nervous cells can also prevent vascularization, or the supply of oxygen and nutrients into the growing tooth bud, which leads to complete degeneration of differentiated odontoblasts (25). This means that even if the tooth has a dental papilla, the cells necessary for proper dental development can not sustain themselves. Another feature of Down Syndrome is an altered craniofacial structure, especially a reduced distance between the sella turcica structure and the trigeminal ganglion, is hypothesized to influence the height of the maxillary bone structure and cause maxillary hypodontia. Individuals with tooth agenesis reported reduced alveolar bone height, which is associated with a smaller oral cavity (29). According to Guilleminault, 2016, a reduced oral cavity can cause the collapse of the upper airway and induce obstructive sleep apnea. All 32 children studied reported symptoms of

obstructive sleep apnea and experienced high and narrow palatal vault which appears as a long face. (30) Obstructive sleep apnea is a comorbidity associated with Down Syndrome as it is caused by an altered craniofacial structure (29).

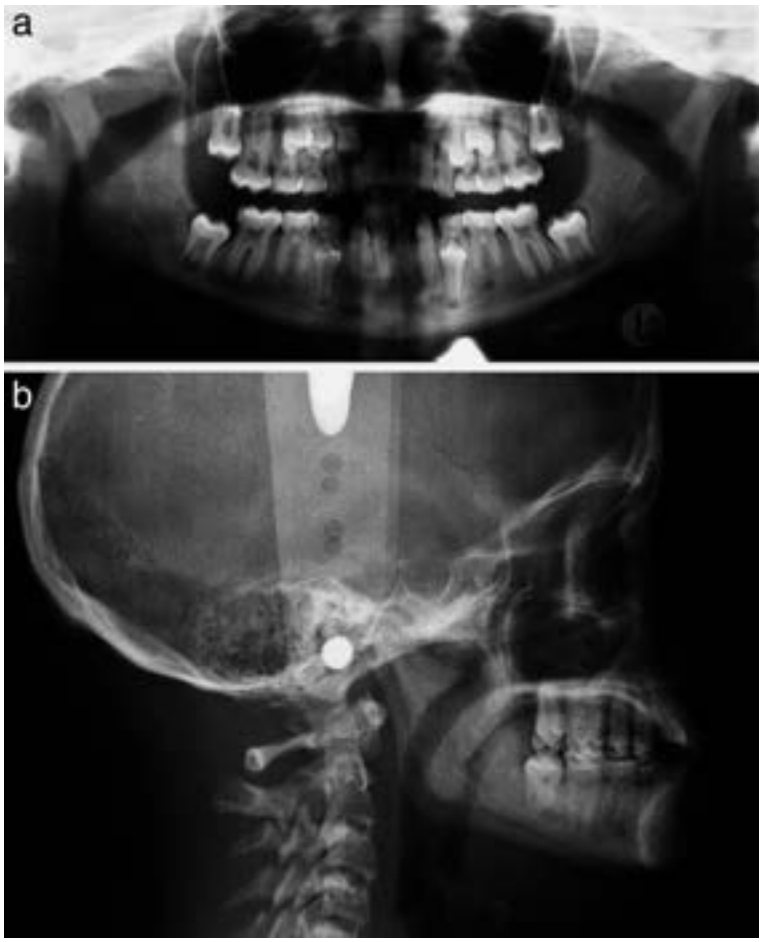

Figure 4: Radiographs of an individual with Down syndrome and tooth agenesis. The maxillary bone is smaller in comparison to subjects with Down syndrome without tooth agenesis.

Other associated conditions are Robin sequence and cleft palate, where tooth agenesis is considered an extended phenotype. Robin sequence is a condition where the mandibular bone structure is underdeveloped, and cleft palate is when the roof of the mouth leads to an opening in the nose. In Robin sequence patients, tooth agenesis was present in 47.8% of patients, whereas 29.8% of Cleft palate patients had the condition (25). For Robin sequence patients, Meckel's cartilage, an important element of the mandible, fails to properly develop and prevents odontoblast development during the bud stage. Furthermore, a smaller mandible presents spatial constraints for dental development, which prevents the growth of teeth like the mandibular second premolars. Although the severity of the cleft palate does not seem to

influence the amount of tooth agenesis, the aforementioned genes, such as PAX9, that regulate morphogenetic patterning signals also influence the lip and palate development.

