

Clinical Genetic Basis of Tooth Agenesis

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Abstract: Tooth agenesis is one of the most common congenital malformations in humans. Hypodontia can either occur as an isolated condition (non-syndromic hypodontia) or can be associated with a syndrome (syndromic hypodontia), highlighting the heterogeneity of the condition. Gene anomalies or mutations in *MSX1*, *PAX9*, *AXIN2* and *EDA* genes, appear to be most critical during the development of tooth, leading to various forms of tooth agenesis and systemic features. The aim of this paper is to review the genetic basis of hypodontia and identify the genes that have been definitively implicated in the agenesis of human dentition.

Key words: congenitally missing teeth, hypodontia, mechanisms, molecular genetics

I. Introduction

Hypodontia (dental agenesis) is the most common developmental anomaly in humans, constituting a clinically challenging problem. Hypodontia is often used as a collective term for congenitally missing teeth, although specifically, it describes the absence of one to six teeth, excluding third molars. Oligodontia (multiple aplasia) refers to the congenital absence of six or more teeth, excluding third molars. Anodontia represents a complete failure of one or both dentitions to develop [1].

In general, the prevalence of dental agenesis in the European Caucasian populations is situated between 4 and 8% [2]. In studies carried out in the Spanish population, we find values between 5.6 and 11.4% [2]. A higher but not significant predominance in females has been reported [2,3]. The prevalence of hypodontia of the primary dentition in the European population varies from 0.4 and 0.9%, and a strong correlation between the congenital absence of the primary and permanent dentitions has been reported [3].

Both environmental and genetic factors can cause failure of tooth development. Numerous different genes have been implicated in tooth development by genes expression and experimental studies in the mouse, and any of these genes may cause tooth agenesis. Variability in expression includes the number and region of missing teeth, and various other dental features associated with the trait.(4)

Missing teeth may occur in isolation, or as part of a syndrome. Isolated cases of missing teeth can be familiar or sporadic in nature. Familiar tooth agenesis is transmitted as an autosomal dominant, autosomal recessive, or X-linked genetic condition.[5]

The role of the genetic factors was suggested by observed familial occurrence, prevalence differences between populations, and association with heritable syndromes as well as by twin and family studies, but definitive evidence has been acquired during the molecular genetic era: defects in several genes have been shown to cause agenesis and anomalies in size and morphology. Tooth agenesis and tooth size reductions have been related to trauma, maternal systemic disease and various external factors. Among the maternal systemic disease, diabetes and different infections have been suggested. For example, developmental dental anomalies and tooth size reduction have been described in association of maternal rubella infection during pregnancy.[6]

The pathogenesis of human tooth agenesis is perhaps best understood in anhidrotic ectodermal dysplasias. In this case the molecular pathogenesis and the phenotypes in human patients and mouse mutants are directly comparable. The gene defects in anhidrotic ectodermal dysplasia (*Eda*), *Eda*-receptor (*Edar*), immunoglobulin K-gamma (*IKKy*) and their mouse homologs, i.e. the signalling ligand, its receptor and the intracellular mediators of the signalling, cause complete inactivation of this signalling pathway. [1,4,7]



Fig.1; Orthopantomograph showing the multiple missing permanent tooth and retained primary molars

In the mutant mice, incisors and third molars commonly fail to develop and first molars are hypoplastic, while in the patients with anhidrotic ectodermal dysplasia, both dentitions are severely affected and tooth morphology is simplified. The phenotypes of the mice with impairment or over expression of *Eda* signalling suggest that early defects of ectodermal placodes and, in teeth, the enamel knots would explain the ectodermal defects in human patients. Thus, failure of signalling at an early stage leads to anomalies that are present also in the deciduous dentition. On the other hand, as the mutant and disease phenotypes are caused by complete inactivation of the signalling pathway, the partial albeit severe tooth agenesis phenotypes suggest redundancy in the function of the signalling pathways, i.e. that different signalling pathways have overlapping functions. This redundancy adds a further element explaining how different gene defects may cause partial agenesis.[7]

