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THE GENETIC BASIS OF DEVELOPMENTAL ANOMALIES OF TEETH

Dentistry

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ABSTRACT

The tooth is a specialized organ of the maxillofacial skeleton and its development involves a number of lengthy and complex stages. Over the years, more than 300 genes have been found to be associated with the process of tooth development. Genetic alterations, environmental factors and developmental timing can hence affect tooth development. The knowledge of the genetic developmental mechanisms of these anomalies is of major interest and understanding this mechanism would also clarify the role of teeth in craniofacial development and would represent an important contribution to the diagnosis, treatment and prognosis of congenital malformations. Future research in this area can lead to development of tests for early diagnosis of these anomalies. This review explores the genetic basis of dental anomalies including defects in the tooth number, size, shape and structure.

KEYWORDS

Genetics, Dental anomalies, Tooth development, Mutation.

INTRODUCTION:

Tooth development is a multilevel, multidimensional and complex process that entails molecular and cellular interactions which have phenotypic outcomes. The series of interactions involve multiple genetic signaling pathways between the ectodermal and the neural crest cells.[1] Interactions, gradients and spatial field effects of multiple genes, epigenetic and environmental factors result in a complex unit of four different tooth types. Mutations in these regulatory genes result in congenital dental defects.[2] Depending on the stage where alteration takes place, different dental anomalies can occur. These anomalies may be either isolated or may be associated with syndromes. Advances in molecular genetics has enabled us to identify the various genes involved in the pathogenesis of dental anomalies.

This article aims to review the genes associated with the development of teeth and to further enlist the etiology of the developmental anomalies.

Tooth Development And The Role Of Genes:

The development of individual teeth is preceded by a thickened epithelial stripe, the dental lamina at the sites of the future dental arches of the maxilla and the mandible. This is followed by the budding of the epithelium, the condensation of the mesenchyme around the bud, and the folding and growth of the epithelium generating the shape of the tooth.[3]

The homeobox (HOX) genes are the most commonly studied genes in relation to tooth development, and are active between 18 and 24 weeks of development.[5]

The key members of the HOX genes include- PAX, MSX, DLX, LHX, BARX AND RUNX2.[6]

The BMP (Bone Morphogenetic Protein), FGF (Fibroblast Growth Factor), TGFb (Transforming Growth factor beta), EGF (Epidermal Growth factor), SHH (Sonic hedgehog), and the WNT (Wingless) families are the major signaling molecules involved in the regulation of tooth embryogenesis.[7]

The position of the tooth germ is determined by the expression of Fgf-8, Pitx-2 and Bmp-4 in the oral epithelium and Pax-9 in the tooth mesenchyme. The tooth type regulation is carried out as a function of the Msx and Dlx gene.[8] The Dlx-7 is expressed in the vestibular lamina site in the bud stage. Dlx-5 and Dlx-7 genes show expression in the lamina-bud transition stage. Dlx- 3 and Dlx-6 play a role in the later stages of tooth development.[9]

Pax-9 is a transcription factor which is expressed in dental mesenchyme at initiation, bud, cap and bell stages of odontogenesis. The expression of Pax- 9 in the mesenchyme is a marker for the sites of tooth formation.[10]

Genes Involved In Dental Anomalies:

Anomalies Associated With The Number Of Teeth-

1. Tooth Agenesis

Tooth agenesis, is one of the most common developmental anomalies that affects the number of teeth.[11] The most frequently missing teeth are the third molars followed by the mandibular second premolars and the lateral incisors.[12] It may present in a syndromic form with the involvement of other organs or tissues, or in an isolated, non-syndromic form. Based on the number of missing teeth, it can further be classified into- hypodontia (< 6), oligodontia (>6) and anodontia (complete agenesis).

Non- Syndromic Tooth Agenesis: -

Non- syndromic tooth agenesis is classified as a sporadic or familial form, inherited in an autosomal dominant, recessive or an X-linked mode. The genes involved in non- syndromic tooth agenesis include:

a. Muscle segment homeobox, Homolog 1 (MSX 1)

MSX 1 was the first gene identified as a causative agent in non-syndromic tooth agenesis.[13] MSX 1 is involved in multiple, epithelial-mesenchymal interactions and appears to be critical during early tooth germ developmental stages.[14] To date, more than 28 MSX1 heterozygous mutations have been reported to cause various types of tooth agenesis, and a majority of these mutations are missense or nonsense mutations.[15]

b. Paired box gene 9 (PAX 9)

A frameshift mutation in PAX, resulting in an alteration in the paired domain of PAX 9, is associated with tooth agenesis.[16] So far, more than 20 PAX 9 mutations have been detected, ranging from missense to deletion of the whole gene.[17] Mutations in PAX 9 preferentially lead to the absence of second molars.[18]

c. Axis inhibitor 2 (AXIN2)

