REVIEW

A review on the role of genetics in craniofacial anomalies and malocclusion: can a minor switch completely affect your aesthetics?

Dipti Shastri, Pradeep Tandon, Priti Shukla*, Shraddha Gupta

Dept. of Orthodontics, FODS, King George's Medical University, Lucknow

*Corresponding author e-mail: drpritishukla22@gmail.com

ABSTRACT

For embryonic development, there are a lot of mediators connected in an interactive network. Other factors including overlapping gene family like homeobox gene superfamily play critical roles in development. Many human syndromes, genetic abnormalities and malocclusion have now been attributed to defects in individual genes, which lose its transcriptional and translational ability etc. and its control over neural crest cell migration. It has been appreciated that each malocclusion has its distinctive genetic slot in the genetics-environmental spectrum. Current developments made on molecular genetics as well as animal models for human malformations have provided us with many insights into abnormal craniofacial development. These will definitely help in prenatal diagnosis and therapeutic intervention for the most dreaded syndromes seen today and as the clinicians dealing with craniofacial area, we should always try to keep abreast with these current developments.

KEYWORDS: Genes, craniofacial anomalies, malocclusion, cleft lip and palate, syndromes, gene therapy.

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INTRODUCTION

Every life event from the initiation of a cell to its multiplication and then to the cellular death is ultimately controlled by the genes. Genetics term was coined by Bateson in 1906. Word gene is derived from a Greek word and gene is the basic unit of hereditary. Embryonic stages of craniofacial morphogenesis have always fascinated researchers in the field of craniofacial biology and recent technical advances in this arena have provided us with a great deal of information on its genetic control. Humans have always been bewildered about matters of inheritance. Breeding experiments on dogs were conducted in 1941 by Stockhard (Stockhard CH et al., 1941) and he documented the presence of gross orofacial deformities and malocclusion. The conclusion was thus derived for different craniofacial features could be inherited according to the principles of Gregor Mendel and also that jaw size and tooth size could have independent inheritance as genetically dominant trait (Mosey P.A. etal., 1999). There are certain genes families that mainly effects the craniofacial region, facial structures and dentition etc. (Dickmeis T et al., 2005).

DEVELOPMENTAL GENE FAMILIES

There are critical gene of developmental gene family that have differentiated pattern of formation and cell specification during the development of multicellular organism All cells are required some general genes but for the highly specialized functions they required some special genes. Developmental control genes are group of critical gene for pattern formation and cell fate specification during the development of multicellular organisms. Developmental gene family includes Segmentation genes, Paired-box genes (PAX), Zinc finger genes, Signal transduction (Signalling) genes and Homeobox genes (HOX) (Dickmeis T et al., 2005).

SEGMENTATION GENES

In insect bodies there are lots of repeated body segments which differentiate into particular structures according to their position. Segmentation determining genes have been classified into 3 main groups according to mutant phenotypes (Jiang P etal., 2009, Jiang P etal 2017).
(A) Gap mutants – delete groups of adjacent segments

(B) Pair-rule mutants – delete alternate segments

(C) Segment polarity mutants – cause portions of each segment to be deleted and duplicated on the wrong side (Jiang P et al., 2017).

(i) Hedgehog (Vertebrates) (Dessaud E et al., 2008)

- Sonic Hedgehog
- Desert Hedgehog
- Indian Hedgehog

(ii) Wingless

Left and right asymmetry controlled by Hedgehog genes and it also determines the polarity of central nervous system, somites, limbs, organogenesis and the formation of the skeleton. Loss of function Sonic hedgehog (SHH) plays a major role in the formation of serious and lethal malformation known as holoprosencephaly as SHH involves in the formation of ventral neural tube (Dessaud E et al., 2008, Hu D et al., 1999).

PAIRED-BOX HOMEOTIC GENES (PAX)

Pax gene belongs to the mammalian family and on the basis of sequence similarity, structural features, and genomic organization Pax family consists of 9 members. All 9 members organized into 4 major groups (Blake JA et al., 2014).