The most compelling evidence for the genetic etiology of tooth agenesis has been provided by the identification of gene defects associated with different types of tooth agenesis. Dominant defects in *Msx1*, *Pax9* and *AXIN2* have been described in families with isolated severe tooth agenesis. However, in association with defects in *Msx1*, nail dysplasia and some patients with oral clefts have each been described in single families. In addition to causing severe tooth agenesis phenotype, a defect in *AXIN2* also predisposed to colorectal cancer. Recently, two defects that affected only dentition were also described in *Eda*. All these gene defects cause severe types of agenesis. However, evidence for association of specific intragenic polymorphisms to tooth agenesis, apparently consisting mostly of common types of tooth agenesis, has been presented for *Msx1*, *Pax9*, *AXIN2*, *TGFa*, *IRF6* and *FGFR1*. [8]

The aim of this paper is to review the genetic basis of hypodontia and identify the genes that have been definitively implicated in the agenesis of human dentition.

II. Molecular Mechanism Of Dentogenesis

During the embryonic development, morphogenesis and differentiation of teeth is the result of complex interactions at molecular level between the ectoderm and the mesenchyma [9]. Until now more than 200 genes involved in these processes have been identified [1,5,8,9]. A crucial role was attributed to those transcription factors that have a homeodomain. The homeodomain consists of 60 amino acids with a helix-turn-helix DNA binding motif and is encoded by a homeobox sequence: short chains of 180 bp, located in the vicinity of the gene's 3' end. In addition to the homeodomain that facilitates the binding to DNA, the transcription factors also contain a transactivation domain that interacts with a RNA polymerase. The homeodomain transcription factors in turn are involved in the regulation of homeobox gene expression sites, thus having a role in the activation of gene expression in multicellular organisms during embryonic development [5,9].

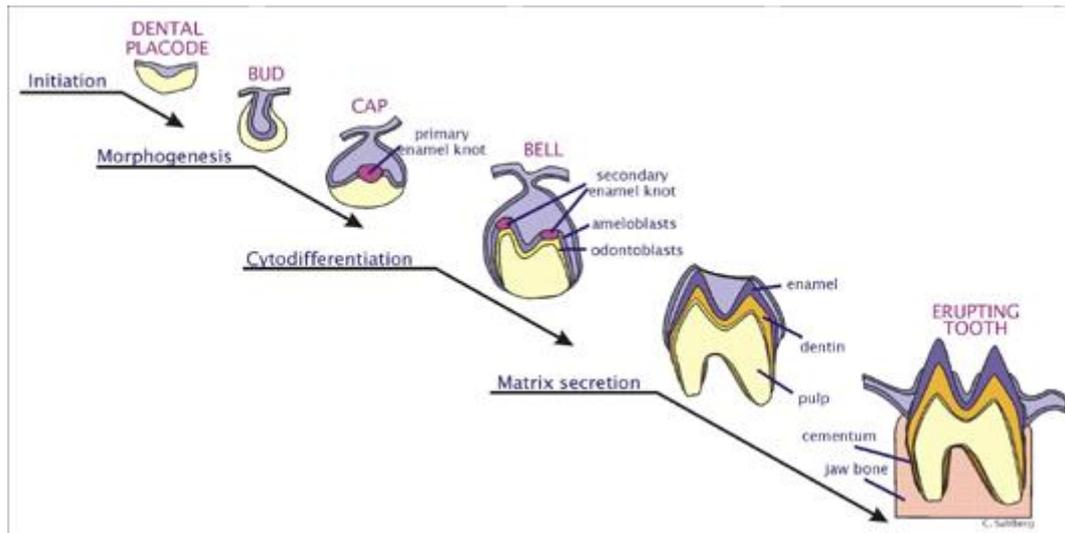


Fig.2; The development of teeth

The first genes containing homeobox sites were identified in the Hox cluster (cluster-related group of genes located on the same chromosome, each coding for a particular protein which are often regulated by the same cellular mechanisms). This cluster is highly conserved during evolution; sequences have remained relatively unchanged (75-90%) for hundreds of millions of years [1,5,9,10]. In embryogenesis, Hox genes cluster controls the development plan of the embryo during development. During tooth morphogenesis, expression of the homeobox genes is under the control of signaling cascades initiated by the interaction of certain proteins (either growth factors or other proteins secreted or available on the surface of neighboring cells) with receptors on the surface of target cells.[5,10]

