Tooth Agenesis: Newer Concept

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Developmental disturbances involving the oral cavity affect the growth and development of a child. Tooth agenesis may be associated with a number of documented syndromes or may present as an isolated entity. The presence or absence of teeth is decided by the influence of various genes and their signaling pathways. These syndromes appear due to chromosomal defects or due to mutations in the genes responsible for organogenesis. Identification of these mutations helps understand the underlying defect and plays an important role in their treatment strategies. This is a comprehensive review of literature on syndromic and non-syndromic forms of dental agenesis and an attempt in enlisting various syndromes associated with dental agenesis.

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INTRODUCTION

Developmental disturbances affecting the oral tissues are manifested in many ways. They can be broadly classified in two categories—those involving hard tissues and the ones involving soft tissues. The spectrum of developmental pathologies affecting teeth includes variation in shape, size, eruption pattern and number. Tooth agenesis can lead to partial or complete Anodontia (Ana-Absence, Dontia-Teeth), though it is an established fact that a few teeth, by evolution, are congenitally absent (eg. 3rd molars). Global literature has reported a wide range in the frequency of congenitally missing teeth as 1.6% to 9.6%. The congenitally missing primary teeth are uncommon but when they do occur, maxillary lateral incisor is the one frequently reported.

The presence or absence of one or more teeth is decided by a complex series of events in an individual. The interplay between various genes and their signaling pathways are responsible for the morphologic character and positioning different teeth in human dentition. Mutations in closely linked polygenic system, most often transmitted in different patterns with incomplete penetrance and variable expressivity lead to various malformations Graber et al.[1-5]

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Tooth agenesis can hamper child's normal growth and development. It will have its effect on the overall craniofacial and psychosomatic development of the child. Tooth agenesis can alter esthetics, cause malocclusion along with speech defects and thereby adversely affect the child's personality. This paper analyzes the molecular events involved in partial and complete anodontia.

Molecular Basis of Tooth Development

First step in the process of tooth development is the formation of tooth bud. The developing tooth buds are formed in the developing jaw bones as early as 8th week of intrauterine life. Tooth bud formation takes place due to the continuous proliferation of basal cells of the oral ectoderm which leads to the formation of epithelial thickenings (primary epithelial band).[1] The epithelial thickening during the tooth development contains genetic determinants for initiating signals that regulate the number and position of the future teeth. The oral ectoderm contains "Instructional signals" for tooth development and perhaps the pattern of entire dentition. In short, these signaling pathways lay down a blue print for the entire dentition. The homeobox gene constitutes a large family of genes that specify correct positioning of body parts during the embryonic development. An overview of these genes and their potential role help us to better understand the events of tooth genesis. All members of this family share a common code of 60-amino acid DNA binding sequence. The homeobox genes are widely expressed during embryonic development (Dlx, Pax, Msx).[2] Four major signaling pathways and their inhibitors control tooth formation; a fine balance between them determines the numbering and patterning of human dentition. They are Bmp, Fgf, Wnt and Shh signaling pathways.[6,7]

The tooth formation also relies on epithelial ectomesenchymal interaction. It has been reported that genes implicated in the epithelial mesenchymal interaction during mouse odontogenesis also serve as potential candidates for tooth agenesis in humans. [8]

Genes: Potential Role in Odontogenesis

Over expression of Bmp1 in transgenic mouse or functional inactivation of FGFR2b or Shh results in arrest of tooth development in the bud stage itself. When the inhibitors or mediators of these signaling pathways are perturbed more teeth are formed with abnormal shape. Defective ameloblast or odontoblast differentiation and reduced amount of matrix deposition may also be manifested. (Tables 1 and 2)

The members of Fgf family ligand, namely Fgf3 and Fgf10, derived from mesenchyme, promote the proliferation of incisor epithelial stem cell niche. Consistently, downregulation of Fgf10 leads to hampered growth of incisors.[6]

The name Wnt was derived from Drosophila wingless and mouse Int1 in late 1980s and early 1990s. The Wnt proteins are a family of secreted growth factors which in association with specific receptors act as repressors or activators of target genes which encode various cell signaling molecules. Research led to the understanding of Wnt/β-catenin pathway in tooth development. It is known that this pathway is found to be mutated or hyperactivated in various types of cancers (e.g. colorectal cancers). It is shown to promote self-renewal and proliferation of various stem cells. It also regulates distinct cell fate decision in neural crest stem cells which play a pivotal role in odontogenesis. The Wnt pathway regulates multiple developmental processes including craniofacial development and may play a role in cleft lip/palate and other defects of craniofacial development such as tooth agenesis.[9]