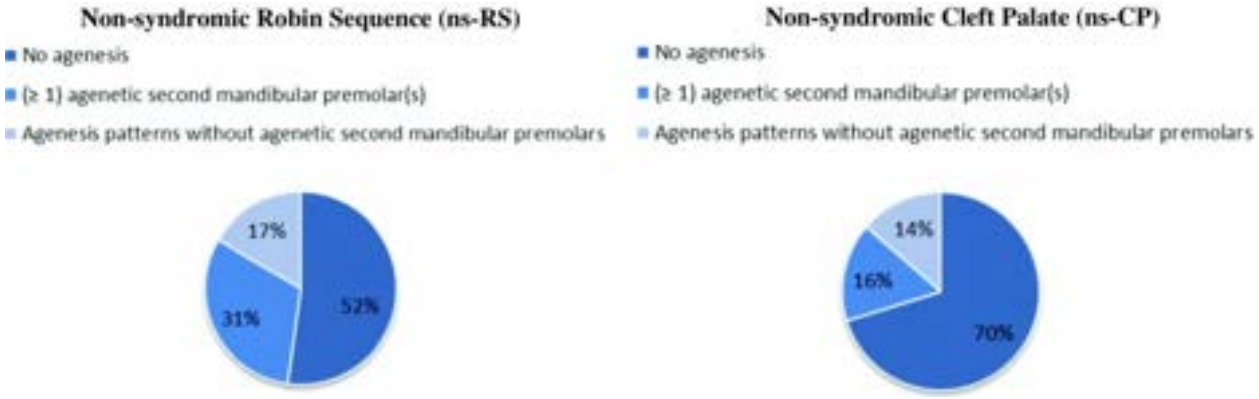

Figure 5: More patients with Robin Sequence exhibited tooth agenesis compared to patients with cleft palate, and is much more likely to occur in the mandible than the maxilla.

Tooth agenesis can also indicate a cancer or tumor development, and especially in women, it can indicate epithelial ovarian cancer or breast cancer. A familial history of tooth agenesis could serve as a screening technique of cancer, and according to Kuchler et al, 2013, patients with tooth agenesis had a statistically higher risk of a family history of cancer than the control group, and breast cancer, prostate cancer, and cancers relating to the brain and the nervous system were mostly reported (28). This is due to the genes discussed above also being involved in the development of cell proliferation capabilities in growing embryos. Gawron-Jakubek, 2019, demonstrated that women with ovarian cancer are 3.3 or 8.1 times more likely to have hypodontia due to reduced PAX9 expression as it is expressed in healthy epithelium cells in the esophagus. As cancerous cells proliferate, the amount of PAX9 expression is reduced, which is associated with the proliferation of ovarian cancer cell lines (31).

Although early diagnosis of tooth agenesis is crucial, novel biotechnologies involving stem cell cultures have the potential to treat agenesis. Stem cell differentiation typically involves the usage of mesenchymal stem cells, which are multipotent stem cells that can differentiate into bone, muscle, and fat cells. Mesenchymal stem cells include aforementioned DPSCs, which have demonstrated high differential potential and pluripotency. For instance, Samiei, 2021, finds that DPSCs display high expression of the transcription factor runt-related transcription factor 2 (RUNX2), alkaline phosphatase (ALP), bone morphogenetic protein 2 (BMP2), and basic fibroblast growth factor (bFGF) genes. DPSCs demonstrate exponential growth for a longer time and faster doubling rate compared to other dental mesenchymal stem cells. Hence, Samiei corroborates that DPSCs show significant potential for regenerative stem cell therapeutics of the pulp-dentin complex for necrotic, immature, and permanent teeth (33). DPSCs can be developed and delivered in cell cultures of the hydrogel scaffolds. Hydrogels can be formed