Important factors in tooth morphogenesis are: the family of fibroblast growth factors (FGF) and transforming growth factors (TGF, including BMP4 - bone morphogenetic protein 4), the family of Wnt (Wingless) and morphogenesis molecule Shh (Sonic hedgehog). The general scheme of dentition is determined even before the development of visible teeth. The proximal area of the molars to be developed is characterized by the expression of growth factors FGF8 and FGF9, while BMP4 is expressed in the distal region of the presumed incisors [11].

Transcription factors define spatially the domains of expression of the homeobox genes in the developing jaw. Basically every combination of homeobox genes expressed is a “code” that specifies the type of the tooth [5,9,10,11]. Tooth formation is a complex process, genetically controlled in two ways: on one side, by specifying the type, size and position of each tooth organ; on the other, by the processes of enamel and dentin formation. Different genes involved in the formation of teeth belong to signaling pathways with functions in regulating morphogenesis of other organs. This explains the fact that mutations in these genes have pleiotropic effects in addition to causing non-syndromic dental abnormalities and dental anomalies associated with different genetic syndromes [12].

III. Tooth Agenesis

In the primary dentition, the maxillary lateral incisors account for over 50 % and together with mandibular incisors for 90 % of all affected teeth [13]. A correlation of agenesis of primary and secondary teeth also exist: agenesis of a primary tooth is nearly always followed by agenesis of the corresponding secondary tooth [13] .

Bilateral agenesis is observed for most teeth in almost half of the possible occurrences, i.e. when at two teeth are affected [14]. Bilaterality may be more common for maxillary lateral incisors than for premolars in either jaw [13,14]. In families the occurrence of agenesis within one tooth class appears more common than agenesis of different tooth classes [9]. However, if agenesis of third molars were taken into account, the tendencies to bilaterality and familial concordance would probably be weakened.[5,9,13]

Hypodontia	Oligodontia	Anodontia
		
<p>Tooth loss except third molars</p> <p>2-10(15)%</p> <p>Msx1, Pax9</p>	<p>More than 6 teeth missing</p> <p>0.1-1%</p> <p>Msx1, Pax9, Axin2</p>	<p>All teeth missing</p> <p>Extremely rare</p>

Fig.3;Classification of tooth agenesis

Tooth agenesis is associated with other anomalies of teeth. Tooth agenesis is prone to cause abnormal occlusion, the severity of which is dependent on the amount of missing teeth. Agenesis may also affect craniofacial development, and especially maxillary retrognathism and reduced anterior facial height have been reported [11]. A reduction in jaw size has also been described. However, as these may be considered secondary to agenesis, they will not be discussed further here. Several studies have addressed associations of agenesis and other dental anomalies [15]. Agenesis is often associated with reduction in tooth dimensions and morphology, delays of development, root anomalies, abnormal positions and also enamel hypoplasia [9,15]. However, these studies have not, with some exceptions, considered different subtypes of agenesis. While the following refers to studies concerning isolated tooth agenesis, these anomalies are rather often present in syndromic forms of tooth agenesis [9].

Although agenesis is occasionally caused by environmental factors (trauma in the dental region such as fractures, surgical procedures, chemotherapy, radiotherapy), in most cases the causes are genetic.[9,11,15]

IV. Evolution And Agenesis

In clinical practice, dentists often assume that teeth which are frequently missing or variable in form are 'on the way out' in evolution. Is this a valid statement? If we set it up as a testable hypothesis, it might be stated as follows: teeth destined for evolutionary loss anticipate that condition by increased variability in size, shape, and/or agenesis. Supporting evidence would be strong selective pressure toward loss of a tooth in evolution. Another evidence might be a series of consecutive fossil specimens as evidence of progressive tooth loss. I am not aware of such studies[16].