Table 1. Abnormalities caused by mutation in transgenic mice affecting tooth formation.[6]

TOOTH PHENOTYPE	GENES INVOLVED
Initiation stage arrest	Msx1, Msx2, Dlx1, Dlx2, Fgf8, Lhx6/ Lhx7, Pitx2, Gil2, P63, Dkkl.
Bud stage arrest	Pax9, Lef1, Max1, Runx2, Barx1, Bmpr1a, Fgfr2b, Shh, Noggin.
Supernumerary teeth	Apc, Sp6, Lrp4, IFT88/ Polaris, Gas1, Qsr2, Sproty 2, 4.

Table 2. Abnormalities caused by mutation in transgenic mice affecting tooth matrix[6]

Table 2a. ENAMEL DEFECT

TOOTH PHENOTYPE	GENES INVOLVED
Enamel hypoplasia	Msx2, Lama3, Enamelin, Mmp20, Sp3, Sp6, Smoothend, Connexin43, Periostin, Amelex.
No Enamel	Gdnf, Eda, Follistatin, Ameloblastin.
Ectopic Enamel	Wnt3, Sprouty2, 4.

Table 2b. DENTIN DEFECT

TOOTH PHENOTYPE	GENES INVOLVED
Dentinogenesis imperfecta	Dspp, Msx2.
Dentin defect	Sp3.
Abnormal dentin structure	Sp6

Table 2c. ROOT DEFECT

TOOTH PHENOTYPE	GENES INVOLVED
Short Root	Shh.
Lacking Root	Nfi-c/ CTF

Shh is a crucial signaling molecule acting during organogenesis, patterning of limb, development of gut, tooth initiation and tooth morphogenesis. The tooth defect results from mid-facial fusion defect. Disturbance in Shh signaling pathway leads to defective growth and development of maxillary arch resulting in the premature fusion of left and right parts of the dental lamina, leading to fusion of incisor buds.[10]

A study conducted by X. P. Wang *et al* (2005) showed that Shh signaling pathway genes Ptc1, Ptc2 and Gli1 were down regulated in Runx2 muted lower molars. But the expression was unaffected in upper molars.[11] Nonsense mutations in Msx have been demonstrated in non-syndromic tooth agenesis.[12,13] Msx mutations also result in mild maxillary anterio-posterior hypoplasia.[14] A study conducted by S. Pirinen *et al* 1996 concluded that palatal displacement of canine is genetic and is related to genetic incisor-premolar hypodontia and peg shaped incisors.[15] M. L. Klein et al (2006) have concluded that novel mutation in the initiation codon of Pax9 (belongs to paired ox gene family and named on the basis of presence of a DNA binding paired domain) has been responsible for non-syndromic oligodontia. It activates the tooth bud to cap transition, and is usually associated with missing permanent molars, all second premolars, upper first premolars but hypodontia in primary dentition is very rare.[10,16]

Syndromes: Their Myriad Expressions

Agenesis can occur in isolated cases or can be associated with variety of syndromes.

Over 200 syndromes exhibit cleft lip/cleft palate along with tooth agenesis as a part of their phenotype and many of their causative genes have now been identified. The Msx mutation causes a wide spectrum of phenotypes ranging from Witkop syndrome to non-syndromic hypodontia. Mutations in Ectodysplasin are well known to cause Ectodermal dysplasia (HED). Shh gene causes developmental disorders ranging from only mild microcephaly or dental defects to very severe autosomal dominant syndromic phenotypes.

The Shh downstream transcription factor GLI3 causes Pallister-Hall syndrome. The Homebox gene Pitx2 is expressed in the oral epithelium at the site of tooth formation and is necessary for the maintenance of the balance of Bmp4/Fgf8 expressed in oral epithelium. Mutation in these genes is responsible for some cases of Reiger syndrome, together with Pax gene family. Along with severe oligodontia this syndrome is characterized by cleft lip/ palate and cranio-facial malformation.

Van der Woude syndrome is the most common syndromic form of cleft palate and is caused by the mutation of IRF6 gene. The translocation mutation in locus 1q32-q42 has been recorded for this syndrome.[8] Mutation in FGFR1 causes severe developmental disturbances including Kallmann Syndrome.[16] Hypodontia features in a number of other syndromes, such as Down's syndrome which is characterized by mental retardation and characteristic facies. Trisomy in chromosome 21 is mapped as the cause and characteristic feature of this syndrome.

