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Genetics and Orthodontics

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in Dental Surgery

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Certification of the supervisor

I certify that this project entitled **"Genetics and Orthodontics"** was prepared by the fifth-year student **Mina Qahtan Hadi** under my supervision at the College of Dentistry/University of Baghdad in partial fulfillment of the graduation requirements for the Bachelor Degree in Dentistry.

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Dedication

Nothing is more precious than seeing your loved ones proud of you, push you up and encourage you to see you getting better by time,

To My father and mother.. I dedicate this project,

for your unconditional love and support and no matter what I do, I will never fulfill even a part of your bid.

To my sisters (Sadeer, Aseel, Danya).. having you is always a treasure, for all the times that you were there, helping, caring, and embracing me with all my flaws.. forever grateful for our bond.

To my best friends.. who make the hard days become lighter by sharing the number of smiles, laughs, thoughts, and tears that we have shared, and make the days passed memorable.

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- **EARR** External Apical Root Resorption.
- **PFE** Primary Failure of Eruption.

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Introduction

A strong influence of heredity on facial features is obvious at a glance, it is easy to recognize familial tendencies in the tilt of the nose, the shape of the jaw, and the look of the smile. The similarity of human faces among relatives -past and present- makes the genetic basis of human craniofacial development even more apparent. Certain types of malocclusion run in families. The Hapsburg jaw, the prognathic mandible of this European royal family, is the best-known example, but dentists routinely see repeated instances of similar malocclusions in parents and their offspring. The pertinent question for the etiology of malocclusion is not whether there are inherited influences on the jaws and teeth, because obviously there are, but whether different types of malocclusion can be directly caused by inherited characteristics. For much of the 20th century, thoughts about how malocclusion could be produced by inherited characteristics focused on two major possibilities, the first would be an inherited disproportion between the size of the teeth and the size of the jaws, which would produce crowding or spacing, the second would be an inherited disproportion between the size and/or shape of the upper and lower jaws, which would cause improper occlusal relationships **(Carlson, 2015).**

Malocclusion is a manifestation of genetic and environmental interaction on the development of the orofacial region, the most important practical question regarding orthodontics and genetics is whether different individuals respond to some degree to a changed environment (treatment) in different ways according to the influence of their particular genetic factors **(Vanco et al., 1995; Manfredi et al., 1997).**

The aims of the study

To highlight the effects of genetic factors on the development of malocclusion and on orthodontic treatment, and the possibility of utilizing genetic therapy to affect orthodontic treatment.

1 Chapter One: Review of Literature

1.1 Basic definitions: Before proceeding, some basic information is required:

- The genome contains the entire genetic content of a set of chromosomes present within a cell or an organism **(Everett and Hartsfield, 2000).**
- A gene can be defined as the entire DNA sequence necessary for the synthesis of a functional polypeptide Genes represent the smallest physical and functional units of inheritance that reside in specific sites (called loci for plural or a locus for a single location) in the genome **(Everett and Hartsfield, 2000).**
- All human beings normally have 22 homologous pairs of chromosomes called autosomes that are numbered by size and other characteristics. In addition, one pair of sex chromosomes may be homologous (X, X) in females or only partly homologous (X, Y) in males **(Mossey, 1999).** Alleles are Genes at the same locus on a pair of homologous chromosomes. When both members of a pair of alleles are identical, the individual is homozygous for that locus. When the two alleles at a specific locus are different, the individual is heterozygous for that locus **(Mossey, 1999)**.
- Genotype generally refers to the set of genes that an individual carries, this usually refers to the particular pair of alleles (alternative forms of a particular gene) that a person has at a given region of the genome. In contrast, phenotypes are observable properties, measurable features, and physical characteristics of an individual **(Baltimore, 2001)**.

1.2 Types of Genetic Effects and Modes of Inheritance:

A trait is a particular aspect or characteristic of the phenotype. When considering genetic influences on traits, it is convenient to think of three types: monogenic, polygenic, and multifactorial. Although defining these types can be helpful in understanding genetic influences, they are to some degree simplistic categorizations **(Mossey, 1999).**

1.2.1 Monogenic Traits:

Traits that develop because of the influence of a single gene locus are monogenic. These types of traits also tend to be described as discrete or qualitative (dichotomous or yes/no) in occurrence **(Mossey, 1999).**

The alleles determining the expression of monogenic traits may be dominant, intermediate, or recessive. The loci for a monogenic trait may contain identical alleles: an individual will be a homozygous for this trait, or the loci may contain two different alleles: an individual will be a heterozygous for this trait **(Hutu et al. 2020).**

1.2.1.1 Autosomal Dominant Traits and Penetrance:

If having only one allele of the two alleles on a homologous pair of autosomes (heterozygosity) is sufficient to lead to the production of the trait then the effect is autosomal dominant. But if production of the trait does not occur with only one particular allele of the two alleles on an autosome but does occur when both alleles are the same (homozygosity), then the effect is autosomal recessive. the terms dominant gene and recessive gene are used commonly to describe these types of inherited traits in families **(Parck et al., 1995).**

The nature of these traits is studied by constructing family trees called pedigrees in which males are denoted by squares and females by circles, noting who in the family has the trait and who does not.