Implicit in the proposed hypothesis is that phylogenetic changes in the dentition correlate with functional adaptation. In understanding agenesis we would have to consider it as a functional adaptation. Is reproductive fitness enhanced by missing teeth? Or, is agenesis just a chance mutation with little consequence except minor inconvenience to the person afflicted.[15,16]

What is the dental future for humans? It has been suggested that one incisor, one canine, one premolar, and two molars per quadrant is likely to be the dental profile of future man. This prediction is predicated on progressive loss of the most distal incisor, premolar, and molar. I find this assumption questionable.

This topic could be argued endlessly and I will enter into this issue only by mentioning a primate odd-ball, the Aye Aye of Madagascar. The dental formula of this critter is as follows:

$$I \frac{1}{1} \quad C \frac{0}{0} \quad Pm \frac{1}{0} \quad M \frac{3}{3} = 9$$

This solitary, nocturnal primate exhibits extreme dental reduction and is highly specialized for a life similar to that of a woodpecker (which is absent in Madagascar). If humans are going to undergo great dental reduction, then you would expect a highly specialized diet. This would seem unlikely for an omnivorous, wide ranging species like humans. Not only is their wide culinary variation within our culture, there are many things eaten in other cultures we don't even consider as food.[17]

V. Gene Anomalies Belong To Tooth Agenesis

MSX1 is a homeobox gene located on chromosome 4 and encodes a DNA-binding protein.17 The main function of MSX1 protein is to interact with TATA box-binding protein (TBP)18 and some transcription factors to increase the rate of the transcription process. [1] This protein regulates gene expression, which is essential for initiating tooth development. MSX1 protein is considered to be critical during early tooth development; it was

found to hold sequence specific DNA-binding activity and supposed to regulate other genes involved in tooth development pathways.[1,17]

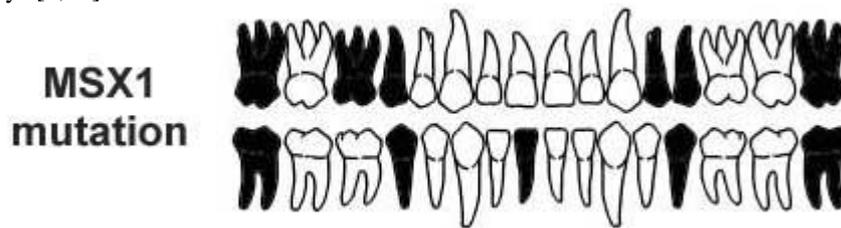


Fig.4 MSX1 mutation

The *Msx1* and *Msx2* genes have arisen by two successive gene duplication events acquiring their expression properties. During mid gestation, *Msx1* and *Msx2* expressions occur at almost all sites of epithelial-mesenchymal tissue interactions. At E11.5, *Msx1* is coexpressed with *Msx2* in the dental mesenchyme. However, the *Msx1* is expressed quite broadly (in high levels) in the mesenchyme and the *Msx2* expression is restricted to the mesenchyme around the tooth-forming regions. *Msx1* is also strongly expressed in the developing molar and incisor tooth germs in a distal-to-proximal gradient in mesenchyme of the mandibular and maxillary processes. The expression of *Msx1* in the dental mesenchymal tissue remains high throughout the cap stage, being down regulated at the early bell stage. The *Msx2* gene is expressed at early cap stage in the enamel knot, in the internal enamel epithelium and the dental papilla mesenchyme. With odontoblast differentiation, *Msx2* becomes strongly expressed in the odontoblastic cells. Mice deficient for *Msx1* exhibit an arrest in molar tooth development at E13.5 bud stage, while mice deficient for *Msx2* exhibit defects in cuspal morphogenesis, root formation and enamel organ differentiation.[1,17,18,19,20]

PAX9 is a member of a gene family encoding transcription factors that play a key role during embryogenesis. Proteins encoded by PAX genes share a unique 128-amino acid long DNA-binding paired domain [8,9]. PAX9 gene products function primarily by binding the enhancer DNA sequences and by modifying transcriptional activity of downstream genes [9]. To date, 11 distinct disease-causing mutations in the PAX9 gene (59 patients in 15 families) have been identified in humans, most of which are located in the paired box domain of PAX9. In contrast to MSX1, both missense and frame-shift mutations in PAX9 have been associated with hypodontia.

