

The genetic basis of dental anomalies and its relation to orthodontics

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ABSTRACT

The interruption of odontogenesis by any etiological factor may result in dental anomalies. Apart from the environmental factors, the impact of genetics in dental anomalies was found to be a factor in different levels. Many authors had questioned a common genetic defect resulting in different phenotypic conditions such as absent, malformed, malposed or ectopic teeth. Because the multidisciplinary treatment of these dental anomalies such as hypodontia, impaction etc., involves orthodontic intervention, orthodontists must be aware of the etiology and possible correlative conditions with dental anomalies.

Key words: Dental anomalies, genetics, orthodontics

INTRODUCTION

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.^[1,2] Dlx-1, Dlx-2^[3,4] and Barx-1 genes^[5,6] are involved in development of molar teeth. Pax9 is a transcription factor required for tooth morphogenesis^[7] 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.^[8] Tumor necrosis factor, fibroblast growth factor, Bmp, Shh and Wnt pathways are involved in signaling pathways of organogenesis on the 9th to 11th 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. These anomalies are listed as follows:

NUMERIC DENTAL ANOMALIES

Tooth agenesis

Tooth agenesis is the most common numeric dental anomaly.^[9] Hypodontia, oligodontia and anodontia are the terms used to describe the numerical values of tooth agenesis. Hypodontia is the absence of 1-6 teeth (excluding third molars), whereas oligodontia refers to the absence of more than 6 teeth (excluding third molars) and anodontia is the complete absence of teeth.

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.^[10] Sometimes, it is caused by environmental factors such as; infection, different

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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. Autosomal dominant inheritance with incomplete penetrance and variable expressivity was first proposed by Burzynski and Escobar.^[11] For a genetic linkage study on hypodontia, Arte *et al.*,^[12] 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.

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. Vastardis *et al.*,^[13] using a linkage analysis in a family with second premolar and third molar agenesis, defined a locus on the chromosome 4p16 as the site of the MSX1. Sequence analysis revealed arg31-to-pro missense mutation in the MSX1 homeodomain for all of the affected subjects. Arg31-to-pro mutation is known to influence the MSX1 interactions, which are critical in the normal development of human teeth.^[13] This finding supported the result of an animal study, which showed a knockout mutation of MSX1 gene leading to the inhibition of dental development;^[14] however, when the premolar agenesis was accompanied with a lateral incisor, the influence of MSX1 and MSX2 genes could not be proved.^[15]

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. According to Das *et al.*, this situation suggests that hypodontia and oligodontia are not fundamentally different or at least can be caused by different mutations in the same gene.^[16]

The frameshift mutation of Pax9 gene located on chromosome 14 was identified as responsible for autosomal dominant oligodontia in a large family for four generations. In some of the affected members, maxillary and mandibular second premolars and mandibular central incisors were absent in addition to the lack of permanent molars; although, a normal primary dentition was present.^[17] In 2001, Nieminen *et al.*,^[18] identified an A-to-T transversion of the Pax9

gene in a family with autosomal dominant oligodontia. They reported that all the second and third permanent molars, maxillary lateral incisors and in some cases all of the first permanent molars and several second premolars were missing, in addition to deciduous second molar agenesis. Another feature observed in the affected individuals was reduced size of permanent teeth.^[18] A year later, Frazier-Bower *et al.*^[19] concluded that the molar oligodontia is due to allelic heterogeneity in Pax9, which is an important regulator of molar teeth development. In 2003, Lamni showed a distinct phenotype with canine agenesis, which is quite rare, in a family segregating autosomal dominant oligodontia.^[20]

In recent studies,^[21,22] different transition, insertion and transversion mutations in Pax9 gene were reported, providing more comprehensive explanations for the pathogenic mechanisms of the interactions between mutations and tooth agenesis. In addition to Pax9 and MSX1 genes, contribution of a regulatory molecule in the mesenchyme, called transforming growth factor alpha, might play a role in isolated dental agenesis.^[23] Furthermore, Axin2 is a negative regulator of canonical Wnt signaling and mutations of this gene can cause tooth agenesis associated with colorectal cancer.