The criteria for autosomal dominant inheritance:

- The trait occurs in successive generations; that is, it shows vertical inheritance.
- On the average 50% of the offspring of each parent who has the trait also will have the trait.
- If an individual has the gene that results in the trait, each child has a 50% chance of inheriting the gene that leads to the expression of the trait.
- Males and females are equally likely to have the trait.

  Parents who do not have the trait have offspring who do not have the trait.

Exceptions to this include traits showing non-penetrance in a particular offspring. When a person with a given genotype fails to demonstrate the trait characteristic for the genotype, the trait is said to show non-penetrance in that individual and incomplete penetrance in any group of individuals who have the genotype.

This is a situation most commonly seen with dominant traits (Figure 1) **(Anderson et al., 1995).**

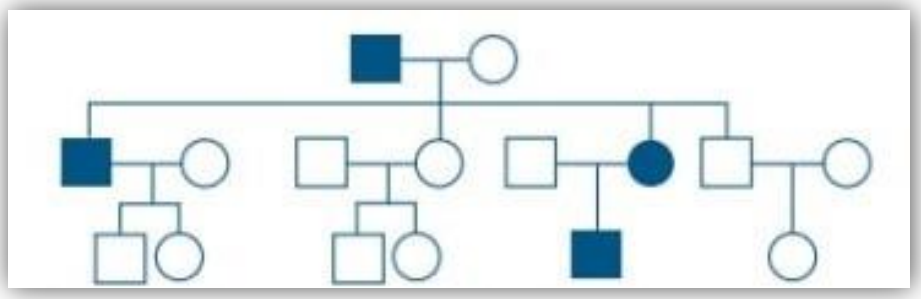

Figure 1 :Three-generation pedigree of a family with an autosomal dominant trait with the younger generations below the older generations. Square symbols are male and round symbols are female. Affected members are denoted by filling in their individual symbol.

1.2.1.2 Variable Expressivity:

Although in each individual the trait is present or not when discussing penetrance, if the trait is present, it may vary in its severity or expression. Thus, not all individuals with the trait have it to the same extent and they may express varying degrees of effect or severity. For example, there are at least four clinical types of osteogenesis imperfecta involving type I collagen abnormalities that help to provide an illustration of variable gene expression: (1) multiple fractures, (2) blue sclera, (3) dentinogenesis imperfecta, and (4) hearing loss **(Baltimore, 2001).**

Variation occurs among the different clinical types of osteogenesis imperfecta. Affected persons in a single family may show a variable combination and severity of the classic signs and symptoms, illustrating the considerable variation in gene expression even within a family, the minimum phenotypic expression of the gene

observed in a family then might be only a blue color to the sclera, which could go unnoticed by the clinician. In this case, highly variable gene expression may fade into non-penetrance **(Hartsfield et al., 2006).**

The craniosynostosis syndromes, along with their effect on craniofacial growth and development associated with premature closure of one or more cranial sutures, often result in maxillary hypoplasia and a Class III malocclusion **(Baltimore, 2001).**

1.2.2 Complex (polygenic\multifactorial) traits:

Traits influenced by polygenic factors are also hereditary and typically exert influence over rather common characteristics. Historically, each gene involved was thought to have a minimal effect by itself, with the additive effect of all genes involved **(Buschang and Hinton, 2005).**

Because these traits show a quantitative distribution of their phenotypes in a population, environmental factors can play a variable and generally greater role

than in monogenic traits, although the use of the term polygenic has inferred the effect of multiple genes on the phenotype (Figure 2) **(Abbas and Hartsfield, 2008)**

A change in phenotype depends on the result of the genetic and environmental factors present at a given time. Thus, one may expect that polygenic traits are more amenable to change (or a greater change) following environmental (treatment) modification as compared to monogenic traits.

Another aspect to consider is time. Although an environmental modification may alter the development of the phenotype at a particular moment, gross structural morphology, already present, may not change readily unless the environmental modification is sufficient to alter preexisting structure **(King et al., 2002).**