Of the seven identified missense mutations, one is a premature termination mutation, and the remaining six are all residue substitution mutations. Of these substitution mutations, only five generate a substitution in the protein, with one believed to prevent PAX9 expression. Three frame-shift mutations have been identified, two of which are caused by the insertion of a single nucleotide and the other by the deletion of eight nucleotides with the insertion of 288 foreign nucleotides [21].

Some of the unique reported mutations, like frame-shift, insertion, missense, nonsense and deletions of entire PAX9 gene.[22] These mutations were identified in the DNA-binding paired domain of PAX9 gene, resulting in a disturbed regulatory process occurring for tooth formation.[15] Missense mutations in PAX9 gene at amino acid position Gly6Arg and Ser43Lys were detected in two Chinese patients with non-syndromic tooth agenesis. [23] Patients and their family members affected with oligodontia and other dental anomalies were carrying transition and nonsense mutation at C175T, resulting in an altered arginine 59 Stop codon, thus leading to premature chain termination (haploinsufficiency) in PAX9 gene. [23]

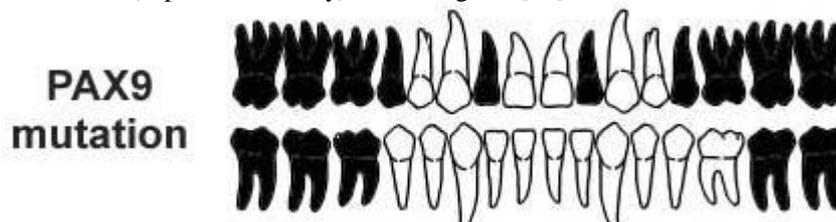


Fig.5;PAX9 mutation

A patient with oligodontia showed missense mutation with the substitution of an arginine by a tryptophan in the paired domain of PAX9 gene and showed dramatically reduced DNA-binding activity[24].

Subsequently, other PAX9 mutations that led to non-syndromic oligodontia were found:

- transitions (C76T) and (C139T) that led to the replacement of arginine with tryptophan in N-terminus of the homeodomain [25].
- transversion (A340T) that created a stop codon at lysine 114 in the DNA binding domain [15];

- three different missense mutations leading to substitution of arginine with proline in the homeodomain (Arg26Pro), glutamic acid with lysine (Glu91Lys) and leucine-to-proline (Leu21Pro) affecting M1 [26];
- a cytosine insertion in exon 4 (insC793), frameshift mutation that led to the appearance of a premature STOP codon at amino acid position 315. [27]

Stockton et al. showed that a mutation in the PAX9 gene modified the open reading frame (frameshift mutation) causing premature termination of translation. The affected individuals were normal, but lacked most permanent molars. The disease was transmitted in autosomal dominant fashion.[28]

In all these cases, permanent parts of the molars were missing, which emphasizes the importance of this gene in development. The sequencing of PAX9 gene in samples from a Chinese family with many cases of oligodontia showed a transition (A → G) in the initiator AUG codon, in exon 1. This is the first mutation found in an initiator codon that supposedly caused a severe inhibition of translation. [29]

Numerous studies suggest the PAX9 mutant phenotype is dosage dependent: deletion of the PAX9 locus manifests as missing permanent teeth and the entire primary dentition; 10 missense mutations result in oligodontia of only the permanent teeth; other mutations that would encode a truncated polypeptide present with missing permanent teeth, as well as some primary teeth.[5,7]These findings, however, fail to fully explain the mechanisms underlying disease-causing mutations that result in less severe and variable phenotypes where not all posterior teeth are affected.[30]