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,^[24] with polygenic inheritance also suggested.^[25,26]

Studies showed that tooth agenesis could be manifested as an isolated feature or as a part of a syndrome.^[27,28] Tooth agenesis was associated with a large number of syndromes,^[27] 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. Ectodermal dysplasia is characterized by small, misshapen and missing teeth, delayed eruption, prominent lip, maxillary hypoplasia, sparse hair and hypohidrotic skin.^[29-31] This disorder is inherited as an X-linked trait,^[27] though the autosomal recessive form has also been reported.^[32] Oral-facial digital syndrome type 1 has symptoms such as hypodontia of lower incisors, facial asymmetry, hypertelorism, micrognathia, supernumerary frenulum and thickened alveolar ridges.

Oral-facial clefting is affected by chromosome 6p24, 2p13, 19q13 and 4q and the prevalence of hypodontia

increases with cleft severity. The upper lateral incisor is the most frequently affected tooth in the cleft area both in primary and in permanent dentitions.

In syndromic cleft lip and palate (CLP) like Pierre-Robin sequence 50% hypodontia and Van Der Woude syndrome 70% hypodontia prevalence is associated with other disorders.

Hyperdontia

Hyperdontia is the term used to describe supernumerary teeth. The genetic basis of hyperdontia has been extensively explained in the literature. In 1932, Stafne^[33] evaluated over 200 cases with hyperdontia and concluded 90% hereditary etiology. Brook^[34] reported a greater occurrence of supernumerary teeth in the close relatives of effected individuals, compared with the general population. Evidence from twin and family studies supported the genetic basis of hyperdontia.^[35-39] It was also reported that the supernumerary and impacted teeth occupied the same location in the identical twins and in their parents.^[40]

The mode of inheritance of hyperdontia has been proposed as autosomal dominant.^[41] Although there is no difference in the sex distribution for the primary dentition, supernumeraries occur more frequently in the permanent dentition of males. Supernumerary teeth may occur in isolation or as part of a syndrome, such as in CLP, cleidocranial dysplasia and Gardner's syndrome and less commonly in Fabry Anderson's syndrome, chondroectodermal dysplasia, Ehlers-danlos syndrome and tricho-rhino-phalangeal syndrome.^[42] Supernumerary and impacted teeth, retarded eruption of primary and permanent dentition, aplasia or hypoplasia of clavicles and other skeletal anomalies are the features of this disorder exhibiting autosomal dominant inheritance.^[27]

STRUCTURAL ANOMALIES

The structural anomalies of teeth are caused by the disturbances at the level of enamel and dentin during tooth development. Amelogenesis imperfecta as one of these disorders, is characterized by discolored teeth and anterior open bite^[43] and exhibits X-linked, autosomal dominant and recessive inheritance^[44-46] caused by mutation of five different genes; Amelogenin AMEL, Enamelin ENAM, Matrix metalloproteinase- 20 MMP20, Kallikrein-related peptidase 4 KLK4 and Family with sequence similarity 83, member H FAM83H. Both deciduous and permanent dentitions are affected. There are three

types of amelogenesis imperfecta; as hypoplastic; with thin, normally calcified enamel, hypocalcified; with less mineralized, but normal thickness enamel and hipomaturation with enamel structure that has the same radiodensity of dentin and which is easily dislodged from dentin. In a study of 50 patients with hypoplastic amelogenesis imperfecta, anterior openbite occurred in 24% of the cases and severe vertical discrepancy was observed in almost all of them.^[47] Furthermore, it was shown that this specific malocclusion with autosomal recessive inheritance was caused by the mutation in the enamel gene,^[46] which is the largest protein in the enamel matrix of developing teeth.^[48] When hypoplastic teeth coexist with an anterior openbite, the orthodontists should investigate the genetic background for any existing condition.