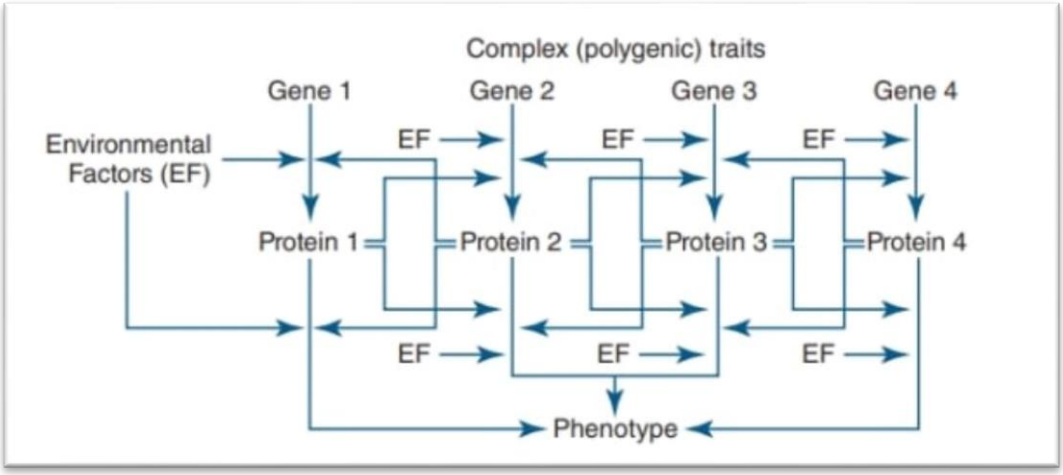

Figure 2: Unlike Mendelian traits, environmental factors and multiple genes are critical to the development of complex (polygenic) traits. These types of physical traits are continuous rather than discrete (although diseases of this type can still be present or not). Such traits are referred to as quantitative traits or multifactorial because they are caused by some number of genes in combination with environmental factors (Abbas and Hartsfield, 2008).

Examples of polygenic traits include height and intelligence quotient, both of which are continuous traits greatly influenced by genetic factors. However, height and intelligence quotient also can be affected greatly by environmental factors, particularly if they are deleterious major gene effect. Non-syndromic

cleft lip-palate, neural tube defects such as Spina Bifda and anencephaly, and congenital hip dislocation are examples of multifactorial traits **(Lidral et al., 2008).**

1.3 Nature Verses Nurture:

The growth and development are not the result of genetic and environmental (non-genetic or epigenetic) factors working in total absence or independence of others. Full siblings share on average half of their genes, and it is apparent that siblings can have similar occlusions. However, this is in some part environmental (e.g., influenced by dietary and respiratory factors in common) and in some part genetic factors that influence development **(Garn et al., 1979; Beecher et al., 1983). Corrucini (1984)** pointed out that the rapid increase in malocclusion comparing industrialized (urban) to non-industrialized (rural) samples of several disparate populations emphasized the importance of environmental factors**.**

Moss (1997) considered genetic factors as intrinsic and prior causes and what he termed "epigenetic" (environmental) causes as extrinsic and proximate, in a revisitation of the functional matrix hypothesis and resolving synthesis of the relative roles of genomic and epigenetic processes and mechanisms that cause and control craniofacial growth and development, concluded that both are necessary. Neither genetic nor epigenetic factors alone are sufficient, and it is only their integrated (interactive) activities provide the necessary and sufficient causes of growth and development. The genetic background of the individual can influence the response to environmental factors, particularly those that are more likely to delineate different individual responses e.g., the shape of the mandibular condyles was "slightly greater" among four different in-bred strains of mice on a hard diet than on a soft diet for 6 weeks **(Lavelle, 1983)**.

To quote **King et al. (1993),** "We propose that the substantive measures of inter-sib similarity for occlusal traits reflect similar responses to environmental factors common to both siblings. That is, given genetically influenced facial types and growth patterns, siblings are likely to respond to environmental factors (e.g., reduced masticatory stress, chronic mouth breathing) in similar fashions. Malocclusions appear to be acquired, but the fundamental genetic control of craniofacial form often diverts siblings into comparable physiologic responses leading to development of similar malocclusions."

1.4 Skeletal Variation and Malocclusions:

Malocclusion is a significant deviation from an ideal or normal occlusion **(Mossey, 1999).**

Malocclusion can either be skeletal or dental, involving discrepancies in the jaw size, tooth size, and shape, crowding, or spacing. It is a manifestation of both genetic factors and environmental influences during the development of the craniofacial complex. However, it might be difficult to differentiate whether the malocclusions are determined by the genetic code or environmental factors, or a combination of both **(Hartsfield, 2011).** The cause of most skeletal- and dentoalveolar based malocclusions is essentially multifactorial in the sense that many diverse causes converge to produce the observed outcome **(King et al. 1993).** Numerous studies have examined how genetic variation contributes to either or both occlusal and skeletal variation among family members **(Harris and Johnson, 1991; Manfredi et al., 1997).**

Extensive cephalometric studies by **Harris (1975)** suggested the concept of polygenic inheritance for Class II division 1 malocclusion. It showed that the craniofacial skeletal patterns of children with class II malocclusions are heritable and that there is a high resemblance to the skeletal patterns in their siblings with normal occlusion**.**

Familial occurrence of Class II division 2 has been documented in several published reports including twin and triplet studies and family pedigrees **(Peck et al., 1998).** Twin studies showed that the identical twins demonstrated 100% concordance for Class II division 2 malocclusion, indicating a strong genetic influence in the development of Class II division 2 deep bite malocclusions **(Ruf, 1999).**

Class III "skeletal" malocclusion (often referred to as mandibular prognathism) may be due to a short maxilla, long mandible, or both when examined in the sagittal plane. Even though it has been said that mandibular prognathism has a polygenic or multifactorial trait; familial aggregation studies have shown that this phenotype can occur in families with an autosomal dominant mode of inheritance, variable expressivity, and incomplete penetrance including the royal Habsburg family and others from middle east **(Litton et al., 1970; Wolff, 1993; El-Gheriani et al. 2003; Cruz et al. 2008).** Analysis of a pedigree comprising 13 European noble families with 409 members in 23 generations determined that the mandibular prognathism trait was inherited in an autosomal dominant manner. Although the penetrance is high, considerable variation exists in the clinical expression of the trait **(Wolff et al., 1993).** Some of the members of the European noble families had in addition to varying degrees of mandibular prognathism, other facial characteristics such as a thickened lower lip, prominent nose, flat malar areas, and mildly everted lower eyelids (which may be associated with a hypoplasia of the infraorbital rims), as also were reported in three generations of a family by **Thompson and Winter (1988).**

