GENETICS AND TOOTH ANOMALIES - AN UPDATE

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Abstract

Tooth development like the development of all epithelial appendages is regulated by inductive tissue interactions between epithelium and mesenchyme. Numerous genes interact, either act in conjunction or antagonize each other in odontogenesis. A number of different mesenchymal molecules and their receptors act as mediators in epithelial mesenchymal interactions. Several genes linked with early tooth positioning and developments belong to signaling pathways and have morphogenesis regulatory functions in morphogenesis of other organs. Their mutations often show pleiotropic effects beyond dental morphogenesis. In contrast, certain genes involved in enamel and dentin structures are highly specific for tooth. Mutations in these genes have been identified as causes of Amelogenesis Imperfecta (AI), Dentinogenesis Imperfecta (DI), Dentin Dysplasia (DD) and anomalies in tooth number. This article focuses on genetic basis of inherited non-syndromic teeth disorders.

Key Words: Amelogenesis imperfecta, Genetics ,Mutation, Odontogenesis

Introduction

In human embryo, deciduous and permanent teeth develop from oral ectoderm and underlying neural mesenchymal cells. Odontogenesis starts at sixth week of IUL[1]. Biomineralization begins during 14-18 weeks of pregnancy, and the crowns of all 20 primary teeth are partially mineralized at birth[2]. During sixth week of IUL, a line of oral epithelial cells thickens to form the dental lamina, which develops several buds , invading the underlying mesenchyme. Reciprocal interactions of epithelial and mesenchymal tissues regulate dental development[3].

Studies of odontogenesis, mostly using mouse teeth as models, have indicated that the position, number, size and shape of different teeth are under genetic control[4]. In the epithelial-mesenchymal interaction of tooth development, the initiating event appears to be the expression of diffusible signaling molecules by oral epithelium that stimulates signal transduction in the underlying ectomesenchyme[5]. These comprise the transforming growth factor β(TGFβ), bone morphogenetic proteins(BMP), fibroblast growth factors(FGF), epidermal growth factors(EGF) and the hedgehog(Hh) and wingless(Wnt) families[6]. Transcription factors are induced that drive the expression of downstream genes that guide odontoblast differentiation.

The expression of Fgf-8 in the first brachial arch epithelium, Lhx-6/7 in the adjacent ectomesenchyme of the 1st brachial arch along with the restricted expression of Gsc in ectomesenchyme finely regulate the oral-aboral axis. The position of tooth germ in the established oral-aboral axis is determined by the expression of Fgf-8, Pitx-2 and Bmp-4 in the oral epithelium and Pax-9 in the tooth mesenchyme.

Once the tooth position is

established, the tooth type determination is regulated through a subfamily of homeobox genes that include Msx gene and Dlx gene. The Dlx-1, Dlx-2 and Barx-1 are seen in posterior regions and Msx-1 and Msx-2 and Dlx-2 are seen in anterior regions of 1st branch tooth ectomesenchyme. The signaling cascades if disturbed may result in dental defects including changes in tooth number, size, morphology and cytodifferentiation. Thesleff has proposed a model of molecular regulation of tooth development from initiation to crown morphogenesis[7]. (Fig.1)

