Role of Homeobox Genes in Developmental Anomalies of Teeth

Yani Corvianindya Rahayu*
*Dept of Oral Biology, Faculty of Dentistry University of Jember
Correspondence: yanicorvi25@gmail.com

Abstract

Introduction: *Development of teeth is under strict genetic control, which ensures the formation and renewal of a certain number of teeth with specific shapes and position. Gene mutations can disturb normal dental development and affect tooth number, shape, eruption or formation of dental hard tissues. The process of odontogenesis is under the control of homeobox (HOX) genes; a number of different mesenchymal regulatory molecules and their receptors.* ***Objective:*** *To review the role of homeobox genes in the developmental anomalies of teeth.* ***Literature review :*** *There are different molecular signalling that regulate tooth development and it is possible to observe that the molecular signals are expressed in different stages of odontogenesis. HOX genes are classified as muscle segment (MSX1 and MSX2), distal-less (Dlx), orthodontical, goosecoid, paired box gene 9 (Pax9) and sonic hedgehog (Shh). Msx1 and Msx2 genes are responsible for the developmental position and further development of tooth buds. Dlx-1, Dlx-2 and Barx-1 genes are involved in development of molar teeth. Pax9 is a transcription factor required for tooth morphogenesis. Dental anomalies are often observed as isolated, that is, only dentition is affected, and especially failure to develop all teeth.* ***Conclusion :*** *The genetic causes of dental pathologies are multiple causing phenotypic changes and the severity of which is dependant on the affected gene, the type and location of mutations.*

Keywords : *homeobox genes, development teeth, anomalies*

Introduction

A dentist must have thorough knowledge of genetic research in order to observe the various abnormalities and to intervene early to remedy the situation, and in more complex cases, recommend patients to specialists in medical genetics or genetic counseling. According to the National Institute of Dental and Craniofacial Research Genetics (2008) in the U.S. more than 700 are craniofacial disorders from the approximately 5500 known genetic disorders in humans. Only in 20% of all known diseases could have been genetically determined. Teeth are serially homologous structures, which allow the localization and quantification of the effects of specific gene mutations. Tooth development may be divided in multiple stages, where the number, size and type of teeth are sequentially determined.

During tooth morphogenesis, expression of these homeobox genes is directly under the control of signalling cascades initiated by the interaction of growth factors and receptors on the surface of the target cells [2]. Cell differentiation and morphogenesis which are controlled by gene expression. Gene expression is defined as an activation of a gene that results in production of polypeptide/protein that can activate/deactivate other genes with the influence of transcription factors (growth factors). Every organism has a unique body pattern because of the influence of Homeobox genes. These seem to be the master genes that help in development of individual structures from different areas of the body. [3]

A homeobox is a DNA sequence found within genes that are involved in the regulation of patterns of anatomical development (morphogenesis) in human beings. The homeobox is about 180 base pairs long. It encodes a protein domain (homeodomain) which when expressed protein in binding with the DNA. The homeodomain is capable of recognizing and binding to specific DNA sequences. These play an important role in specifying cell, identity and positioning during embryonic development and mutations in these genes can cause developmental disturbances in tooth genesis like of specific structures as well as changes in the dentistry of a body part causing phenotypic changes in the patterning of an organism due to mutations [4].

The process of odontogenesis is under the control of homeobox (HOX) genes; a number of different mesenchymal regulatory molecules and their receptors. HOX genes are classified as muscle segment (MSX1 and MSX2), distal-less (Dlx), orthodontical, goosecoid, paired box gene 9 (Pax9) and sonic hedgehog (Shh). Msx1 and Msx2 genes are responsible for the developmental position and further development of tooth buds, respectively. Dlx-1, Dlx-2 and Barx-1 genes are involved in development of molar teeth. Pax9 is a transcription factor required for tooth morphogenesis and plays a role in the establishment of the inductive capacity of the tooth mesenchyme as it is necessary for the mesenchymal expression of bone morphogenetic protein (Bmp4), MSX1 and Lef1 genes. Tumor necrosis factor, fibroblast growth factor, Bmp, Shh and Wnt pathways are involved in signaling pathways of organogenesis on the 9^{th} to 11^{th} embryonic days to initiate tooth epithelium. Any mutation in these genes and any disruption of regulatory molecules may result in the anomaly of dental characteristics [5,6]