In that family, one member had oxycephaly because of multiple suture synostosis, which also was suspected in Charles V, a severely affected member of the Hapsburg family (Figure 3). Apparent maxillary hypoplasia, as well as malar flattening and downward eversion of the lower eyelids, may indicate that the overall clinical effect may be at least in part due to hypoplasia of the maxilla **(Wolff et al., 1993).**

El-Gheriani et al. (2003) performed segregation analysis on 37 Libyan families of patients who had a Class III malocclusion and also concluded that the overall inheritance pattern best fit an autosomal dominant model.

The prevalence of Class III malocclusion varies among races and can show different anatomic characteristics between races **(Ishii et al., 2002).**

Figure 3 : Profile view of Carlos V of Spain and Germany at 17 years of age. His family included 13 lineages of European royalty and 409 documented individuals, with 321 with mandibular prognathism varying from mild to severe. Analyses suggested that mandibular prognathism has an autosomal dominant mode of inheritance, and cases that did not fit well may be due to consanguinity. In some cases, the prognathism escaped a generation and penetrance was estimated at 0.88 (Wolff et al., 1993).

1.5 Genetic Variation in Muscle and its Influence on Malocclusion:

A research by **Sciote et al. (2013)** and collaborators has shown that variations in masseter muscle fiber type, gene expression in masseter muscle, and epigenetic changes that alter gene expression are associated with anterior open versus deep bites, mandibular retrognathism versus prognathism, and mandibular asymmetry.

Skeletal muscle cells produce many proteins that when it comes in combination, they define the unique characteristics and function of the muscle fiber tissue **(Staron, 1991).** Interestingly, differences in muscle fiber composition have been noted in masseter muscle tissue obtained from patients with a mandibular asymmetry **(Raoul et al., 2011).** Significant increases in type II muscle fiber area and frequency on the same side as the deviation were discovered when compared to muscle fibers on the side opposite the deviation. Moreover, no significant differences were noted when comparing the muscle composition on the right and left sides of symmetrical patients **(Raoul et al., 2011).**

Additional studies have shown that greater human facial height (i.e., vertical dimension) is inversely related to the size and proportion of masseter muscle fast, short-faced, deep bite phenotypes correlated with increased type II fiber area and frequency, while long faced, open bite phenotypes showed increased type I fiber area and frequency **(Rowlerson et al., 2005)**.

Better understanding of the genetics of muscle composition, and how muscle can be re-programmed prior to surgical correction of either Class II or III surgical cases, may greatly aid in reducing the number of surgical relapse cases (and may also aid in the identification of late growers and/or slow growers) **(Raoul et al., 2011).**

1.6 Genetic Effects on Individual Tooth Variations:

Genetic factors control the tooth size, morphology, number, position, and its inheritance, as stated in various twin studies **(Lundström, 1963; Ludwig, 1957)**.

HOX genes refers to a conserved subgroup of the homeobox superfamily, have crucial roles in development, regulating numerous processes including receptor signaling, differentiation, motility and angiogenesis; aberrations in its expression have been reported in abnormal development and malignancy **(Gonzalez et al., 2007).**

Additive genetic variation for mesiodistal and buccolingual crown dimensions of the permanent 28 teeth (excluding third molars) ranged from 56% to 92% of phenotypic variation **(Brook et al., 2002).**

1.6.1 Dental Agenesis:

Dental agenesis is a condition of congenital absence of one or more teeth resulting from disturbances at early stages of odontogenesis. It is the most common developmental anomaly seen in humans, it is genetically and phenotypically a heterogeneous condition **(Kuchler et al., 2013).**

Based on the current knowledge of genes and the factors involved in the tooth development and morphogenesis, it is assumed that different phenotypic forms are caused by different genes involving different interacting molecular pathways, providing an explanation not only for the wide variety in agenesis patterns but also for associations of dental agenesis with other oral anomalies. More than 200 genes have been so far identified, which are expressed during tooth development, and mutations in several of these genes are known to cause arrested tooth development in mice **(De Coster, 2009).**

Although the hypodontia is often familial, it may occur without a family history of hypodontia, it may also occur as part of a syndrome, especially in one of the many types of ectodermal dysplasia, although it usually occurs alone (isolated), which means not a part of a syndrome, it still may be familial (Figure 4). A general trend in patients with hypodontia is to have the mesiodistal size crowns of the teeth present to be relatively small (especially if more teeth are missing). the mesiodistal size of the permanent maxillary incisor and canine crowns tends to be large in cases with supernumerary teeth **(Brook et al., 2002).**