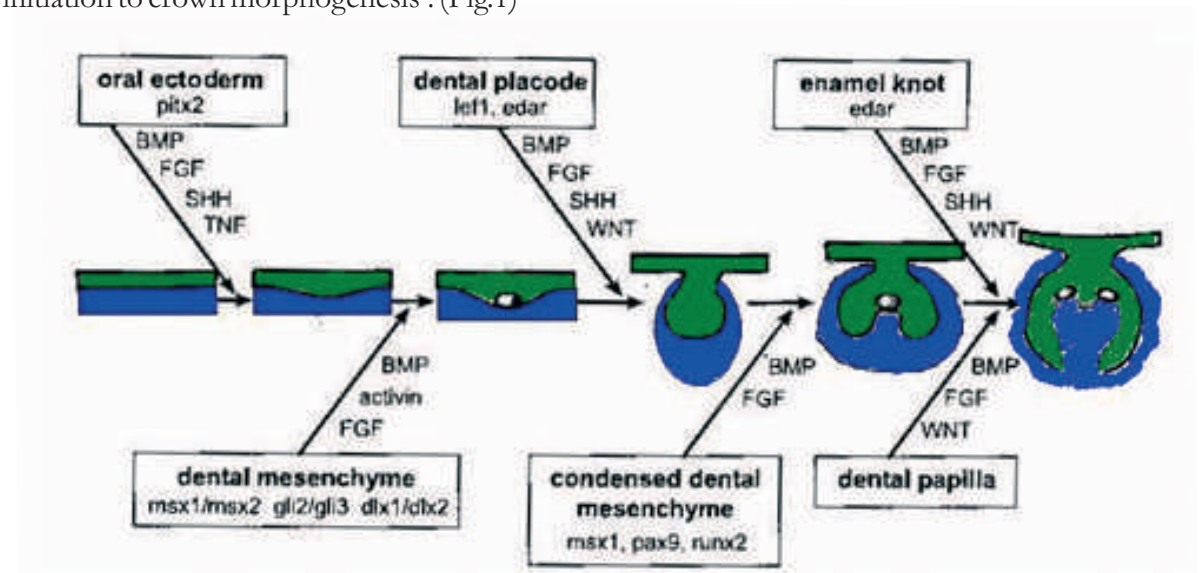

Fig. 1. Molecular regulation tooth development.from initiation to crown morphogenesis. Signaling molecules (BMP-bone morphogenic proteins, FGF- fibroblast growth factors,SHH-sonic hedgehog, TNF- tumor necrosis factor, WNT- wingless type) mediate the epithelial (green color) mesenchymal (blue color) interactions. These signals operate throughout development and regulate the expression of genes.

investigated extensively. Based on the mode of inheritance, AI can be autosomal dominant, autosomal recessive, or X-linked. The enamel of erupted teeth contains only trace amounts of protein, but developing enamel is about 35% protein. The bulk of the enamel protein is expressed from amelogenin gene on X-chromosome (AMELX). Defects in these genes lead to X-linked AI. Besides amelogenin, two other proteins are found in developing enamel: enamelin (ENAM) and ameloblastin (AMBN).

Genetic Basis of Inherited Enamel Defects

Amelogenesis imperfecta is a genetically and clinically heterogeneous group of inheritable disorders primarily affecting formation of enamel. The prevalence of AI varies in different populations, ranging from 1 in 700 in to 1 in 4000[8,9]. Based on enamel appearance and hypothesized developmental defects, AI can be classified into hypoplastic (secretory defect), hypocalcified (mineralization defect), and hypomaturation (protein processing and maturation defect) forms[10]. The human amelogenin genes on X and Y chromosome have been cloned and

Defects in ENAM cause autosomal dominant AI. Enamel matrix proteins are secreted along with enamelysin encoded by MMP20[5]. Mutation of it leads to autosomal recessive pigmented hypomaturation AI. When secretory ameloblasts enter transition stage, they reduce their secretion and initiate expression of KLK4 (kallikrein) and AMTN (amelotin). Like MMP20, mutation of KLK4 causes autosomal recessive pigmented hypomaturation AI.