Homeobox Genes Involved in Odontogenesis

All studies show that there is a direct genetic control on odontogenesis, which determines the position, number, size and shape of the teeth. Tooth formation undergoes different stages like bud, cap and bell stage during its developmental process. During the bell stage cyto differentiation occurs which lead to the formation of enamel, dentin, Periodontal ligament which is a supporting structure of the tooth [7]. Like other development processes during the embryonic phase morpho differentiation of teeth occurs under the influence of first branchial arch, where complex interactions between the stomodaeal epithelium which is ectodermal derivative and the underlying mesenchyme which cranial neural crest derivative take place. More than 300 genes are involved in this processes and prominent role is played by the transcription factors that have a homeodomain. The homeodomain consists of 60 aminoacids with a helix-turn-helix DNA binding protein and is encoded by a homeobox sequence. Not only homeodomain facilitates it binding with DNA but transcription factors also contain a transactivation domain that interacts with a RNA polymerase and these transcription factors are in turn involved in the regulation of homeobox gene expression sites thus having a role in activation of genes in embryogenesis [8].

Role Of Growth Factors in Odontogenesis

During embryonic development, the neural crest cells differentiate into most of the skeletal and connective tissue structures of the craniofacial region. Establishment of pattern in the craniofacial region is determined partly by the axial origin of the neural crest cells present within each arch and partly by regional epithelial mesenchymal interactions mediated by several growth factors signaling pathways. Important factors belong to Fibroblast growth factors (FGF) and Transforming growth factors (TGF, containing BMP4-bone morphogenetic protein 4), the family of Wnt (Wingless) and morphogenesis molecule Shh (Sonic hedgehog). The general pattern of dentition is developed much before the teeth erupt into the oral cavity. Generally tooth formation is genetically a complicated processes controlled in two different ways: on one end by specifying the type, position, size of each tooth bud; and on the other end by the processes of enamel and dentin formation. All the above mentioned transcription factors define spatially the domains of expression of the

homeobox genes in the developing jaws. This explains the reason why the mutation of these genes have pleiotropic effects in addition to nonsyndromic /syndromic related dental abnormalities [9,10].