A) Pax1 and Pax9
B) Pax2, Pax5, and Pax8
C) Pax3 and Pax7 and
D) Pax4 and Pax6

Paired box homeotic gene binds the different genes sequences and further modifying the transcriptional activity of downstream genes. Out of the whole group of Pax genes, Pax9 mainly involves with the development of teeth (Sridhar P et al., 2011).

Zinc finger genes

As the name implies, a series of four amino acids which form the complex with Zn ions with finger like projections are known as Zinc fingers genes. With the binding of zinc finger to DNA zinc finger motif, they act as transcription factors (Klug A et al., 2010).

Signal transduction genes

Extracellular growth factors play a major role in signal transduction process, which regulates cell division and differentiation by complex genetically determined intermediate pathways. Developmental abnormalities can occur due to mutations in many genes that are involved in signal transduction. Fibroblast growth factor receptors (FGFRs) come under the category of signal transduction genes (Krauss G et al., 2008).

Homeobox genes (HOX) and their importance

Homeobox genes consist of conserved helix-turn-helix DNA motif of 180 base pairs sequence, which specialize in genes that are involved in spatial pattern control and development. Homeobox genes encode the proteins with homeodomain, which consists of 60 amino acids. Homeobox proteins are transcription factors that establishes a regional anterior/posterior axis and specify the cell fate (Sridhar P et al., 2011; Klug A et al., 2010, Krauss G et al., 2008, Scott MP et al., 1992). The term "Homeobox" is derived from the homeotic genes that encode homeodomain proteins found in Drosophila (Krumlauf R etal., 1992). All homeobox genes are not homeotic genes, there is a difference between them as homeotic is a functional description for genes that cause homeotic transformation and homeobox is a sequence motif (Thesleff I et al., 1995). HOXA, HOXB, HOXC, and HOXD are shown in Table 1, and are known as homeobox cluster that consists of 39 genes that have been found in humans. Homeobox cluster contains genes that are closely related to each other and play an important role in early morphogenesis. Hox genes in lower numbers are expressed more anteriorly and proximally in early development than the higher number of Hox genes.

Growth factors

Growth factors are signaling molecules that are involved in the cellular proliferation, differentiation, and morphogenesis of tissues and organs during embryogenesis, postnatal growth and adulthood. For proper functioning, growth factor always require mediators and it is mediated through the binding with specific cell surface receptors. Many growth factors act as signals between tissue layers during the embryonic development and it can stimulate as well as inhibit the growth. Growth factors mechanism is based on feedback loops that require other growth factors, enzymes and binding proteins for their function (Sridhar P et al., 2011). For craniofacial developments, bone morphogenetic proteins (BMPs) and fibroblast growth factors (FGFs) are important for craniofacial development and their mechanism is stimulated by homeobox genes (Galazios G et al., 2009, Mailloux AW et al., 2012, Fiore M, et al., 2009).

Table: 1. Homeobox gene clusters in humans (Sridhar P et al., 2011, Krauss G et al., 2008, Scott MP et al., 1992, Krumlauf R et al., 1992)

Cluster	Number of genes	Chromosome location
HOXA (=HOX1)	11 (1-7, 9-11, 13)	7p
HOXB (=HOX2)	10 (1-9, 13)	17q

HOXC (=HOX3)	9 (4-6, 8-13)	12q
HOXD (=HOX4)	9 (1, 3, 4, 8-13)	2q

Bone morphogenic proteins (BMPs)

Transforming growth factor β includes bone morphogenetic proteins, which are a group of proteins responsible for osteo-inductive activity in bone matrix and cartilage. Different Bone morphogenetic proteins are mediated through condensed mesenchymal cells of bone primordial from different bones. BMPs have different modifications on the basis of small secondary structural elements (Bellus GA et al., 1996). During tooth formation, for the formation of hard tissues, epithelial-mesenchymal interactions play an important role. For tooth formation during morphogenesis stage, BMP-2, BMP-4 and BMP-7 are mainly associated and expression of MSX-1 and MSX-2 and positions of future tooth forming germs are determined by BMP-4 (Sridhar P et al., 2011).