Another structural anomaly is dentinogenesis imperfecta (DGI), an autosomal dominant condition. There are three types of DGI. Type I is syndromic form of DGI which is inherited with osteogenesis imperfecta and the genes encoding collagen, type I, alpha 1, (COL1A1) and COL1A2. The teeth of both dentitions are typically amber, translucent and show significant attrition. Radiographically, the teeth have short, constricted roots and dentin hypertrophy leading to pulpal obliteration either before or just after eruption. Expressivity is variable even within an individual, with some teeth showing total pulpal obliteration while in others the dentin appears normal. The other two forms seem to result from mutations in the gene dentin sialophosphoprotein, encoding dentin phosphoprotein and dentin sialoprotein.^[49] Bulbous crown are typical features of DGI type II, with hypotrophy in dentine structure. Dentin dysplasia (DD), which has radicular and coronal subtypes is another structural anomaly and has the same genetic disorder with DGI, except DD type I (radicular type).

DENTAL MORPHOLOGY, SIZE AND POSITIONAL ANOMALIES

The importance of the genetic factors controlling tooth size and morphology has been shown by twin studies.^[50-52] Some authors reported that tooth crown dimensions, especially buccolingually and mesiodistally were genetically determined.^[53,54]

It has been suggested that there is an association between oversized teeth and supernumerary teeth.^[34] Similarly, the existence of peg shaped or strongly

mesiodistally reduced lateral incisors may be the result of a variation in the expression of hypodontia.^[12]

The displacement of canines in a palatal direction is a positional dental anomaly and can generally happen even if there is adequate place in the dental arch. This situation frequently results in the impaction of the ectopic tooth. There is an association between the malpositions of certain teeth, such as palatally displaced canines, mandibular lateral incisor-canine transposition and maxillary canine-first premolar transpositions and tooth agenesis. Similar for tooth agenesis, the positional anomalies of canines have been shown to affect some family members and thought to be under strong genetic control. Some authors suggested that the ectopic canines exhibit a multifactorial inheritance pattern with high phenotypic variance and low penetrance.^[37,55-60] Peck *et al.*^[26] reported that palatally displaced and frequently impacted canines and mandibular lateral incisor-canine transposition were related to congenitally missing third molars in the posterior orofacial area. Similarly, an association between the maxillary canine-first premolar transposition and maxillary lateral incisor agenesis in the anterior orofacial area may exist. Furthermore, the agenesis of the lower second premolar, which is located in an intermediate zone is related to all the positional anomalies of canines.

The anteroposterior morphogenetic field concept, proposed by Butler in 1939,^[61] supports the current molecular investigations such as the determination of the interaction between a single gene and site specific orofacial expressivity. HOX genes, which play a role in oral and dental development are known to show site specific anteroposterior expression patterns.^[62,63] MSX1, regulator gene in the third molar and lower second premolar agenesis, may be responsible for posterior site development.^[13] In addition to the other posterior area genes, which are Dlx-1, Dlx-2^[3,4] and Barx-1,^[5,6] Pax9 also control the development of all of the molars.^[19] Furthermore, Neubüser *et al.*,^[7] 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.^[64,65]

CONCLUSION

The etiology of dental anomalies is partly environmental and partly genetic. Because of the polygenic nature of dental characteristics, it is very challenging to identify one single defective gene responsible for a specific dental anomaly. However, recent studies provide new data about the candidate genes. Further studies are required and the rapid progress in the field of genetics may help the clinicians to more accurately discern the environmental and genetic factors contributing to the development of dental anomalies. Currently, the orthodontist, probably the first to diagnose hereditary dental anomalies and malocclusion of an individual, will remain responsible for the detection of any additional defects in the same patient in order to provide the best treatment. The clinician should always keep in mind that some of those dental anomalies can coexist with certain syndromes and other family members might also have been affected. Whenever it seems necessary, a genetic consultation should be added as part of the orthodontic treatment. Finally, this interdisciplinary approach may help to reveal any risk of recurrence in subsequent generations.

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