Mental retardation and dental agenesis together is expressed in a few other syndromes, out of which Rubenstin-Taybi is not very infrequent. This syndrome is caused by the mutation in 16p13.3 and is characterized by dental agenesis, mental retardation, broad thumbs/ toes and facial dysmorphism. Laurence-Moon syndrome caused by mutation in gene 20p12 is also found to be associated with dental agenesis and mental retardation. The other features of this syndrome are spastic paraplegia and pigmentary retinopathy.[8]

Severe skull deformity, midface hypoplasia and syndactyly together are characters of Apert Syndrome; which is an autosomal dominant disorder with the locus of mutation at FGFR2 on chromosome 10q. Along with supernumerary teeth and severe skull malformation, dental agenesis is also a marked feature of this syndrome.[17] Another syndrome associated with skull deformity, Acanthosis Nigricans and severe scoliosis is Crouzonodermoskeletal syndrome. Point mutation in the FGFR3 gene on chromosome 4p is noted.[18] ADULT syndrome is an uncommon syndrome, featuring dental agenesis, ectrodactyly, nail dysplasia, breast hypoplasia. Mutation of chromosome 3q27 is reported in this syndrome.[19, 20]

Most commonly encountered features with dental agenesis are the presence of cleft lip/ palate and marked skeletal disorders. Few like Cleft lip/ palate syndrome or Ectodermal dysplasia syndrome, Coffin-Lowry syndrome and Hay-Wells syndrome are reported with these features. Cleft lip/ palate syndrome presents with dental agenesis in association with syndactyly, ectodermal dysplasia and cleft lip/ palate. The defect in this syndrome is in the genetic locus as a translocation mutation in 11q23-q24.[8] Another form of ectodermal dysplasia syndrome is X-linked translocation from Xq12-Xq13.1.[21,22] Hay-Wells syndrome is associated with the mutation in p63 causing the amino acid substitution of sterile alpha motif (SAM) domain which results in the defective protein interaction.[23] Coffin-Lowry syndrome is an X-linked disorder with a mutation in Xp22.2 which is responsible for the major skeletal disorder.[24]

Syndromes associated with dental agenesis express a wide variety of phenotypic patterns ranging from skin pigmentation, neuropathies, hypermobility of joints, limb and organ malformations to growth retardation. Explanation for the Ehlers-Danlos syndrome-hypermobility type is intracellular retention of type III collagen mutations of COL3A1 (glycine 637 to serine substitution in type III collagen).[25] But the Ehlers-Danlos syndrome-dermatosparaxis type is characterized by extensive skin bruising and short stature. Mutations for this syndrome is recorded in the pNPI gene (i.e. Absence of activity of procollagen I N-proteinase). [26]

Syndromes expressing phenotypic pattern of severe growth retardation are Aarskog syndrome, Ellis-van Creveld syndrome and Johanson-Blizzard syndrome. Aarskog syndrome is an X-linked recessive disorder. The person suffering from this syndrome is recognized soon after birth and is characterized by proportionate short stature along with severe dental agenesis.[27,28] Short limbs, postaxial polydactyly, nail hypoplasia and cardiac defects are the diagnostic features of Ellis-van Creveld syndrome. Mutations of the *EVC1* and *EVC2* genes, on chromosome 4p16 are mapped for this syndrome.[29] Johanson-Blizzard syndrome is characterized by beak-like nose, abnormal hair patterns, aplastic nasal alae, hypotonia and growth retardation. Translocation mutation in chromosome 15q15-q21 is recorded for this syndrome.[30]

Some of less commonly encountered syndromes are Hallermann-Streiff syndrome and Seckel syndrome. Hallermann-Streiff syndrome characterized by short stature and bird-like face is also associated with dental agenesis. It is a dominantly inherited disorder due to mutations in the connexin 43 gene *GJA1*.[31] Seckel syndrome is associated with severe growth retardation, microcephaly and beak-like facies. On the basis of genetic mutation this syndrome is divided into three types.