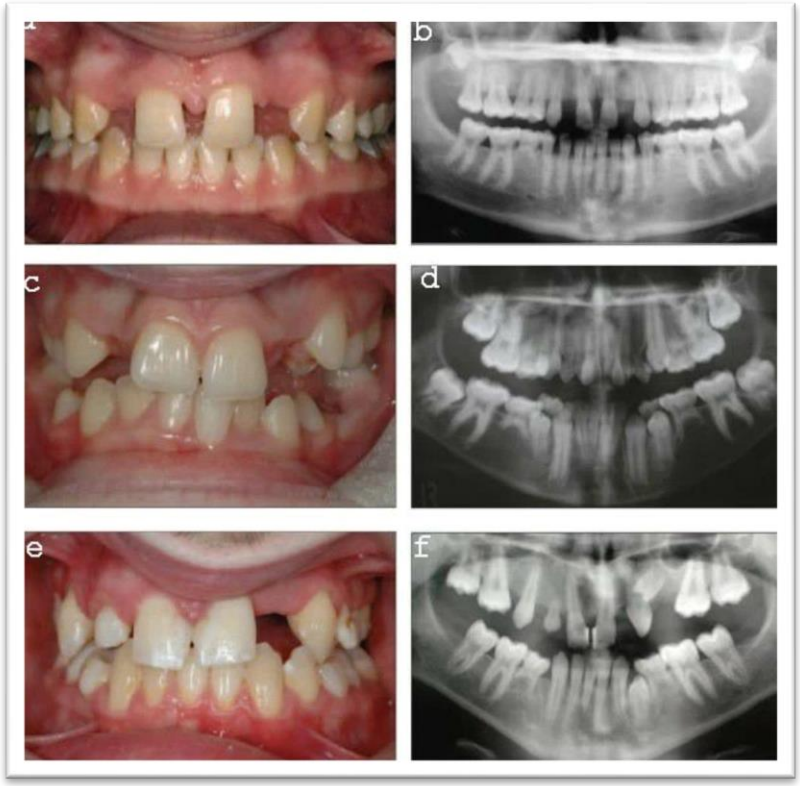

Figure 4 : Familial human hypodontia (Hobkrik et al., 1994).

One of the most common patterns of hypodontia (excluding the third molars) involves the maxillary lateral incisors, this can be an autosomal dominant trait with incomplete penetrance and variable expressivity as evidenced by the phenotype sometimes "skipping" generations and sometimes being a peg-shaped lateral instead of agenesis and sometimes involving one or the other or both sides **(Woolf, 1971).**

1.6.2 Supernumerary Teeth:

Supernumerary teeth are more frequently seen in the premaxillary region with a greater prevalence for males; they appear to be genetically determined **(Liu, 1995).**

Niswander and Sujaku (1963) analyzed data from family studies, and they suggested that, like hypodontia, the genetics of less prevalent condition of supernumerary teeth is under control of several genes in different loci and may be associated with an autosomal recessive gene with lesser penetrance in

females. This was later supported by **Gallas and Garcia (2000)** while an autosomal dominant inheritance with incomplete penetrance has been suggested, the increased incidence in males suggests the possibility of sex-linked heredity. Although this inheritance does not follow a simple Mendelian pattern, these are more commonly present in parents and siblings of patients who present with this condition. Evidence from twins with supernumerary teeth also supports this theory **(Mercuri and O'Neill, 1980).**

1.6.3 Primary Failure of Eruption:

Tooth eruption is a complex process that represents an integral part of the broader tooth developmental process **(Sharpe, 2001).** It is known that the tooth follicle interacts with both osteoblasts and osteoclasts during the tooth eruption process **(Wise, 2008).** However, neither the eruption mechanism nor the factors controlling eruption are completely understood **(Takahashi, 2019).** Eruption disorders are ideally classified based on their etiology; those secondary to obstruction (cysts, ankylosis, lateral tongue pressure, impaction, etc.), or those with genetic underpinnings (e.g., primary failure of eruption (PFE); cleidocranial dysplasia, Hunter's disease and osteopetrosis) **(Frazier, 2010).**

PFE is one of the more common diagnostic distinctions, which is an example of non-syndromic eruption disorder (Figure 5). Primary failure of eruption was first described by **Proffit and Vig (1981)** as a condition in which non-ankylosed teeth fail to erupt, involved teeth can erupt partially and then cease to erupt, becoming relatively submerged although not being ankylosed.

Posterior teeth are also affected in PFE, resulting in a posterior open bite. Diagnosis of PFE is extremely important to avoid the consequences of employing a continuous archwire **(Frazier, 2010).**