AXIN2 mutations have been reported in patients with syndromic or non- syndromic tooth agenesis and oral clefts.[21] Further, loss-of-function mutation in AXIN2 displays a mixed pattern of dental agenesis.[22]

d. Other genes
EDAR and EDARADD are two genes that have been implicated in non- syndromic tooth agenesis.[23] Mutations in Keratin 17 (KRT17) have been identified in patients with oligodontia.[24] FGFR1, transmembrane receptor of fibroblast growth factors (FGFs), has been associated with families of non- syndromic hypodontia, particularly premolar agenesis.[25]

Syndromic Tooth Agenesis: -
a. Interferon regulatory factor 6 (IRF6)
Mutations in IRF6 have been identified in patients with Van der Woude syndrome. IRF6 mediates interactions between members of the TGF-beta superfamily of signaling peptides.[26]

b. p63
p63 gene mutations have been found in several oral clefting syndromes. Ectrodactyly-ED-clefting (EEC) syndrome is a rare autosomal dominant condition characterized by split hand and feet, ectodermal dysplasia, and cleft lip- palate.[27]

c. Ectodysplasin A (EDA)
Mutations in the EDA gene localized to Xq12-q13 are associated with XLHED.[28]

Recently, mutations in EDA have been reported in cases of non-syndromic hypodontia as well.[28]

d. Other syndromes
Tooth agenesis is also noted in other syndromes like Rieger's syndrome caused by mutation in a homeobox gene, RIEG[29] ; Ellis van Creveld syndrome caused by mutations in the EvC and the EvC2 genes located close to each other[30]; Sotos syndrome caused by a pathogenic variant of NSD1 gene.

2. Supernumerary Teeth
Non- Syndromic Supernumerary Teeth: -
a. Sclerostin domain containing 1 (SOSTDC 1)
Usag-1, a rat gene has been shown to be a causative agent in supernumerary teeth formation. The human homolog gene for Usag-1, SOSTDC-1, shows 85% identity with mouse Usag-1. Studies with larger case groups may reveal a hereditary pattern.[32]

b. APC gene
The APC gene encodes a multidomain tumor suppressor protein that has an important role in assembling the AXIN-CK1-GSK3beta-APC destruction complex that modulates the level of WNT/beta catenin signaling. APC missense variants have been identified in cases of isolated mesiodens and isolated supernumerary tooth formation.[33]

Syndromic Tooth Agenesis: -
a. RUNX2
RUNX2 is required for primary tooth development and it prevents the growth of dental lamina in successional tooth formation.[34] Cleidocranial dysplasia (CCD) is a rare autosomal dominant disorder characterized by general bone dysplasia, patent cranial sutures and fontanelles, hypoplastic clavicles, short stature and dental abnormalities including variable number of supernumerary teeth along with dental crowding and malocclusion.[35] Genetic studies mapped CCD to chromosomal 6p21, and heterozygous mutations in RUNX2 gene. These mutations include insertion, deletion, nonsense and missense variations.[36]

b. APC
Adenomatous polyposis of the colon, is an autosomal dominant hereditary disorder characterized by the development of precancerous colorectal adenomatous polyps, osteomas, dental abnormalities which include supernumerary teeth.[37] APC is located on chromosomes 5q21-q22. Approximately 11-27 % of patients with Gardner's syndrome have supernumerary teeth, but so far, no specific codon mutation of the APC gene was found to correlate with supernumerary teeth.[38]

c. Other syndromes
A number of syndromes are associated with supernumerary teeth such as Ehler- Danlos syndrome, caused due to mutation in Tenascin- XB gene[39]; Nance Horan syndrome due to mutation in the NHS gene[40].

Anomalies Associated With Structure Of Teeth-
1. Amelogenesis Imperfecta
Amelogenesis imperfecta is the name given to a heterogenous group of conditions characterized by inherited developmental enamel defects. In the year 1991, mutations in the AMELX gene was first described as the cause of AI.[41] AMELX mutations cause X-linked AI.[42] Over 20 AMELX mutations have been described including, deletions, frameshifts, nonsense and missense variations.[43]ENAM gene mutation has been shown to cause an autosomal dominant AI of the hypoplastic variant.[44] Autosomal recessive inheritance has also been documented for ENAM mutations.[45] AMBN which can further influence the differentiation and proliferation of ameloblasts has also been reported to be mutated in patients with AI.[46] Further, mutations in the genes (MMP20 and KLK4) encoding for the enamel matrix proteases have also been implicated in the pathogenesis of AI.[41] ITGB6, LAMA3, LAMB3, COL17A1, AMTN and FAM83H are other genes, the mutations of which lead to different phenotypes of amelogenesis imperfecta.