Fibroblast growth factors (FGFs)

FGFs comprise a family of 22 genes and six subfamilies grouped by sequence similarity. It shares biochemical and functional properties and is expressed in specific development patterns (Bottcher RT et al., 2005). Splicing of mRNA produces FGFs receptors with unique ligand binding properties. FGF activity and specificity are regulated by the heparan sulphate proteoglycans. FGFs expressions are regulated during craniofacial development and it plays an important role in intramembranous and endochondral bone formation. FGF2, FGF4, and FGF9 are expressed in sutural mesenchyme during the early craniofacial development and are involved in calvarial osteogenesis. Deviation in the expression of FGFs and FGFRs tend to cause craniosynostosis (Deng C et al., 1996).

Role of genetics in development of skeletal malocclusion

The etiology of numerous skeletal malocclusions seems to have genetics as a key factor. The prognathism of the mandible Angle's Class III, Angle's Class II division 1 and Angles's Class II division 2 which were initially considered to have a dominant inheritance have been seen to have their transmission as polygenic traits. The variability in the expression of a malocclusion in one family is also due to the different numbers of genes involved (intensity) with an agglomeration of numerous environmental factors (Dickmeis T et al., 2005). Certain malocclusions like class III malocclusions and some open bite problems though have shown a typical familial tendency. Continued mandibular growth and the development of true prognathism are much more likely when there is a familial incidence of such a condition than when there is not. The best-known example of Class III malocclusion which runs in families is – "HAPSBURG JAW", in which prognathic mandible was seen in German royal family (Nakasima A et al., 1982).

Class II division 1 malocclusion

Certain craniofacial parameters in Class II div 1 malocclusion are determined by genetics. In some Class II division 1 cases, mandible is retruded as compared to Class I with both the body of mandible and the overall length of mandible (Nakasima A et al., 1982). Previous studies supported the concept of polygenic inheritance in Class II division 1 malocclusion cases as having the same characteristic features in patients and their siblings (Jacobson A et al., 1974).

Class II division 2 malocclusion

Twin studies have been used by many investigators to analyze the genetic influence of malocclusion etiology. Angle's class II division 2 malocclusion has been called as more of a syndrome than a malocclusion due to its clinical morphological features. The clinical features presented are a class II skeletal relationship, retroclined incisors, deep bite, high lip line with a hyperactive mentalis. Various twin and triplet studies have documented a familial occurrence of class II division 2 malocclusions that include studies of Kloeppel (Kloeppel, W et al., 1953) and Markovic (Markovic, M. D et al., 1992). It has also been studied in family pedigree trees, which are included in detailed studies carried out by Korkhaus (Korkhaus, G et al., 1930) and Peck and Peck (Peck, S et al., 1998). Markovic documented 114 cases with clinical and cephalometric study, 48 twin pairs and six sets of triplets and concluded that of the monozygotic twin pairs, 100 percent demonstrated concordance for the Class II division 2 malocclusion, whilst almost 90 per cent of the dizygotic twin pairs were discordant (Markovic, M. D et al., 1992). Genes involved in Class II division 1 & division 2 phenotypes are shown in Table 2.

Table: 2. Growth Factors (Galazios G etal., 2009, Mailloux AW etal., 2012, Fiore M, et al., 2009)

Growth Factor Family	
Transforming growth factor- beta (TGF-β)	a) TGF-β 1-5
	b) Bone morphogenetic protein (BMP) 2-8
	c) Growth and Differentiation factor (GDF) 1-7
Growth and Differentiation factor (GDF) 1-7	a) EGF
	b) TGF-α
	c) Amphiregulin
	d) HB-EGF
Fibroblast growth factor (FGF)	a) FGF 1-8
Insulin like growth factor (IGF)	a) IGF 1-2
Platelet derived growth factor (PDGF)	a) PGDF A, B
Neurotrophins	a) Nerve growth factor (NGF)
	b) Brain-derived neurotrophic factor (BDNF)
	c) Neurotrophin (NT) 3-4