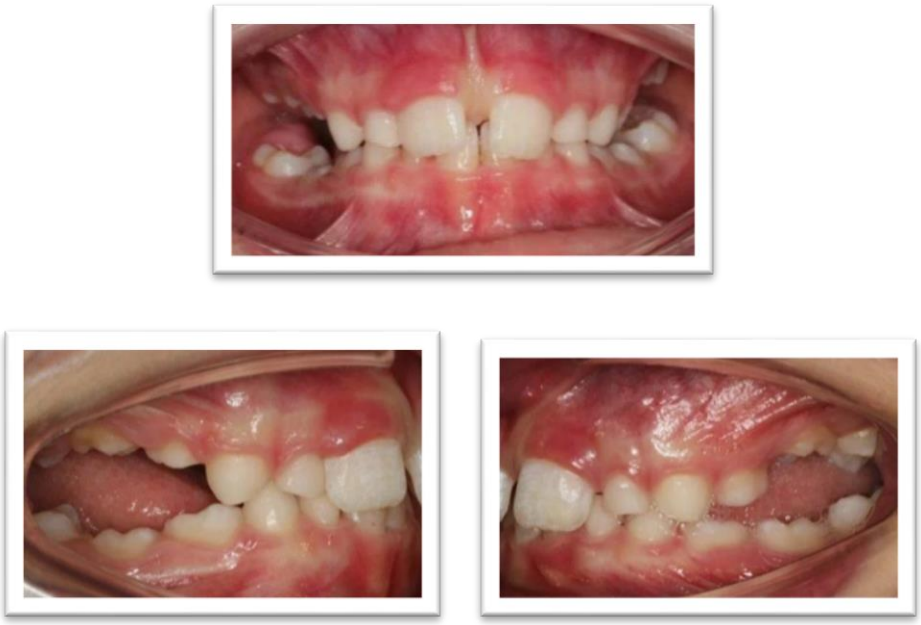

Figure 5: Clinical features of patient with primary failure of eruption (Grippaudo et al., 2018).

These broad categories of dental eruption failure can be distinguished based on the following diagnostic parameters: patient dental history, clinical and phenotypic characterization and genetic characterization. The well-documented patient dental history is critical and allows understanding the developmental trajectory through serial photographs and radiographs of the eruption sequence. PFE-affected teeth have little or no response to orthodontic treatment with a tendency to encounter ankylosis or intrude adjacent teeth. PFE can present in a unilateral or symmetrically bilateral pattern, with one or all posterior quadrants involved **(Frazier, 2016).**

Although the presence of specific clinical signs allows suspicion of PFE, there is wide variability of phenotypic expression, and the diagnosis can be established by sequencing the parathyroid hormone 1 receptor gene (PTH1R). Ongoing genetic characterization of PFE is largely associated with autosomal dominant loss-of-function variants in the PTH1R gene, located on chromosome 3p21-p22.1, causing haploinsufficiency of the receptor **(Proffit and Vig, 1981).**

When analysis of the PTH1R gene is available, it represents an early diagnosis that is independent of family history **(Grippaudo, 2018)**. A family history through interviews and detailed clinical records on multiple family members is quite powerful **(Decker et al., 2008).**

1.7 Craniofacial Skeletal and Dentoalveolar Occlusal Heritability Studies:

Many reviews of the genetics of malocclusion focused on the cephalometric component of craniofacial form, not on the occlusal component. Although the heritability estimates are low, most of the studies that looked at occlusal traits found that genetic variation has more to do with phenotypic variation for arch width and arch length than for overjet, overbite, and molar relationship. Still, arch size and shape are associated more with environmental variation than with genetic variation **(Cassidy et al., 1998).**

Because many occlusal variables reflect the combined variations of tooth position and basal and alveolar bone development, these variables (e.g., overjet, overbite, and molar relationship) cannot be less variable than the supporting structures.

The example of reported heritability estimates for anterior and posterior face height and the observed effect of perennial allergic rhinitis and mouth breathing are interesting. Some studies suggest that a greater heritability exists for total anterior face height and lower anterior face height than for upper anterior face height and posterior face, one hypothesis is that the lower anterior face height may have a greater heritability than the upper anterior face height in some groups of individuals unless increased nasal obstruction resulting in mouth breathing becomes a predominating factor in group members **(Hartsfield, 2002).**

1.8 Genetic Factors Influencing the Dental Arch Formation:

The early stages of human organ development from initiation to terminal differentiation depend upon inductive interaction between epithelium and adjacent mesenchymal tissue **(Zhang et al. 2005).**

Dental arch and tooth development need multilevel molecular and cellular interactions that will result in phenotypic outcomes, disturbances in the interaction between ectodermal and neural crest-derived mesenchymal cells will result in teeth abnormalities and dental arch shape and size variation (Figure 6) **(Kouskoura et al., 2011).**

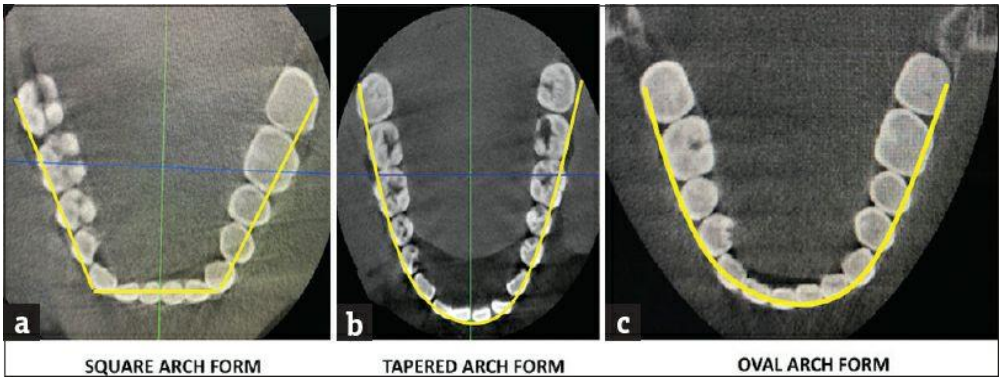

Figure 6: Various arch form in horizontal section of CBCT: a) square arch form, b) tapered arch form, c) oval arch form.