from amphiphilic molecules that are biocompatible, flexible, and high in cellular adhesion in order to successfully form cells that can restore or replace the defective regions. During this process, functional groups can be introduced through natural polymers or synthetic polymers in the hydrogel that exhibit characteristics of the extracellular matrix in tissues. These functional groups increase the hydrophilicity of the surface of the hydrogel and provide the stem cells with an environment where they can successfully differentiate. Jitpibull, 2020, demonstrates that dental pulp stem cells differentiated from cells from exfoliated deciduous dentition and experienced a significant amount of osteogenesis on a hydrogel scaffold that was coated in gelatin, because amino groups in gelatin initiated the expression of calcium in the matrix of the cells (32). This is crucial to the proper development of the dentition as the release of calcium strengthens the enamel coating of the teeth. Regenerative cells can be transplanted through the hydrogel by injections in the target regions.

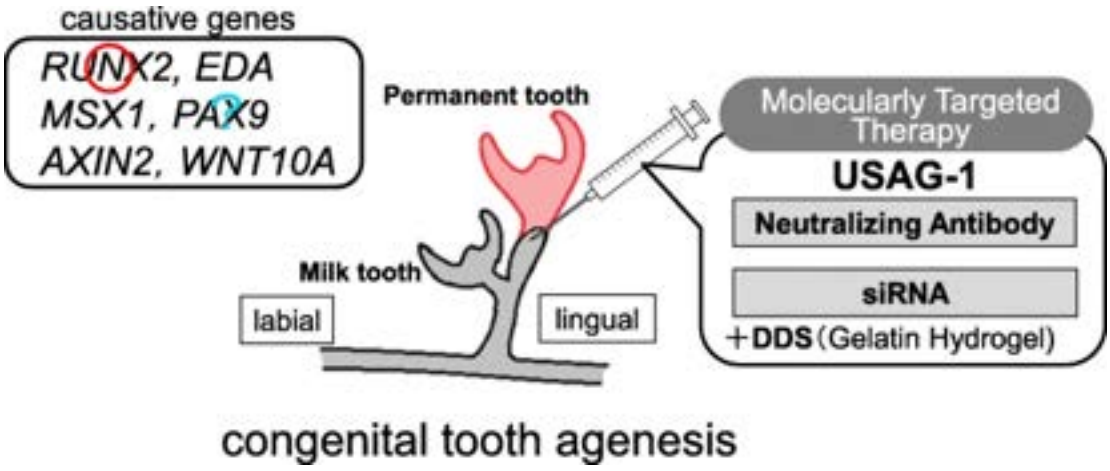

Figure 6: Molecular gene targeted therapy applications can stimulate the growth of the third dentition through the inactivation of USAG-1 and increase of RUNX2 expression.

Another area of future therapeutic development is the regeneration of teeth through the activation of the third dentition, or one more set of teeth in addition to the permanent dentition. Takahashi et al, 2020, provides supporting information as targeted molecular therapy rescued arrested tooth germs. The third dentition is stimulated when the second successional lamina is formed from the developing permanent tooth due to BMP activity and RUNX2 expression. Takahashi demonstrated that Uterine sensitization associated gene-1 (USAG-1), a protein that prevents the growth of the dentition through the inhibition of BMP activity, can be inactivated with the application of a neutralizing antibody and siRNA in a gelatin hydrogel (34). These findings were confirmed through the transplantation of therapeutics on the maxillary incisor tooth primordia of mice, which later demonstrated the stimulation of tooth rudiments and developed supernumerary tooth development.

Conclusion

Some possible treatments of tooth agenesis require multidisciplinary combinations between orthodontia, surgical implants, surgical care, and restoratives, which include dental crowns, bridge, or dentures that can improve chewing and dental compatibility. These treatments are essential for patients' lifestyle, health, and welfare, due to aesthetics and an easier chewing process.

Genes like MSX1, PAX9, and AXIN2 significantly contribute to the development of tooth agenesis. In order to treat tooth agenesis, novel biotechnologies such as stem cell cultures will have to target the individual mutations that affect the transcription and expression of these genes. The molecular changes during odontoblast development will also be affected by the pluripotency of the dental stem cells, which have the potential to stimulate the growth of the dentition for individuals diagnosed with tooth agenesis.

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