Mutations in Seckel syndrome-[32]
Seckel 1- 3q22.1-q24
Seckel 2- 18p11.31-q11.2
Seckel 3- 14q23

Some of the syndromes frequently associated with skin pigmentation are Goltz-Gorlin syndrome and McCune-Albright syndrome. Dental agenesis and skin pigmentation along with polyostotic fibrous dysplasia is a well documented feature of McCune-Albright syndrome. Mutation in chromosome number 20q13.2 causes this syndrome.[8] Goltz-Gorlin syndrome is reported to be caused due to heterozygous loss-of-function mutations in the PORCN gene. This syndrome expresses itself as linear skin pigmentation, fat herniation and syndactyly.[33]

Organ malformation is a rare manifestation well documented in the medical literature and directly affects the life expectancy of the patient. Alagile syndrome, Branchio-oto-renal syndrome, Rieger syndrome and Rothmund-Thomson syndrome are a few rare syndromes associated with the malformation of an entire organ or a part of it and is associated with dental agenesis. Mutation in short arm of chromosome 20 is responsible for Alagile syndrome. The main feature of this syndrome is cardiac and ocular anomalies, characteristic facies along with dental agenesis.[34] Branchio-oto-renal syndrome is associated with mutated gene on 8q13.3, 14q23.1 and 19q13.3. The characteristic features of this syndrome are branchial cysts, structural ear defects and renal hypoplasia.[35]

Rieger syndrome is found to be associated with mutation on 4q25 and undefined mutation on 13q14 and 16q24. Hypoplastic iris, umbilical hernia and anal stenosis are the features of this syndrome.[36] Mutation in 8q24.3 leads to phenotypic features like dermatosis, bone defects, scalp defects and hypogonadism which are collectively known as Rothmund-Thomson syndrome.[37]

Charcot-Marie-Tooth disease is characterized by progressive late onset neuropathy and is an autosomal dominant condition. It occurs due to mutations in the NF-L gene (NEFL); the neurofilament light chain (NF-L) is a major constituent of intermediate filament.[24] Fanconi renotubular syndrome occurs due to mutation in 15q15.3, and is characterized by retarded growth, rickets and hypophosphatemia.[8] Missense mutations or small deletions in the X-linked gene, FLNA leads to Frontometaphyseal dysplasia characterized by frontal hyperostosis and metaphyseal dysplasia.[38,39]

Dental agenesis and limb malformation are common to Moebius syndrome, Oral-facial-digital syndrome, Pseudoxanthoma elasticum syndrome, Rapp-Hodgkin syndrome and Larsen syndrome. These syndromes are usually detected early in life and the management of these patients usually requires a multidisciplinary approach. Moebius syndrome is an autosomal dominant condition which shows X-linked patterns of inheritance.[40] Oral-facial-digital syndrome is characterized by malformations of face, oral cavity and fingers. Translocation in Xp22.2 to 22.3 is recorded for this syndrome.[41]

Mutation in 16p13.1 is mapped for Pseudoxanthoma elasticum syndrome which is characterized by yellowish papules on skin leading to sagging of skin along with cardiovascular involvement.[42] Rapp-Hodgkin syndrome is caused due to missene mutations in the p63 gene. This syndrome is characterized by anhidrotic ectodermal dysplasia and cleft lip / palate.[43] Bilateral knee dislocation and characteristic facies are the features of Larsen syndrome. This syndrome is caused due to mutations in gene encoding filamin B (FLNB). This gene has an important role in vertebral segmentation, joint formation and endochondral ossification.[44]

Non Syndromic Mutations: A Missing Link

At times, local factors like trauma and intrauterine disturbances can also lead to dental agenesis especially if affected during initiation (bud stage). Usually in these cases, a single tooth or multiple teeth with similar timing for development are affected. Evolution has reduced the jaw size and changes in the dietary habits have already shown to cause agenesis of 3rd molars, second premolars and lateral incisors.

The homebox genes as well as alteration in epithelial mesenchymal interactions could lead to non-formation of tooth. Correlation such as mutation on Msx1 causing severe oligodontia and mutation of Pax9 causing loss of permanent molars are well established.

CONCLUSION

This is a comprehensive review of literature on the relationship of alterations in the genetic signaling mechanism and anodontia. We are just beginning to uncover the myth of this cellular phenotype transition that plays an important role during development and homeostasis. Human tooth agenesis is probably caused by several independent defective genes, acting alone or in combination with other genes, leading to specific phenotypic patterns.

Biologists have taken huge leaps that will take us a long way in detecting the loci that contribute to dental agenesis. Further research in characterizing the unique syndromic and non-syndromic forms will help us to establish molecular relationship between various signaling genes and their pathways responsible for tooth agenesis. These insights will significantly add to our knowledge of complex cellular events that give rise to molecular development strategies that control the pattering of the human dentition.

A day is not too far where this knowledge can be applied in experimental and clinical trials to develop tooth buds using stem cells. Hope is on the horizon to create teeth *in vitro* to replace the missing teeth.

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