The particular mixes of homeobox genes direct the morphology of the creating tooth. The presence or non-appearance of a gene and covering of gene codes can bring about a variety of tooth shapes and sizes. This variety in tooth advancement will impact the dental arch measurement and shape **(Cobourne and Diabiase, 2015).**

1.8.1 Genetic Markers and Mutation Associated with Dental Arch Variation:

Heritability studies need to be supplemented with genetic studies linking genetic variation with specific phenotypic outcomes. Several studies have been done to evaluate genetic roles in the horizontal growth of the jaws as the base of the dental arch **(Hartsfield, 2012).**

Fontoura et al. (2015) assessed the association of facial skeletal variation and the type of skeletal malocclusion. The main findings indicated that there is a gene (TWIST1 rs2189000) related to variation from short to long mandibular bodies. The inactivation of this gene in the mandibular curve neural peak brings about mandibular shortening and irregular ramus development. It was also shown that this gene is related to mandibular solidification and molar cusp arrangement **(Zhang et al., 2012).**

Christiane Cruz et al. (2008) found that polymorphism in Myosin 1H (MYO1H rs10850110 A<G) is associated with mandibular prognathism and horizontal maxillomandibular discrepancies.

Weaver et al. (2017) suggested that genotype-phenotype correlates with the asymmetric components of dentoalveolar dental arch variation associated with TBX1, AJUBA, and SNAI3, SATB2, TP63, and 1p22.1.

The homeobox gene MSX1, which controls proliferation and differentiation, is one of the many candidate genes underlying tooth agenesis. Besides MSX1, other multiple genes have been identified as being causative of congenitally missing teeth, including PAX9, WNT10A, AXIN2, and EDA **(Galluccio et al., 2012).** The MSX1 gene was recently definitively connected to malocclusion. As it is affecting the nasal cycles, maxilla, and mandible advancement. The past examination has affirmed a significant relationship between the MSX1 gene and Class I and II malocclusions **(Yang et al., 2020).**

1.9 The Genetic Basis for Variable Response to Treatment:

The increased understanding of the various morphogenetic signaling pathways regulating development of the craniofacial structures should allow for the manipulation of the proliferation, patterning, and differentiation of tissue to treat skeletal discrepancies that contribute to malocclusion **(Nuckolls et al., 1999)**. An important aspect of this is an increased comprehension of how epigenetic factors affect expression of genes that influence postnatal growth **(Carlson, 1999).** Since the relative influence of genetic factors on development of an occlusion does not necessarily determine the response to treatment, the future of genetics in orthodontics will primarily involve analyzing the genetic basis for variable response to treatment. In other words, are there genetic factors that influence the response to treatment? If so, what are they? Can they be identified before treatment to assist in devising the most effective and efficacious treatment, including the avoidance of unwanted responses? **(Mancinelli et al., 2000).**

1.9.1 Genetic Factors and External Apical Root Resorption:

Analysis of the genetic basis for variable response to treatment has been applied to the specific adverse outcome sometimes associated with orthodontic treatment called external apical root resorption (EARR), which has been attributed to the use of excessive forces on the teeth. The degree and severity of EARR

associated with orthodontic treatment are multifactorial, involving host and environmental factors **(Harris et al., 1993).**

Individuals with bruxism, chronic nail-biting, and anterior open bites with concomitant tongue thrust also may show an increased extent of EARR before orthodontic treatment **(Harris and Butler, 1992).** EARR is also increased as a pathologic consequence of orthodontic mechanical loading in some patients

(Brezniak and Wasserstein, 1993). The amount of orthodontic movement is positively associated with the resulting extent of EARR **(DeShields, 1969; Sharpe et al., 1987; Parker and Harris, 1998).** Orthodontic tooth movement, or "biomechanics," has been found to account for approximately one-tenth to one third of the total variation in EARR **(Linge and Linge, 1991; Horiuchi et al., 1998).** However, there is a considerable individual variation in EARR associated with orthodontic treatment, indicating an individual predisposition and multifactorial (complex) etiology **(Massler and Malone, 1954).**

Heritability estimates have shown that approximately half of EARR variation concurrent with orthodontia, and almost two-thirds of maxillary central incisor EARR can be attributed to genetic variation **(Harris et al., 1997; Hartsfield et al., 2004).** A retrospective twin study on EARR found evidence for both genetic and environmental factors influencing EARR **(Ngan et al., 2004).**

The mechanical forces of orthodontic treatment and other environmental factors do not adequately explain the variation seen among individual expressions of EARR. Interest has increased on genetic factors influencing the susceptibility to EARR, The reaction to orthodontic force including rate of tooth movement, can differ depending on the individual's genetic background **(Harris et al., 1997).**