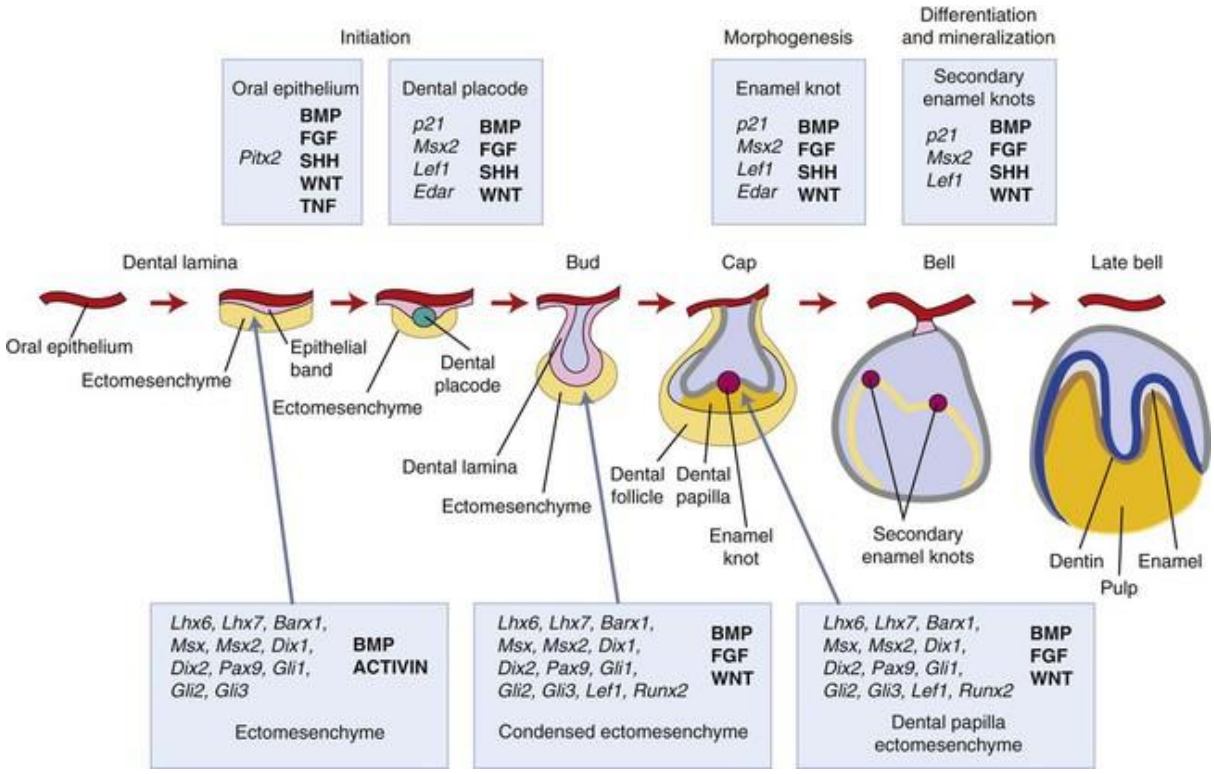


Fig 1. .Model of the molecular regulation of tooth development from initiation to crown morphogenesis. Expression sites of transcription factors (*italic*) and signaling molecules (bold). Interactions between epithelial and mesenchymal tissues are mediated by signal molecules (BMP, bone morphogenetic proteins, FGF, fibroblast growth factors, SHH, sonic hedgehog, WNT, TNF, tumor necrosis factor). These signals operate throughout development and regulate the expression of genes in the responding tissues. [11]

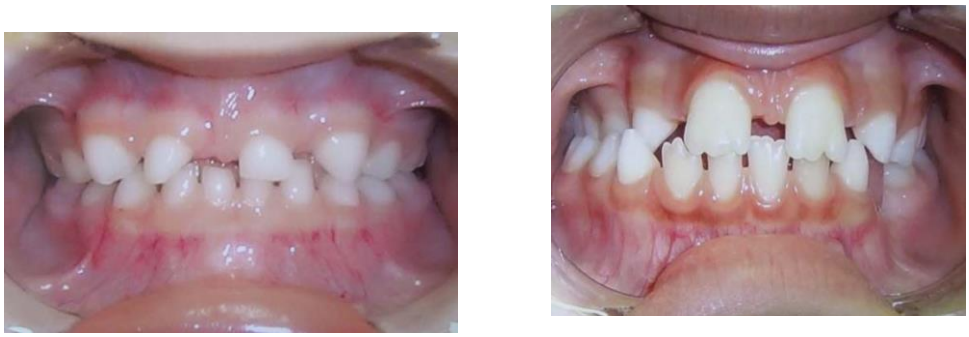
Numeric dental anomalies

Tooth agenesis is the most common numeric dental anomaly. Hypodontia, oligodontia and anodontia are the terms used to describe the numerical values of tooth agenesis. Different inheritance modes were found for tooth agenesis. Hypodontia is frequently accompanied with cleft-lip or palate, reduction in tooth size, short root anomaly, malformation of other teeth, impaction, maxillary canine and first premolar transposition,

delayed formation or eruption of other teeth, microdontia, taurodontism, enamel hypoplasia and altered craniofacial growth. Sometimes, it is caused by environmental factors such as; infection, different kinds of trauma in the apical area of dentoalveolar process, chemical substances or drugs, radiation therapy or disturbances in the jaw innervations, but in the majority of cases, hypodontia is impacted by genetics. Arte *et al*., evaluated 214 family members in three generations and concluded that incisor-premolar agenesis is transmitted by autosomal dominant genes with small upper incisors, ectopic canines, taurodontism and rotated premolars as accompanying anomalies [12].

Several candidate genes have been investigated for tooth agenesis. A familial autosomal dominant hypodontia was demonstrated to be caused by a point mutation in the MSX1 gene. This finding supported the result of an animal study, which showed a knockout mutation of MSX1 gene leading to the inhibition of dental development. [13] Another gene, causing tooth agenesis is Pax9 in chromosome 14 (14q21-q13). In hypodontia cases, a deletion of the Pax9 gene resulting in haploinsufficiency has been described. A frameshift mutation and a nonsense termination mutation of the same gene have been observed in oligodontia. Hypodontia and oligodontia are not fundamentally different or at least can be caused by different mutations in the same gene. [14]

Another mode of inheritance for hypodontia associated with other dental anomalies such as dental malformations, enamel hypoplasia and eruption failure is the autosomal recessive inheritance, with polygenic inheritance also suggested. Tooth agenesis was associated with a large number of syndromes, which indicating that the development of teeth and certain organs are under the control of the same molecular mechanisms. Hypodontia is a major component of ectodermal dysplasia, oral-facial digital syndromes with oral-facial clefting. [15]

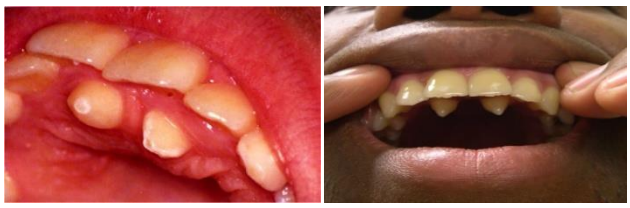


2A 2B

Fig 2. A. Deciduous dentition with increased overbite, cone-shaped maxillary right central incisor, malformed lower anterior teeth and dental agenesis . B. Mixed dentition with atresic maxilla, posterior crossbite on the right side, presence of irregularities on incisal margins of upper and inferior incisors and dental agenesis [16]