Hereditary enamel defects	*Inheritance*	*Genes involved*	*Locus*	*Proteins*	*Associated defects*
Amelogenesis Imperfecta	Autosomal dominant	TUFT 1	1q21	tuftelin	Hypoplastic type
		AMTN		amelotin	
		ENAM	4q21	enamelin	
		DLX3	17q21		Hypoplastic hypomaturation with taurodontism
		AMBN	4q21	Ameloblastin	
	Autosomal recessive	MMP20	11q22.3-q23	Enamelysin (protienase)	Pigmented hypomaturation
		KLK4	19q13.4	Kallikrein (protease)	
	X-linked	AMELX	Xp22.1-p22.3 xq 22-q28	Amelogenin	Generalized thin diffuse hypomaturation, Snow cap hypomaturation
		AMELY	Yp11.2		No pathology reported yet

Table 1. Genes,locus,proteins and associated defects seen in Hereditary enamel defects[4,5,6]

Genetic Basis of Inherited Dentin Defects

Shields (1973, 1983) have classified dentin defects associated with genetic disorders as Dentinogenesis imperfecta (DGI) type I, type II, type III and dentin dysplasia (DD) type I and type II[11].One of the major proteins of dentin is type 1 collagen, encoded by 2 genes COL1A1 and COL1A2[5]. Defects in these genes cause osteogenesis imperfecta which has dentinogenesis imperfecta phenotype in about 50% of cases (DGI type I). DSPP genes encodes for other major extracellular dentin proteins. Recent studies indicate that defects in DSPP gene are predominant cause of dentin dyspasia II, dentinogenesis imperfecta II and III, together known as DSPP associated dentin defects. DSPP is bicistronic: dentine sialoprotein (DSP) and dentine phosphoprotein (DPP), are cleavage products of its single transcript[12]. Silva et al.(2004) suggested that dentin matrix proteins could have an active role in inflammatory cell recruitment during the pathological processes associated with dentin and bone matrix resorption. The incidence of dentinogenesis imperfecta is evaluated between 1/6000 and 1/8000 in children[13].

Hereditary Dentinal Defects	*Inheritance*	*Genes involved*	*Locus*	*Proteins*	*Associated defects*
Dentinogenesis imperfecta type-I	Autosomal dominant or recessive	COL1A1 COLIA2	17q21.31-q22 7q22.1	typeI collagen	
Dentinogenesis imperfecta type II &III	Autosomal dominant	DSPP	4q21	Dentin sialo-phospho protein	Shell teeth
Dentin dysplasia type I	Autosomal dominant	DSPP		Dentin sialo-phospho protein	Radicular dentin dysplasia
Dentin dysplasia type II	Autosomal dominant	DSPP		Dentin sialo-phospho protein	Coronal dentin dysplasia

Table 2. Genes, locus, proteins and associated defects seen in Hereditary Dentinal defects [4,5,6]

Genetic Basis of Anomalies in Tooth Number

Tooth agenesis is the most prevalent craniofacial congenital malformation in human. Mutations in the MSX1(*4p16.1*) gene lead to specific hypo/oligodontia. A nonsense mutation in the MSX1 gene was associated with tooth agenesis and various combinations of cleft lip and /or palate. Mutations in the transcription factor gene, PAX9 (*14q12-q13)* cause absence of most permanent molars with or without hypodontia in primary teeth[14]. AXIN 2 (*17q23-24)* mutations lead to tooth agenesis and colorectal cancer.

To explain the occurance of supernumerary teeth, in 1984, Brook proposed a combination of genetics and environmental factors[15]. This genetic component in hyperdontia was further evidenced by their simultaneous occurance in monozygotic twins[16].

Conclusion

Genetic diseases are caused by gene mutations that are inherited from one or both parent's. Certain genetic diseases can cause abnormalities in teeth, affecting the rate of development of primary and secondary teeth or their physical characteristics. The identification of major genes and knowledge of their functions, their regulations by local, systemic and environmental factors should provide clearest understanding of clinical manifestations. Oral health professional should understand the advances in dental health research and genetic studies, thus identifying the etiologic mechanisms of craniofacial anomalies.

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Source of Support - Nil

Conflict of Interest - None declared

How to cite this article:

Raj Aswathy, MS Deepa, T Farooqi Hasan Ahmed, Brahmanandan Aswathy:Genetics and tooth anomalies - an update, Oral Max Path J, 4(1), Jan-Jun 2013: 334-338