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## Research Article

### GENETICS AND DEVELOPMENT OF HUMAN DENTITION

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#### ABSTRACT

Influence of genetics and environmental factors in the etiology of malocclusion has been a matter of debate in Orthodontic literature. Both genetic and environmental factors interact to develop the phenotype of an individual (nature and nurture). A sound knowledge of various etiologies of malocclusion is an essential pre requisite, also considering a genetic basis for occlusal variations is a major focus of interest for an orthodontist. Contemporary clinical opinion emphasizes the role of heredity as a major cause of malocclusion. The key to determination of etiology of malocclusion and its treatability lies in the ability to differentiate the effect of genes and environment on the development of craniofacial skeleton in a particular individual. It is well known that genetics as well as environmental play important roles in the etiology of various dentofacial and skeletal anomalies. Genetic mechanisms underlying development are particularly predominant during embryonic craniomorphogenesis. The process of tooth development is strictly regulated by various epithelial and mesenchymal factors. It is of great value in making preventive and interceptive orthodontic procedures so that malocclusions could be prevented or least intercepted by timely removal of the causative factor. Recent advances in genomic technologies and research offer exciting possibilities to reveal genetic basis for differences in orthodontic tooth movement between humans. Recent studies in genetic sciences allow the orthodontist to better understand the effect of genetics on the development of dentofacial characteristics, therefore formulate a treatment plan accordingly. The purpose of this article is to collect comprehensive data on various dentofacial anomalies associated with a genetic etiology, add genetic information in orthodontic literature on the interaction between genetics and orthodontics and review the application of genetic studies to the etiology of malocclusions.

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#### INTRODUCTION

Growth is the combined result of interaction between genetic and environmental factors over time. Also malocclusion is a manifestation of interaction between genetic and environmental factors over time on the development of orofacial region. It is important to consider genetic factors in orthodontic diagnosis in order to understand the causative factors of malocclusions which have an overall influence on the final outcome of orthodontic therapy<sup>1</sup>. The genetic profile of an individual influences his reaction to environmental challenges including orthodontic forces therefore mechanotherapy. Malocclusions with genetic causes are generally less amenable to treatment

than those with developmental causes. Greater the genetic component worse is the prognosis for patient for successful outcome by orthodontic intervention. Gene is a particular segment of DNA which is responsible for inheritance and expression of character. They are the structural units of heredity located on the chromosomes. *Genome*<sup>2</sup> is defined as the entire genetic content of a set of chromosomes present in a cell or an organism while *genotype* is the genetic constitution of an individual. Heredity refers to the transfer of characters or traits from parents to the offspring. *Phenotype* denotes the observable physical characteristics while trait is referred to as a characteristic of phenotype. Traits resulting from a complex interaction of genes are called polygenic traits. The nature of

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these traits can be studied by constructing family trees called pedigrees. The association of two or more traits together more often than would be expected is referred to as a syndrome.

Genetic mechanisms are mainly predominant during embryonic craniomorphogenesis. Various modes of inheritance include autosomal dominant, autosomal recessive, sex linked and polygenic. HOMEBOX genes are the master genes of the head and face controlling patterning, induction and mesenchymal interactions during development. Those of particular interest in craniofacial development include HOX gp, MSX-1, MSX-2, Dlx, Otx (Orthodontical), SHH gene (Sonic Hedgehog).

Some of the dentofacial anomalies with a proven genetic etiology or the causative factors are presented here in this article. These craniofacial disorders with genetic etiology and associated malocclusions include Cleft lip and palate<sup>3</sup>, Cleidocranial dysplasia<sup>4</sup> Gardners syndrome<sup>5</sup>, Down's syndrome and Osteogenesis Imperfecta<sup>6</sup>. Several others anomalies include Agnathia, supernumerary teeth, Palatally displaced or impacted canines, Amelogenesis Imperfecta, Dentinogenesis Imperfecta, Taurodontism Peutz Jeghers syndrome, Fibromatosis Gingivae, Atresia, geminated teeth and Stafne bone cyst.

Agnathia, a lethal anomaly is a hereditary disorder with an autosomal dominant mode of inheritance. Micrognathia i.e. A small jaw is associated with other congenital abnormalities such as congenital Heart disease and Pierre Robin syndrome.

Various familial and twin studies have indicated that malocclusions are highly influenced by genetics<sup>7</sup>. Studies have postulated that Class- II Div- 1 and Class- II div-2 malocclusions are multifactorial while Class-III malocclusion is influenced by genetics<sup>8</sup>. Generally heredity and environment appear equally important but heredity is considered a major etiological factor for severe malocclusions. Simultaneous and synergistic influence of genetics and environment (multifactorial Inheritance) is attributed to the development of Class-II div-1 and Class-II div-2 malocclusions.

The most common example of a genetic trait in humans is the Hapsburgs Jaw<sup>9</sup>. It was first observed in Austrian dual monarchy. Studies have indicated that mandible and maxilla are under separate genetic control while ramus, body and symphysis are under genetic as well as environmental influences.

Tooth development is regulated by epithelial and mesenchymal factors while MSX-1, PAX-9, and AXN-2 genes play a role in Amelogenesis and agenesis. Tooth agenesis affects 20% of the population and is the most common congenital disorder<sup>10</sup>. True anodontia or the congenital absence of teeth, in which all teeth are missing, is usually associated with hereditary ectodermal dysplasia. *Oligodontia* excluding third molars affects 1.1% of the population. Most commonly congenitally missing teeth are mandibular second premolars, maxillary lateral incisors and maxillary second premolars. It has been commonly attributed to the mutation in PAX-9 gene<sup>11</sup>.

