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THE CHANGING CONCEPTS OF GENETICS IN ORTHODONTICS: FROM 19TH CENTURY TILL DATE

Orthodontics

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ABSTRACT

Advancement in the field of genetics has given a new insight to the precision medicine and its application in clinical orthodontics is opening new hope in terms of efficient and efficacious diagnosis and treatment planning. This mini review shall be focused to highlight the journey of orthodontics from just correction of malocclusion to the understanding of various concepts related to growth and development, the potential role of various genes in certain abnormalities and effect of bio-modulators on treatment duration.

KEYWORDS

Genetics, Orthodontics, Gene, Malocclusion

INTRODUCTION

"If you look deeply into the palm of your hand, you will see your parents and all generations of your ancestors. All of them are alive in this moment. Each is present in your body. You are the continuation of each of these people" -Thich Nhat Hanh

Genetics is a discipline of biology which deals with the mechanism of heredity. Since 20th century, this branch of knowledge has evolved through a series of era based conceptual and technical breakthroughs. Due to lack of understanding of principles of inheritance in past, the view regarding genetics and malocclusion was naive. Latest advancements and continuous researches concerning heredity and malocclusion and dentofacial deformities have provided a new insight in orthodontics.

It is said that "the heritage of the past are the seeds that bring forth the harvest of the future". The early concepts of heredity and genetics laid the foundation for understanding of growth and development of craniofacial structures and clinical treatment of malocclusion and dentofacial abnormalities.

The aim of this mini review is to provide current knowledge about the alteration in the concept of growth and development as well as the diagnosis and treatment planning in orthodontics with respect to the advancement in genetics.

Dilemma between clinical orthodontics and heredity in 19th and 20th century

Before 19th century, the irregularity of teeth was thought to be the result of either abnormal pressure habits, dietary deficiencies or supernumerary teeth or only few researchers believed on factors such as heredity and congenital malformations.[1]

Early 20th century

Form and function philosophy was the fundamental basis of treatment during the early part of 20th century. Angle's philosophy was to accommodate the full complement of teeth irrespective of degree of crowding or lack of availability of bony support.[2] When Calvin Suveril Case reviewed some cases treated by Angle EH, he recognized that those cases showed unaesthetic results.[3] It was the same time when Calvin Case opposed Angle's view of correction of malocclusion and a great extraction debate in 1911 took place. Case wrote that "*The correctness of the statement that the mandible will grow to a harmonizing size will depend entirely upon whether it has been stunted in normal growth development, which is quite improbable, unless we assume the absurdity that the same cause at the same time produced the over-development of the upper jaw. Malrelations of this character point directly to heredity. Case explained that it will be incorrect to say that the mandible will harmonize with maxilla even if the growth of mandible is retarted and vice versa. The malrelation of maxilla to mandible of this type points directly to heredity. He said that "The claim and recently repeated inference that the mandible can be made to grow by artificial stimuli beyond its inherent size is not in accord with any law of organic development".*[3] He felt that inheritance was the primary cause of malocclusion and tried to highlight the role of heredity in malocclusion but, creationalist dogma of Edward H. Angle won over the Darwinian thinking.[3]

Mid 20th Century

During third, fourth and fifth decade of 20th century, it was acknowledged that most malocclusions have genetic inheritance but, it was difficult to quantify the effect of genetic or environmental factors.[4] Genealogies and pedigrees were helpful in recording family history but not very informative in terms of pattern of dentofacial inheritance.[4] Twin studies and triplet studies have shown a high concordance of dentofacial traits suggesting the role of genetic inheritance in etiology of malocclusion. At the same time use of various exercises and physical therapies were done to counteract the influence of the environmental factors. Reintroduction of extraction therapy in orthodontic treatment was accompanied with a probability of hereditary discrepancy between tooth size and jaw size.[3] several authors such as Noyes, Kraus and Van der Liden thought that genetic concepts had questionable value in orthodontic practice thereafter, the quest for inheritance had decreased.[5-7]

Late 20th Century

Melvin Moss, a craniofacial biologist proposed the Functional Matrix Hypothesis which became a source for functional paradigm.[8] With advancement in the field of genetics the broader consideration of epigenetic and environmental factors in terms of understanding of growth and development and treatment of dentofacial complex was possible.[9]

New era of precision medicine and scopes in clinical orthodontics

Beginning of 21st century brings forth the human genome concept which was a break through. Precision medicine is a brain child of these latest advances in the field of genetics and is based on the idea that each patients genome furthermore the way epigenetic factors affect gene expression can vary from individual to individual.[10] This rapid advancement in the field of molecular genetics and bioinformatics is providing superlative information in terms of craniofacial growth and development.[11] The discovery of Homeobox gene provided a valuable guide to deepen the understanding of pattern formation and morphogenesis of body.[11] The knowledge of the ability to differentiate

the effect of genes and environment on craniofacial skeleton was a key determinant in interpretation of cause of craniofacial anomalies and their treatment.[12]