Class III malocclusion

Strohmayer (Strohmayer, W et al., 1937) studied in detail the pedigree tree of the Hapsburg jaw family for mandibular prognathism and came to the conclusion that mandibular prognathism was transmitted as an autosomal dominant trait. Suzuki undertook a study on 243 Japanese families that included 1362 persons and concluded that there was a higher incidence of mandibular prognathism traits in Hapsburg families as compared to families with normal occlusion (Suzuki, S et al., 1967). Monozygotic twins had six times higher incidence of mandibular prognathism as compared to the dizygotic twins (Schulze, C et al., 1965). There is a strong genetic association in class III malocclusion and genes involved in Class III phenotypes are shown in Table 3.

Genetics of cleft lip palate

The most common craniofacial anomalies are cleft lip palate with the greatest prevalence cited amongst Afghans with an average of 4.9 per 1000 live births and the least in the Negroid population, 0.4 per 1000 live births. The first detailed study for an indication towards the genetic basis of cleft lip palate was given in the thesis work by Fogh-Anderson in 1942 (Fogh-Anderson, P et al., 1942). Transforming growth factor alpha (TGFA) and beta3 (TGFB3) and MSX1 genes are responsible for the development of cleft lip and palate through linkage (Schutte, B.C et al., 1999). For the cleft, there in an interaction of genetic and environmental factors that seem to play an important role. There are lots of studies related to the polygenic inheritance, genetic linkages and their association have identified multiple loci and genes that are connected to malocclusion (Vanarasdall GV et al., 2017). Genes involved in cleft lip and palate are shown in Table 3.

Table 3. Genes involved with different malocclusions (Gutierrez SJ et al., 2010, Nieto MA et al., 2002, Da Fontoura CS et al., 2015, Yamaguchi T et al., 2005, Jang JY et al., 2010, Xue F et al., 2010, Li Q et al., 2011, Li Q et al., 2010, Ikuno K et al., 2014)

Genes connected to Class II malocclusion	NOG gene rs1348322 (Gutierrez SJ et al., 2010)
	SNAIL family of zinc-finger transcription factors (Nieto MA et al., 2002)
	FGFR2 , (Da Fontoura CS et al., 2015)
Genes connected to Class III Malocclusion	(1p22.3, 1q32.2, 1p35-36) MANT1, matrillin-1
	Erythrocytes membrane protein band 4.1 (EPB4.1)
	Heparin sulphate proteoglycan 2 (HSPG2)
	Alkaline phosphatase (ALPL) ,3q31.2, 4p16.1, 6q25, 12q13
	Collagen type II alpha 1 (COL2A1) , 14p24.3, 19p13.2
	Mutation in Dual specificity phosphatase 6 (DUSP6) in a family from Estonia, Rho GTPase activating protein 21(ARHGAP21) gene in an Italian family, Fibroblast growth factor 23 gene (FGF23) in family from Henan Province of China new, ADAM Metallopeptidase with Thrombospondin Type 1, motif 1 gene in a Chinese family new. (Chen F et al., 2015, Guan X et al., 2015)
	ADAMTS1, GHR, EPB41, TGFB3, LTBP2, MYO1H

Genes involved in Cleft lip and palate	Various transcription factors and growth factors are involved in non-syndromic cleft lip/cleft palate where mutations in these factors results in the disorder (Sridhar P et al., 2011) Growth Factors: Transcription factors involved in CL/CP Homeobox gene MSX-1 (Muscle segment) Lim Homeobox (LHX8) Bar class (BARX) Distal less (DLX2) Growth Factors involved in CL/CP Transforming growth factor α Transforming growth factor β Retinoic acid Receptor Alpha (RARA) GABA receptor β 3 (GABRAB3) B Cell leukemia/lymphoma (3BCL3) Jagged 2 (Jagg2) Apolipoprotein C II (APOC2)