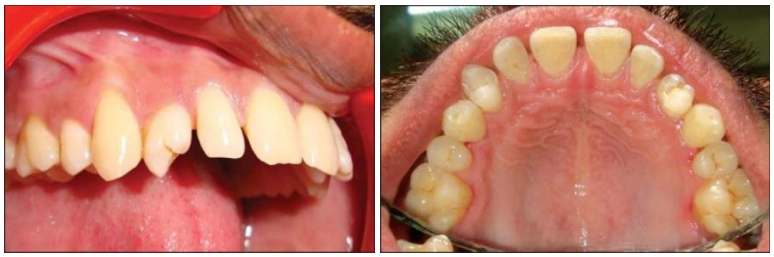
Dental morphology, size and positional anomalies

HOX genes, which play a role in oral and dental development are known to show site specific anteroposterior expression patterns. MSX1, regulator gene in the third molar and lower second premolar agenesis, may be responsible for posterior site development. In addition to the other posterior area genes, which are Dlx-1, Dlx-2 and Barx-1, Pax9 also control the development of all of the molars. Furthermore, Neubüser *et al*., reported that there is an association between Pax9 transcription factor and repositioning of tooth buds on the mesenchymal level. This theory might give a clue to researchers about the genetic mechanisms of dental positional anomalies such as palatally displaced canines or different kind of transpositions. It appears that tooth agenesis, tooth size and position anomalies, which are often seen together, are the components of a complex, genetically controlled dental condition. Dental malpositions such as rotations, eruption failures and ankylosis are among other anomalies complicating this dental condition. [8,13]



3A 3B

Fig 3. Anomalies of tooth position [17]



4A 4B

Fig 4. a.Clinical photograph of case-2 showing maxillary right canine-premolar transposition b. Intra-oral photograph showing bilateral maxillary canine premolar transposition. [18]

Discussion

Tooth formation is considered to be a more complex process, which also is genetically controlled in two different ways: on one side, each tooth organ is specified by its type, size and position and on the other, by the processes of formation of enamel and dentin. Different genes involved in the formation of teeth belong to signaling pathways with functions in regulating the morphogenesis of other organs [19]. 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. There are different molecular signalling that regulate tooth development and it is possible to observe that the molecular signals are expressed in different stages of odontogenesis. The expression of Msx 1 in the dental mesenchyme is initially by epithelially derived Bmps and Fgfs. Interestingly, Bmp4 cannot induce Fgfs, neither the contrary, suggesting that Bmp4 and Fgf8 act by independant pathways in inducing dental mesenchyme. The arrest of tooth development in Msx 1 mutant mice was associated with a down-regulation of Bmp4, Fgfe, Lef1, Ptc, Dlx 2 and Syndecan 1 in the molar mesenchyme. This suggests that Msx 1 is placed upstream of those genes. In addition mesenchymal Bmp4 provides a positive feedback signal for maintenance of Msx 1 expression. Recent studies have clarified some aspects of the molecular signalling that occur during the bud stage of odontogenesis. The down regulation of Lef 1 and Dlx 2 in the epithelial bud is caused by the down regulation of Bmp4 in the molar mesenchyme [20].

This was deduced from the observations that addition of exogenous BMP4 could partly rescue the tooth phenotype and induces Lef 1 and Dlx 2 expression in the Msx1

mutant molar tooth germ. Moreover, mesenchymal BMP4 is also required for the maintenance of Shh and Bmp2 expression in dental epithelium and may be responsible for inducing the formation of enamel knot in tooth epithelium. On the other hand, over-expression of Bmp4 in the wild type molar mesenchyme represents Shh and Bmp2 expression in the enamel knot, suggesting that Shh and Bmp2 may not be critical signals in regulating the formation of tooth cusps [21]. Similar to the many other embryonic organs, the mammalian tooth development also relies largely on epithelial-mesenchymal interactions. It is also reported that approximately 8% of the newborn double-mutants generated exhibited clefts in the mandible and tongue, whereas the mandibular processes of the double-mutant mice generated lacked the midline symphysis and were fused. In these double-mutants, either a single incisor arrested in the bud stage or no incisors were present. The arrested incisor tooth buds showed decreases in the expression of Pax-9 and patched. The phenotypic abnormalities in Prx-l and Prx-l/Prx-2 mutants indicate redundant but essential roles for Prx-l and Prx-2 in the signaling network regulating epithelial-mesenchymal interactions that promote outgrowth and skeletogenesis in the mandible [22].