AXIN2 gene (17q23-q24) encodes the Axin2 protein that has an important role in regulating the stability of β -catenin, which is involved in the Wnt signalling pathway (wingless). When cells receive Wnt signals, β -catenin binds to stabilized transcription factors (TCF family), regulating the expression of Wnt target genes. It was found that changes in the functioning of the Wnt signaling pathway leads to cancer predisposition.[15,31]

Oligodontia as the results of mutations in the AXIN2 gene was more severe than that described for mutations in MSX1 and PAX9 genes; there were more missing molars, premolars, upper lateral incisors and lower incisors, but upper central incisors were present.[31]

EDA1 gene (Xq12-q13.1). Mutations in this gene cause X-linked hypohydrotic ectodermal dysplasia (HED), a rare disease characterized by hypoplasia or absence of sweat glands, dry skin, sparse hair and pronounced oligodontia. In 2010 Khabour et al. [32] identified a nonsense mutation in the EDA gene in a Jordanian family. The mutation resulted in the replacement of arginine with cysteine that has led to intolerance to heat, the absence of 17 teeth, speech problems and anhidrosis (reduced sweating) in affected individuals. In 2006 Tao et al. [33] found a point mutation in the EDA gene in a Mongolian family in which affected males (females are carriers) did not present other features of the disease than hypodontia. Other cases of non-syndromic hypodontia were described by Li et al. [34], in 2008 in two families in China with two nonsense mutations in the same gene is accompanied by the lack of central and lateral incisors, and canine teeth of the maxilla and mandible [35].

LTBP3 (latent transforming growth factor beta binding protein 3) is a gene that modulates the bioavailability of TGF-beta and is located on the long arm of chromosome 11. A study on a Pakistani family with a history of consanguineous marriage found that a mutation in the LTBP3 gene causes an autosomal recessive form of familial oligodontia [36].

VI. Discussion

Identifying a hereditary dental pathology and defining its unique characteristics are the first steps toward the dissection of its genetic basis[1]. A thorough interview of the patient and his or her relatives is the next step to defining the trait as familial; if it proves to be so, it is imperative to define the pattern of inheritance of the anomaly. In this respect, several genes that are pivotal in initiating the development of teeth have been subjected to intense study in the past decade. Mutations in a number of genes were found to interrupt tooth development in mice. However, to date there are only three genes associated with the nonsyndromic form of human tooth agenesis: AXIN2, Msx1, and Pax9. Among them, Msx1 and Pax9 was more intensively studied[5,9,15]. Recently, the general structure of the Pax paired domain was described and the phylogenetics and relation between the several members of the Pax family were established. In addition, both gene expression and molecular pathogenesis of Msx1 and Pax9 have been relatively well characterized, making it a special candidate to explain at least part of primate tooth variation.[5,9,15,37,38]

Msx1 homeobox gene is highly expressed in the dental mesenchyme and is essential for tooth development, since targeted gene disruption results in arrested tooth formation at an early stage in Msx1. In addition to its expression in the tooth primordia, Msx1 expression is prominent in regions of epithelial-mesenchymal interactions in several other embryonic structures, including other craniofacial structures and the limb.[5,7,13,14,38] These findings have led to the hypothesis that Msx1 is an important component in the signalling events that occur between epithelial and mesenchymal tissues Both Msx1 and Pax9 are also needed for the mesenchymal cell condensation around the growing epithelial bud. The reduced condensation which is also seen in the Pax9 hypomorphic mutants, perhaps indicating a decreased amount of committed dental

mesenchymal cells, may be related to tooth agenesis. As Msx1 is known to be important for the commitment of neural crest, an early defect in the migration of neural crest cells could also be responsible for the tooth agenesis, if it caused a reduction in the amount of competent ectomesenchymal cells.[20,38]

Tooth agenesis is a consequence of a qualitatively and quantitatively impaired function of genetic networks, which regulate tooth development. Impaired function of genetic networks are reflected as reduced signalling or impaired signal regulation, cell proliferation, migration and differentiation. The most critical are the stages of formation of signalling centres that have an organizing role for the future development. The reduction of the “tooth forming potential” may follow from a reduced functional activity of a single gene as in the case of defects in Msx1 and Pax9.[7,15,19,38]