Table 4. Genes involved in Local Occlusal Variables (Ting TY et al ., 2011, Niswander, J. D et al., 1963, Alvesalo, L et al., 1969, Brook, A. H et al., 1974, Peck S et al., 1994, Ishida K et al., 2011, Ting TY et al., 2011, Bergendal B et al., 2011, Liang J et al., 2012, Yamaguchi S et al., 2014, Kimura M et al 2014, Kim JW et al., 2006, Song S et al 2014, Abdalla EM et al., 2014, Vieira AR et al., 2004, Vieira AR et al., 2007, Antunes LS et al., 2012, Stockton DW et al., 2000)

Tooth morphology and tooth size	SHH (Sonic Hedgehog) gene (Major influence) (Ishida K et al., 2011)
	SNPs in Ectodysplasin – A (EDA; OMIM 300451) (Ting TY et al., 2011)
Dental Agenesis	PAX9 Ala240Pro (mainly Third molar agenesis) (Bergendal B et al., 2011; Liang J et al., 2012)
	MSX1 gene (Hypodontia/oligodontia) (Yamaguchi S et al., 2014, Kimura M et al 2014, Kim JW et al., 2006)
	MMTV 10A family (WNT10A; OMIM606268) (Song S et al 2014, Abdalla EM et al., 2014)
	EDA receptor associated death domain gene (EDARADD)
	Transforming growth factor alpha gene (TNFA) (Vieira AR et al., 2004)

	Interferon regulatory factor 6 (IRF6) (Vieira AR et al., 2007)
	Fibroblast growth factor 1 (FGFR1) (Antunes LS et al., 2012)
	Transforming growth factor (Stockton DW et al., 2000)
	Latent transforming growth factor beta binding protein 3 (LTBP3 OMIM602090) gene (Bartzela TN et al., 2017)
Tooth development and eruption	MSX1
	PAX9 (Sridhar P et al., 2011)
Ectopic eruption	PAX9Transcription factor (Sridhar P et al., 2011)

Genetic influence on local occlusal variables

Genetics and environmental factors that affect the local dental/occlusal variables are important (Bernabe F et al., 2006; Ting TY et al., 2011). Epithelial-mesenchymal interactions during tooth generation lead to such local occlusal problems. Genes involved in local occlusal variables are shown in Table 4.

Tooth morphology and tooth size

The mesiodistal dimensions of the tooth are strongly under the genetic control. Maxillary lateral incisors show the highest variability whereas canines show the smallest genetic influence on the size (Bernabe F et al., 2006). In addition to specific genetic factors that control the size of individual teeth, there also appears to be some generalized genetic regulation of tooth size that is common to adjacent teeth in addition to sex influence, asymmetry and the environmental factors (Table 4) (Mosey P.A et al., 1999, Bernabe F et al.,2006, Ting TY et al., 2011). Monozygotic twins show concordance in tooth morphology than the dizygotic twins. The shape of upper incisors, the number of cusps on posterior teeth and groove pattern on molar and premolar are known to vary in different populations under the genetic influence, like appearance of "carabelli's cusp". Abnormalities in the lateral incisor region shows familial trends and it varies from "peg shaped", to "microdontia", to missing teeth.

Dental agenesis

There is abundant literature on the congenital absence (anodontia & oligodontia) of various teeth, which shows the strong influence of genetics on it. In permanent dentition, most frequently missing teeth are: maxillary lateral incisor, maxillary & mandibular second premolar, mandibular central incisor, maxillary first premolar etc. Hypodontia in families are hereditary in nature, proved in twin studies in which children and half of their siblings/parents had missing teeth. Girls have a higher incidence than boys and one out of four have third molar missing or abnormally shaped while three out of hundred have one or two maxillary lateral incisors malformed or congenitally absent (Niswander, J. D et al., 1963, Alvesalo, L et al., 1969).