Conclusion

Teeth are serially homologous structures, which allow the localization and quantification of the effects of specific gene mutations. Tooth development may be divided in multiple stages, where the number, size and type of teeth are sequentially determined. Furthermore, it is also possible to determine the phase of odontogenesis affected by these conditions. These features make tooth development an important system to understand the intricate molecular mechanisms that regulate development and genetics. The genetic causes of dental pathologies are multiple causing phenotypic changes and the severity of which is dependant on the affected gene, the type and location of mutations.All the causes of dental diseases is still not known, but their genetic basis is never a neglected factor. Hence, it can be stated that tooth morphogenesis occurs by numerous genetic and epigenetic factors not just by a single gene and also most of the developmental defects in teeth usually occur as a result of mutations in genes encoding signalling molecules and transcriptional factors.

Referrences

1. Thesleff I. How to build a tooth? Developmental biology is revealing the instructions. Nor Tannlegeforen Tid 2004; 114: 328—34.
2. PT Mc Collum, HP Sharpe. Developmental genetics and early hominid craniodental evolution. Bioessays. 2001;23:481–93.
3. Thesleff I. The genetic basis of tooth development and dental defects. Am J Med Genet A. 2006;140:2530–35.
4. PT Mc Collum, HP Sharpe. Developmental genetics and early hominid craniodental evolution. Bioessays. 2001;23:481–93.
5. Cobourne MT. The genetic control of early odontogenesis. Br J Orthod. 1999;26:21–8.
6. Peters H, Neubüser A, Kratochwil K, Balling R. Pax9-deficient mice lack pharyngeal pouch derivatives and teeth and exhibit craniofacial and limb abnormalities. Genes Dev. 1998;12:2735–47.
7. AS Tucker. Encyclopedia of life sciences, JohnWiley & sons LTD; 2009. Tooth morphogenesis and patterning molecular genetics.
8. Thesleff. Homeobox genes and growth factors in regulation of craniofacial and tooth morphogenesis. Acta Odontol scand. 1995;53:129–34.
9. KE Haworth, C Healy, P Morgan, PT Sharpe. Regionalisation of early head ectoderm is regulated by endoderm and prepatterns the orofacial epithelium. Development. 2004;131:4797–806.
10. K Kurisu, MJ Tabata. Hereditary diseases with tooth anomalies and their casual genes. Kaibogaku Zasshi. 1998;73:201–08.
11. http://www. *pocketdentistry.com/5-development-of-teeth/*. Pocket Dentistry 2015. Development of the Tooth and Its Supporting Tissues.
12. Arte S, Nieminen P, Apajalahti S, Haavikko K, Thesleff I, Pirinen S. Characteristics of incisor-premolar hypodontia in families. J Dent Res. 2001;80:1445–50.
13. Vastardis H, Karimbux N, Guthua SW, Seidman JG, Seidman CE. A human MSX1 homeodomain missense mutation causes selective tooth agenesis. Nat Genet. 1996;13:417–21.
14. Das P, Stockton DW, Bauer C, Shaffer LG, D'Souza RN, Wright T, et al. Haploinsufficiency of PAX9 is associated with autosomal dominant hypodontia. Hum Genet. 2002;110:371–6.
15. Vieira AR, Meira R, Modesto A, Murray JC. MSX1, PAX9, and TGFA contribute to tooth agenesis in humans. J Dent Res. 2004;83:723–7.
16. Cláudia Schermann Poziomczyk , Júlia Kanaan Recuero , Luana Bringhenti. Incontinentia pigmenti. An. Bras. Dermatol. 2014 : 89{1}.
17. VrachFree. Anomalies of tooth position. http://vrachfree.ru/en/diseases-en/item/9778-anomalies-of-tooth-position-en.
18. Deepa Dhruvakumar, Vidhi Munjal, Saras Mediratta. Mandibular canine-lateral incisor and maxillary bilateral canine-premolar transposition: Report of two cases. Journal of Orafacial Sciences. 2014. 6 (2); 122-124.
19. Genes and dental disorders. Clujul Medical. 2013;86(4):305–08.

20. Z Zhao, D Stock, A Buchanan, K Weiss. Expression of Dlx genes during the development of murine dentition. Dev Genes Evol. 2000;210:270–75.
21. RR Doshi, AS Patil. A role of genes in craniofacial growth. IIOABJ. 2012;3(2):19–36.
22. Y Zhang, Z Zhang, X Zhao, X Yu, Y Hu, B Geronimo. A new function of BMP 4 in regulation of sonic hedgehog expression in the mouse tooth germ development. 2000;127:1431–43.