Das et al. described the absence of upper lateral incisors and Jumlongras et al. of the upper canines and the lower central incisor. These characteristics were different from the ones that we could observe in the previously published MSX1 mutations, where the most frequent affected teeth are first and second premolars and lateral incisors. Consequently, we observed a very different phenotypic pattern between the mutations described in PAX9 and MSX1.[26]

According to the studies by **Ogawa et al.** [24] and **Nakatomi et al.**[39] a functional relationship between these genes during teeth development has been identified, establishing another potential point of regulation. Thereby, epigenetic intervention directly over DNA or in post-transcriptional activities of one of them, can alter those phases of dental organ development dependents of the mentioned interaction. In addition, these authors suggest that a combined reduction of PAX9 and MSX1 gene dosage in humans may increase the possibility of oligodontia.

Phillips et al. [40] provides valuable information regarding the evolutionary history of PAX9, supporting the hypothesis that post-transcriptional modulation in the expression of this gene could have an effect on the dental formula evolution, suggestion that is supported for the studies realized by Kirst et al. [41]. Considering our study, it is interesting to note in Table 1 the high incidence of third molars and second premolars agenesis. This observation is consistent with studies that indicate that progressive reduction in the teeth number was observed in inverse order to how they were formed during development. More studies are needed to investigate the incidence of epigenetic factors on transcription/translation of MSX1 and PAX9 genes that could trigger non-syndromic dental agenesis in human.[40,41]

Lammi et al. [31] identified mutations that caused severe oligodontia in a Finnish family (11 members lacked at least eight permanent teeth, two of whom developed only 3 permanent teeth) with a predisposition for colorectal cancer (8 patients). It was found that oligodontia and predisposition to cancer was caused by a nonsense mutation (Arg656Stop) in the AXIN2 gene.

Song et al. [42] identified three new mutations of the EDA gene in four male individuals (27%) from 15 analyzed individuals with non-syndromic oligodontia.

This approach has been used in other craniofacial conditions, such as craniosynostosis. Using this approach, the authors will likely unveil the mutation causing the sporadic anodontia in the case by testing only one or two DNA samples of good quality for a current cost of less than US\$1,000.[43]

Chosack et al assumed that hypodontia is the result of polygenic inheritance with a threshold effect. Those individuals who are below the threshold remain unaffected and those who are above are affected [44]

Grahen in 1956 was the first to consider agenesis as a hereditary anomaly whose transmission is determined by a dominant autosome, with incomplete penetrance and variable expressivity; this is currently the most agreed upon definition. In Grahen's sample, the penetrance was higher when the proband of the family had more than 6 missing teeth. Studies by Grahen have shown that the penetrance (defined as the percentage of individuals with a particular gene combination showing the respective characteristic at a particular degree) is 86%, whereas the variable expressivity (the degree of phenotypic expression in an individual) means that the inherited teeth, when they are not agenic, can be shown to be modified in shape and or size. Burzynski and Escobar calculated the penetrance of numeric anomalies of dentition to be 86% with the use of Grahen's data [45]

Chalothorn et al. (12) have demonstrated a relation between hypodontia and epithelial ovarian cancer – congenital lack of tooth buds was observed in 20% of patients with EOC compared to 3% in a control group.[46]

Brook and Bailit assumed that hypodontia is a quasi-continuous trait based on an underlying continuous distribution of tooth size. Brook suggested a multifactorial model in which polygenic factors play a major part but environmental factors are included but environmental factors are included.[47]

Woolf has suggested that in families exhibiting dominant inheritance of incisor agenesis, the responsible gene extends to show reduced penetrance and variable expressivity. Peg lateral incisors or rudimentary third molars may reflect incomplete expression of a gene defect that causes tooth agenesis; unilateral agenesis may be a result of reduced penetrance. 16q12.1 Chromosome (autosomal recessive hypodontia) defect is an autosomal recessive type of hypodontia associated with several tooth anomalies e.g. malformations, enamel hypoplasia and missed eruption. It was found in a Pakistani kinship from Sind, having several consanguineous marriages[48].