Tooth development and eruption

On the basis of clinical observation, the impression is that children of the same family tend to have the same eruption pattern of the third molars (Niswander, J. D et al., 1963). Heredity plays an essential role in determining the eruptive time of deciduous teeth, as shown in a study on twins for beginning of tooth calcification and for eruptive movements of teeth, the sequence of beginning of tooth calcification shows greater similarity among siblings than among unrelated individuals,

suggesting genetic determination of this process (Vanarasdall VG et al., 2017, Brook, A. H et al., 1974, Peck S et al., 1994).

Supernumerary teeth

Most frequently supernumerary teeth are seen in the premaxillary region with genetic determination and male dominance (Brook, A. H et al., 1974). A study in 1963 by Niswander & Sugaky (Niswander, J. D et al., 1963) suggested that supernumerary teeth are controlled by the genetics like hypodontia. Mesiodens is the most common supernumerary teeth formed in premaxillary region and commonly seen in parents and siblings (Niswander, J. D et al., 1963). These are more commonly present in parents and siblings and is a genetically determined trait (Alvesalo, L et al., 1969, Brook, A. H et al., 1974).

Ectopic eruption

Peck et al (1994) showed that the eruption of ectopic maxillary canines is genetically associated and palatally erupted canines are a strong inherited trait. This is one of the anomalies in complex genetically related dental disturbances often occurring in combination with missing teeth, tooth size, reduction, supernumerary and ectopically positioned teeth.

Genetic syndromes related to craniofacial region

As compared to others, small number of patients are affected by genetic syndrome that affects the craniofacial regions. The most common orthodontic problem that may be a part of a genetic syndrome is cleft lip and palate. Some syndromes with craniofacial malformations with oral manifestation (Sridhar P et al., 2011, Bartzela TN et al., 2017) are tabulated below (Table 5).

Table: 5. Genetic syndromes related to craniofacial features (Bartzela TN et al., 2017, Vincent, M et al., 2016, King, N et al., 1994, Hsieh S T et al., 2019, Akram, A et al., 2015).

Syndromes	Genes and locus	Craniofacial features	Oro-dental Features
Treacher Collins Syndrome (TCS) Treacher Collins syndrome (TCS1) Treacher Collins syndrome (TCS2) Treacher Collins syndrome (TCS3)	TCOF1 5q32 POLR1D 13q12.2 POLR1C 6p21.1	- malar hypoplasia -microtonia -mandibular hypoplasia -facial asymmetry -narrow arched palate -retrognathic mandible -abnormal (TMJ) temporomandibular Joint -open bite	-Tooth agenesis (TA) is the most frequent anomaly and it most commonly affects the mandibular second premolars -Impacted maxillary supernumerary teeth -Hypoplastic and malpositioned maxillary central incisors -Ectopic eruption of the maxillary first molars
Velocardiofacial syndrome (VCFS) or Di George's Syndrome	TBX1 22q11.2	-cleft palate or palatal - hypertelorism - large cranial base angle - micrognathia or retrognathia	- missing permanent teeth, especially mandibular incisors, - eruption of permanent teeth is often delayed, h

		- facial hypoplasia -Velopharyngeal Insufficiency	-hypomineralization -Impaired salivary flow etc
Ectodermal dysplasia, Ectrodactyly, Cleft syndrome (EEC3)	TP63 3q28	- orofacial cleft -midfacial, zygomatic, maxillary& mandibular hypoplasia, - microcephaly, -premaxillary protrusion	- most common dental features are hypodontia or even anodontia - enamel hypoplasia - generalized microdontia - peg-shaped teeth -xerostomia -tongue fissures
Kabuki syndrome	KMT2D 12q13 KDM6A Xp12	-cleft palate -high arched palate -microcephaly, -short columella, -flat broadened tip nose, - arched eyebrows, -long eyelashes, -long palpebral fissures -large protruding or cupped earlobes	- hypodontia, mainly with agenesis of incisors and /or premolars - microdontia and "screwdriver"— or peg-shaped incisors - supernumerary teeth -retention of primary and permanent teeth
Kallmann syndrome	ANOS1 Xp22.3 (&PROKR2 FGFR2 10q26.13 (&FGF8, &GNRHR)	-Cleft palate - increased angulation of Mandible due to retrognathia	-tooth agenesis - multiple congenitally missing teeth - screwdriver"-shaped mandibular incisors, and thin molar roots
Pierre Robin sequence	SOX9 17q24.3	- cleft palate is a common finding - micrognathia, -smaller cranial base and maxillary length	-glossptosis - tooth agenesis
Van der Woude syndrome	IRF6 1q32.2 GRHL3 1p36.11	-Clefts -underdevelopment of the maxillary sagittal length and maxillary height	- paramedian lower-lip pits - hypodontia and dental hypoplasia -tooth agenesis, most affected teeth are the maxillary second premolars