Genes of Homeobox family such as SHH, MSX-1,2 gene, Lhx-6,7 have important role in normal development of dentofacial structure and any mutation leads to craniofacial anomalies.[11] Goosecoid (GSC genes), MSX, PAX, BRAX, DLX genes have prominent role in formation of mandible and any alteration can lead to mandibular deformities and anomalies in teeth. [13-15] Genes and their association with various malformations are described in table 1. Retrognathia and high arch palate in Marfan syndrome has been linked with mutation in Fibrin (FBN1) gene.[16] Mutation in treacle (TCOF1) gene leads to mandibular deficiency in case of Treacher Collin syndrome. [11]

The molecular genetics has given an insight about the effect of orthodontic tooth movement in gene expression.[17] The role of cytokines in tooth movement became evident and importance of pro inflammatory mediators such as IL-6 and TNF –beta has been identified.[17] The association of root resorption as a side effect of orthodontic treatment has been documented since 1914.[18] It has been proposed that external root resorption is likely to be influenced by the combination of environmental and genetic factors. A twin study was performed to assess the effect of genetic and environmental factors in apical external root resorption and concluded that apical external root resorption was not dependent on pre treatment root length rather quantitative and qualitative estimates indicated a genetic component of root resorption. [19] Using candidate gene approach, a possible linkage between orthodontically induced apical external root resorption and TNFRSF11A locus has been found. [20]

Precision medicine gave insight to the diagnosis and orthodontic treatment planning. Frazier-Bowers et al. (2010) found that the cause of primary failure of eruption was mutation in parathyroid hormone receptors (PTHr) and teeth fail to respond to the orthodontic forces.[21]
The β-2 adrenergic receptor (Adrb2) in mice have been associated with the regulation of bone resorption and hence confirmed the role of sympathetic nervous system in orthodontic tooth movement. [22] The upregulation of β-2 adrenergic receptor following compressive forces in the human periodontal ligament cell that occurs through increased concentration of intracellular calcium ions. This results into the activation of Adrb2 in the periodontal ligament cells and promotes the osteoclastogenesis, thereby enhancing tooth movement. [22]

A better understanding in terms of cytokine involvement and regional acceleratory phenomena has given a new sight to orthodontics and researches are going on to reduce the treatment time by the introduction of new techniques such as piezocision, micro-osteoperforations, low level laser therapy, low intensity pulse ultrasound, local injections of bio-modulators and gene therapy.[23] The role of gene in acceleration of orthodontic tooth movement is summarized in table 2 and abbreviations for various terms used have been tabulated in table 3.

CONCLUSION

Heredity plays an important role in craniofacial development but lack of understanding in the remote past did not give any significant value to it. With the advancement in the field of genetics and longing for application of this advancement in the field of orthodontics have provided a new insight to the researchers which lead to the improvement in understanding the craniofacial development and their deformities. Furthermore, with the help of these advancements we can further work on how to produce an efficient and biologically meaningful orthodontic treatment.

Legands and captions:

Table 1: Genes and their association with various malformations

Gene	Abnormality	Syndrome
SHH	Cleft palate, Hypodontia	Gorlin-Goltz syndrome
Wnt (family)	Cleft lip with or without palate	Tetra-amelia
PITX-2	Mid face hypoplasia, severe oligodontia	Rieger syndrome
MSX-1	Partial tooth agenesis (upper lateral/upper and lower premolar)Cleft palate	Witkop syndrome
PAX-9 & FGF	Agenesis of molars	

Table 2: Genetics and accelerated tooth movement

LASER	Photobiomodulation	It is believed that it increases RANKL, IL-1, M-CSF and Cathespin K level
LIPUS	Mechanical strains produced by vibrations of appliance when received by cells are translated into biochemical events	Phosphorylation of MAPK, Upregulationof Cyclo-oxygenase, RUNX-2 and OSX activation, Stimulation of BAMP, Altered OPG/RANKL ratio
Local injection of biomodulators	RANKL OPG MMP TIMP	Enhances or inhibit recruitment, differentiation or activation of osteoclasts.
Gene therapy	Human recombinant proteins	Allows inserted gene product to be expressed constitutively (research is still going on the gene therapy at phase II level)

Table 3: Abbreviations for various terms used

S.No		
1	Dlx	Distless gene
2	MSX	Muscle segment homeobox gene
3	Lhx	LIM homeobox containing gene
4	SHH	Sonic Hedgehog gene
5	Wnt	Wingless homologue in vertebrates
6	PITX	Pitutary Specific Transcription Factor
7	PAX	Paired box domain
8	FGF	Fibroblast growth factor
9	GSC	Gooscoid gene
10	BRAX	Bar Class of Homebox Containing gene
11	IL	Interlukin
12	RUNX	Runt related transcription factor
13	MAPK	Mitogen activated protein kinase
14	TNFRSF	Tumor necrosis factor receptor superfamily
15	TNF	Tumor necrosis factor
16	RANKL	receptor activator of nuclear factor-kappa B ligand
17	FBN	Fibrilin gene
18	TOCP	Treacle gene
19	OPG	Osteoprotegerin
20	Adrb2	β-2 adrenergic receptor

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