Supernumary teeth are most commonly seen in the premaxillary region and are also genetically predetermined. Mesiodens is commonly seen in parents and siblings of the patients who exhibit them. The syndrome *Cleidocranial*

*dysplasia* is commonly associated with supernumerary a tooth which has been linked to RUN- X2 gene.

The genes influencing dental patterning and development i.e. PAX-9, MSX-1, AXN-2 affect canine development and impaction<sup>12</sup>. During normal development, permanent canine tooth bud originates apically, distally and palatally to its final position in the arch. Palatal displacement of canines and ensuing impaction occurs in 85% of general population. Various studies have indicated a genetic tendency for ectopically erupted maxillary canines<sup>13</sup>.

*Amelogenesis imperfecta*<sup>14</sup> is a structural defect of tooth enamel whose etiology has been attributed to the alteration of genes involved in the maturation of enamel. The defective gene has been linked to locus DSX85 at Xp22. Similarly *Dentinogenesis imperfecta*<sup>15</sup> is autosomal dominant condition affecting both deciduous and permanent teeth caused by mutation in DSPP gene (genelocus4q21.3) encoding dentine phosphoproteins and sialoproteins. The teeth are blue grey or Amber brown and opalescent. Radiographically they lack pulp chambers and root canals. Enamel is easily broken leading to exposure of dentine that undergoes accelerated attrition.

#### **Hereditary Nature of Cleft Palate**

Heredity is the most important factor to be considered in the etiology of cleft palate<sup>16</sup>. It may have polygenic or monogenic inheritance. During the seventh week of intrauterine life, medial nasal, front nasal and maxillary processes fuse to form primary plate which becomes the medial portion of upper lip, alveolus and the anterior part of palate up to the incisive foramen. Linkage studies have identified the region on chromosome 9 that contains genes when mutated cause orofacial clefting. Genes involved in cleft palate include IRF-6, TGF-A, MSX-1 and TGF-B3. *Vander Voude syndrome*<sup>17</sup> is an autosomal dominant clefting consisting of lower lip pits and hypodontia. The gene has been mapped on the long arm of chromosome1, 1q32-q41. Cleft palate is also seen in association with ankyloglossia (CPX), the causal gene has been identified as TBX22 expressed in palatal shelves during development.

*Peutz Jeghers syndrome*<sup>18</sup> is an autosomal dominant disorder characterized by intestinal hamartomatous polyps along with muco cutaneous melanocytic macules. The etiological factor lies in mutation in STX11 gene located on band 19p.13.3. Cutaneous pigmentation is seen in the perioral region crossing the vermilion border, perinasal and perioral areas. Mucous membranes affect buccal mucosa (66%) involving intestinal mucosa in rare instances.

*Taurodontism*<sup>19</sup> is a peculiar dental anomaly in which the body of the tooth is enlarged at the expense of roots. The term bull like teeth is use for these teeth to describe the similarity of these teeth to cud- chewing animals. Causes include a genetic predisposition with a familial tendency due to deficiency of odontoblasts during Dentinogenesis of roots. The teeth most commonly involved include the molars, a single tooth or several molars in the same quadrant.

*Fibromatosis gingivae*<sup>20</sup> is a diffuse fibrous overgrowth of the gingival tissues condition being genetically transmitted through autosomal dominant gene. It appears as a nodular

overgrowth of the gingiva of one or both the arches appearing at the time of eruption of permanent incisors.

*Geminated teeth* are abnormalities which arise from attempt of division of a single tooth germ by invagination, with a resultant incomplete formation of two teeth as incompletely separated crowns having a single root canal. This is seen in deciduous as well as permanent dentition and exhibits a hereditary tendency. *Atresia* is the absence or congenital occlusion of one or more of the major salivary gland ducts. It results in the formation of a cyst or produces xerostomia. Also *Stafne bone cyst*<sup>21</sup> is an aberrant salivary gland tissue adjacent to the lingual surface of the body of the mandible. It is believed to be a congenital defect, and is rarely observed in children. This cyst is usually found in the posterior mandible. However it may occur in central incisor or premolar region.

#### Diagnosis of Genetic Disorders

When a specific allele occurs in >1% of the population, it is called as genetic polymorphism. Location of a particular gene or a nucleotide sequence on a chromosome is called locus. Mutations at specific gene locus result in simple mono-genic diseases, syndromic condition or traits with Mendelian transmission (autosomal dominant or recessive, X- linked). Generally familial aggregation and twin studies identify condition with important genetic basis. Also familial aggregation studies involve identification of a given trait among family members. In these studies, differences between mother-child, father child and siblings are analyzed. Twin studies involving comparison between monozygous and dizygous twins are helpful in determining contribution of genetics versus environment to a given trait or disease.

Segregation analysis is also used to identify models of genetic transmission while linkage analysis is used to localize genes for a trait to a specific chromosomal location. Other approaches used to identify disease causing genes include association analysis, susceptibility profiles and medical sequencing.

#### Treatment Options and Methods

Examination of parents and older siblings gives information regarding treatment needs for the child and treatment can then be begun at an early age. Consideration of genetic factors is an essential element of diagnosis that underlies all dentofacial abnormalities. This part of diagnosis is important to understand the cause of the problem before attempting treatment. Knowing the relative influence of genetic and environmental factors would greatly enhance the clinician's ability to treat malocclusions successfully.

#### CONCLUSION

How genetic factors influence response to environmental factors particularly treatment and long term stability should be the greatest concern for the clinician. Future studies should be aimed at determining the interaction of genes with each other which would help in improved genetic counseling and formulating public health policies. Till date, little study has been devoted to specific genetic factors that influence tooth movement. However recent advances in genomic technologies and research offer exciting possibilities to reveal genetic basis for differences in orthodontic tooth movement between humans.

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