			- ankyloglossia -hypodontia - supernumerary incisors and molars, -crown and root patterning anomalies, -taurodontic mandibular second molars
Crouzon's syndrome	FGFR2 4p	-craniofacial dysostosis -premature synostosis of both coronal sutures -midface hypoplasia -hypoplastic orbits with proptosis -short cranial base -parrot beak nose	-angle's class III malocclusion
Apert's syndromes	FGFR2	-skull malformation -acrocephaly of brachysphenocephalic type	-irregular dentition -impacted tooth
Hemifacial macrosomia or Goldenhar syndrome	OTX2 14q32 ATP13A3 3q29 XXYLT1 3q29 MYT1 20q13.33 ROBO1, 13 asso GATA3, GBX2 FGF3 NRP2 EDNRB SHROOM3 SEMA7A PLCD3 KLF12 EPAS1	-craniofacial growth Asymmetry -condylar hypoplasia -hypoplasia of zygomatic, Maxillary and Mandibular bone -coloboma of upper eyelid -small mandibular body -retrognathic mandible	-can't in occlusal plane - small mesiodistal dimensions of molars -tooth agenesis

Gene therapy in orthodontics

With the introduction of gene therapy in dentistry, in the orthodontics field gene therapy can also be used (Baum, B.J et al., 1995). Gene therapy technique involves the insertion of genes into the tissue or diseased cell to cure the disease. For successful gene therapy, the gene must target to a specific cell population or tissue in a controlled way (Havens B etal., 2007). Recent advances in molecular biology research have identified genes for a number of dental problems and their protein products may solve the problem by way of gene therapy. However, it is important that gene therapy

is presented as the new goal in orthodontics, which can impact the diagnosis and treatment plan for the betterment of the patients. In future, the use of gene therapy in orthodontics is presented in Table 6.

Table: 6. Uses of gene therapy in orthodontics (Havens B et al., 2007)	
Gene therapy for sutural growth disturbances	In craniosynostosis involving mutations in FGFR2, so temporarily blocking FGFR2 signaling provides a different anti-proliferation signal to these cells would allow normal sutural growth without surgical intervention
Gene therapy for mandibular growth	Successful gene transfer to the TMJ with the use of recombinant adeno-associated virus and lentivirus has been reported in animal models. Use of functional appliances causes transient up-regulation of a number of genes (PTHrP, Indian hedgehog, Runx2, collagen type X and VEGF) in the mandibular condylar cartilage.
Gene therapy for orthodontic tooth movement	-Local RANKL and Local OPG gene transfer for orthodontic tooth movement and gene transfer is advantageous than pharmacological therapy because gene transfer "can maintain a local effective concentration and prolonged protein expression, regardless of blood circulation

CONCLUSION

This is the orthodontics genomics era and literature in this field supports the role of molecular genetics in the development of the craniofacial complex. It has also been understood that these evidences will hold a firm ground in future research in the field of orthodontic treatment, ranging from simple tooth movement to complex phenomenon like prevention of developmental deformities. The future of orthodontics diagnosis and treatment planning of patients should focus on the identification of key genes that are responsible for various anomalies and malocclusions. Along with this, the therapeutic intervention for correction of the minor switches may lead to complete change in an individual's esthetics.

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