Mutations in the PAX9 gene are associated with multiple missing molars, whereas mutations in the MSX1 gene are responsible for oligodontia involving second premolars and lateral incisors or lateral incisors and canines. All mutations in the PAX9 and MSX1 genes described so far have been identified in heterozygous state in single families with oligodontia or hypodontia covering many generations. PAX9 and MSX1 genes encode transcription factors playing significant roles during facial craniofacial development.[16]

According to **McNamara et al.** the agenesis of at least 6 tooth buds is observed only in 1% of those with congenital lack of tooth buds.[49]

In 1996, **Vastardis et al.** [18] identified an Arg to Pro substitution in position 31 of the MSX1 gene homeodomain that caused hypodontia and was transmitted in an autosomal dominant way in the analyzed family for 4 generations. The mutant protein had an abnormal structure, but low thermal stability compared with the normal protein. The ability of the mutant protein to bind to DNA, and interact with other transcription factors were significantly altered.

Chishti et al. [45] identified a new point mutation in the MSX1 gene which resulted in the substitution of alanine to threonine (A219T) in the MSX1 homeodomain in 2 Pakistani families, causing oligodontia. This mutation was the first recessive mutation identified in the MSX1 gene.[50]

The molecular and genetic studies of tooth development, tooth agenesis is a consequence of a qualitatively or quantitatively impaired function of genetic networks, which regulate tooth development. Reduced amount of functional Msx1 or Pax9 protein in the tooth forming cells is able to cause severe and selective tooth agenesis. Another conclusion, based on the analysis of the phenotypes associated with the known defects in these genes, is that the phenotypes associated with the defects in Msx1 and those associated with the defects in Pax9 are different. Despite the similarities, there are clearcut differences in the frequency of agenesis of specific teeth.[38]

The psychosocial impact of hypodontia has received little attention in the literature. **Hobkirk et al.**, in a retrospective study of 451 patients with hypodontia, found that the most common complaints were spacing between the teeth and poor esthetics, and some patients were aware that they had missing teeth. Functional problems because of the reduced surface area of the occlusal table comprised only 8.7% of patients' complaints.[51,52]

Missing permanent teeth in a child are a matter of concern to most parents. The ability to rebuild a tooth that is congenitally missing or lost due to disease is therefore a great boon to the pediatric dentist. Although the dream of genetically engineering teeth still remains a distant one, the study of tooth agenesis and genes producing the molecules involved in tooth agenesis have led to the development of experimental tooth regeneration techniques such as tissue scaffolding and tooth engineering. In addition, the association of genes such as AXIN2 and PAX9 to both tooth agenesis and colorectal cancer has shown the potential of using tooth agenesis as a genetic marker for the diagnosis of cancer.[31,38,52,53]

While this paper has reviewed the genes and their mutations, most likely to cause tooth agenesis the list is far from complete. Several forms of tooth agenesis remain unexplained. Research into tooth agenesis today is increasingly relying on familial studies to locate mutations in the genes. As the person who first detects the problem the pediatric dentist is in the best position to chart the pedigree of the family and determine the type of inheritance pattern. An understanding of the basic concepts of genetics will enable pediatric dentists to contribute greatly to future research into the emerging fields of tooth regeneration and molecular dentistry.[38,53,54,55]

VII. Conclusion

Tooth agenesis is genetically and phenotypically a heterogeneous condition, caused by several independent defective genes, which act along or in combination with other genes and lead to specific phenotypes. During the past decades, significant efforts have been made for detecting gene loci that contributes to dental agenesis. In conclusion, the genetic causes of dental pathologies are multiple. Phenotype and severity is dependent on the affected gene, the type and location of the mutations. We still do not know all the causes of the dental diseases, but their genetic basis is not a neglected factor.

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