2. Dentinogenesis Imperfecta
Dentinogenesis imperfecta is a hereditary dentin disorder characterized clinically by the presence of gray to yellowish- brown, broad crowns with a cervical constriction. Enamel is easily broken, leading to the exposure of dentin and simultaneous attrition. Dentinogenesis imperfecta type- I is associated with osteogenesis imperfecta which is an autosomal dominant condition resulting from mis-sense mutation of genes COL1A1 and COL1A2.[47]

The dentin sialophosphoprotien gene (DSPP) is located on chromosome 4q22.1, and mutations in this particular gene has been associated with the phenotype of Dentinogenesis imperfecta Type II.[48]

3. Dentin Dysplasia
Dentin dysplasia can be classified into- DD-I and DD-II. DD-I is characterized by teeth presenting with a normal shape and crown colour with absent roots. DD-II is manifested by the presence of amber- translucent crowns, accompanied by significant attrition, extending to the alveolar crest, with short, thin roots and obliterated pulp.[49] Splice mutations in the SMOC2 gene and VPS4B gene have been implicated in the pathogenesis of DD-I.[50,51] A missense mutation in SSUH2 has been reported to cause DD-I.[52] Molecular biology and genetic studies have further shown that DSPP is the pathogenic gene in DD-II.[53]

Anomalies Associated With The Shape Of Teeth-
Tooth development is a complex process and any interruptions in this process can manifest as changes in the shape of the tooth.

Dilaceration is applied to teeth which have the long axis of either the whole or part of the root formed at an angle to the crown. Mutations in the genes BMP2 and BMP4 have been shown to be involved in the dilaceration of the maxillary lateral incisor.[54] Dilaceration of teeth is also associated with a number of syndromes which are caused by genetic disturbances; a few examples of which include the otodental syndrome (FGF3 gene mutation)[55], Hurler syndrome (IDUA gene mutation)[56], cleidocranial dysplasia (RUNX2 gene mutation)[57].

Taurodontism is a developmental anomaly characterized by a large pulp chamber of multirooted teeth with an apical displacement of pulp floor and bifurcation of the roots.[58] It is associated with several syndromes like TDO syndrome (DLX3 gene mutation) and Torg Winchester syndrome (MMP2 gene mutation).[59]

A number of complex signaling pathways play a role in the development of the tooth. Any deviation from normal in any of these pathways can lead to various malformations including, fusion, gemination and Talon's cusp; however, the exact genetic basis of these malformations has not been outlined in the literature.

Table 1: Genes Involved In Dental Anomalies

SR. NO.	DENTAL ANOMALY	GENE
1.	Non- syndromic tooth agenesis.	MSX1, PAX9, AXIN2, EDAR, EDARADD, KRT17,
2.	Syndromic tooth agenesis a. Van der Woude syndrome b. EEC syndrome c. X-linked hypohidroticED d. Rieger's syndrome e. Ellis van Creveld syndrome	IRF6 P63 EDA RIEG EVC and EVC2 NSD1 gene

2.	f. Sotos syndrome	NSD1 gene
3.	Non- syndromic supernumerary teeth	SOSTDC1 APC
4.	Syndromic tooth agenesis a. Cleidocranial dysplasia b. Adenomatous polyposis of colon c. Ehler- Danlos syndrome d. Nance Horan syndrome	RUNX2 APC Tenascin-XP NHS
5.	Amelogenesis imperfecta	AMELX ENAM AMBN MMP20 KLK4 ITGB6, LAMA3, LAMB3, COL17A1, AMTN, FAM83H
6.	Dentinogenesis imperfecta-type-I	COL1A1, COL1A2
7.	Dentinogenesis imperfecta type- II	DSPP
8.	Dentin dysplasia type- I	SMOC2 VPS4B
9.	Dentin dysplasia type- II	DSPP
10.	Dilaceration	BMP2 BMP4
11.	Syndromic dilaceration a. Otodental syndrome b. Hurler syndrome c. Cleidocranial dysplasia	FGF3 IDUA RUNX2
12.	Syndromic taurodontism a. Tricho-dento-osseous syndrome b. Torg-Winchester syndrome	DLX3 MMP2

CONCLUSION:

The development of teeth is carried out by the interaction of various molecular signaling pathways which are under the control of genes. Any mutations in these genes can lead to alterations in the shape, size, number and the development pattern of the teeth. The understanding of these complex interactions between the genetic, epigenetic and environmental factors enables clinicians and researchers for a better understanding of the molecular pathogenesis. In the near future, this can help provide biological based treatment for these conditions.

Conflicts Of Interest:

None.

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