Variation in the interleukin-1β gene (IL-1β) in orthodontically treated individuals accounts for 15% of the variation in EARR. Persons in the orthodontically treated sample who were homozygous for (IL-1β) allele "1" were estimated to be 5.6 times more likely to experience EARR of 2 mm or more than those who were heterozygous or homozygous for allele "2" (Figure 7) **(Bastos et al., 2015).**

Nonetheless, there are patients who have the DNA marker that usually accompanies EARR who do not have EARR, and there are some patients with EARR who do not have the marker, so the "predictive" value of this single marker is limited by itself, without information about other DNA (gene) markers and other variables that may be involved **(Harris et al., 1997).**

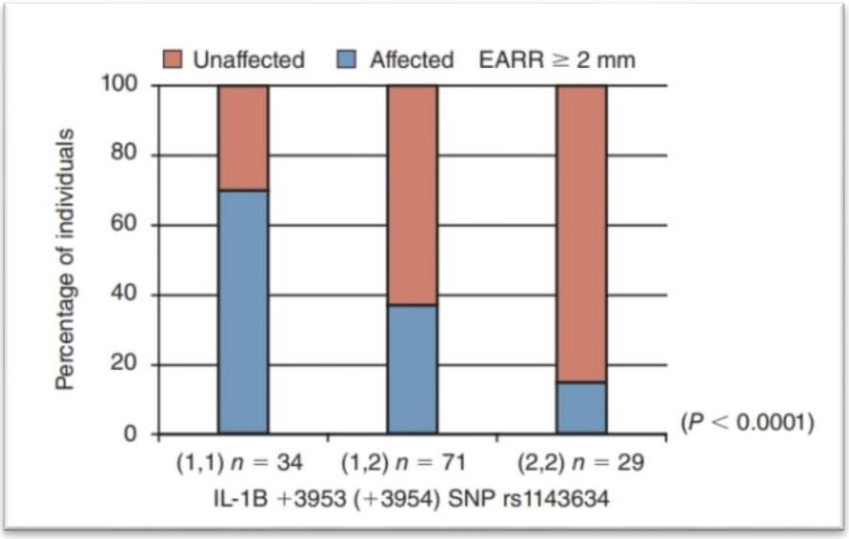

Figure7: Percentage of orthodontic patients with 2 mm or more of external apical root resorption (EARR) by IL-1B +3953 (previously designated as +3954) SNP rs1143634 genotype.

Iwasaki et al. (2001) found individual differences in a ratio of IL-1β to IL-1RA (receptor antagonist) cytokines in crevicular fluid that correlated with individual differences in canine retraction using identical force.

Although the relation to genetic markers was not undertaken, this study indicates a variable individual response to orthodontic force that may be mediated at least in part by IL-1β and IL-1RA cytokines. This supports the hypothesis that bone modeling mediated, at least in part, by IL-1β as an individual response to orthodontic force can be a factor in EARR. Many other genes and their proteins that affect bone physiology could also be involved in the rate of tooth movement, as well as EARR **(Iwasaki et al., 2008).**

Future estimation of susceptibility to EARR likely will require the analysis of several genes as mentioned previously, root morphology, skeletodental values, and the treatment method to be used, or essentially the amount of tooth movement planned for treatment **(Hartsfield et al., 2009).**

1.10 Gene Therapy:

Gene therapy techniques involve identification and isolation of the target gene coding for the protein of interest, transfer of this gene into an appropriate production host and finally expression of the gene **(Primrose and Twyman, 2006).**

1.10.1 Gene Therapy Fundamentals:

It involves the deliberate introduction of exogenous gene/DNA/RNA into somatic cells of body organs, express its protein and produce a desired therapeutic effect and thereby correct the cellular dysfunction or provide a new desired cellular function **(Rashid and Ankathil, 2020).** If mutation causes a crucial protein to be defective or missing, gene therapy may be able to introduce a normal copy of a mutated gene to restore the normal function of the protein. Once the gene that encodes the target protein is integrated into a patient's genetic machinery, the required protein can be constantly produced at high therapeutic level **(Wirth et al., 2013).**

In other words gene therapy deals with replacing the defective genes with their correct analogues to produce functional proteins. Evidence suggests that gene therapy can be used to prevent, alleviate, or cure underlying disorders including cancers, infectious diseases, and genetic and autoimmune disorders **(Misra, 2013).** Knocking out or inactivating a mutated gene that is functioning improperly, and replacing of mitochondrial DNA by spindle transfer that changes entire mitochondria. Gene transfer or gene replacement involves direct delivery of DNA into nucleus, released from its complex and rendered competent for expression and/or interaction with the host genome **(Chatterjee et al., 2013; Patil et al., 2012; Rashid and Ankathil, 2020).**

1.10.2 Applications of gene Therapy in Dentistry:

Remarkable progress has been made in the field of genetic therapy for a range of applications in dentistry, in order to improve the quality of life, gene

therapy has promising outcomes for potential treatment for multiple disorders. For bone repair, salivary gland disorders, implants osseointegration, head, neck and oral cancer and for pain management (Figure 8) **(Baum, 1995).**

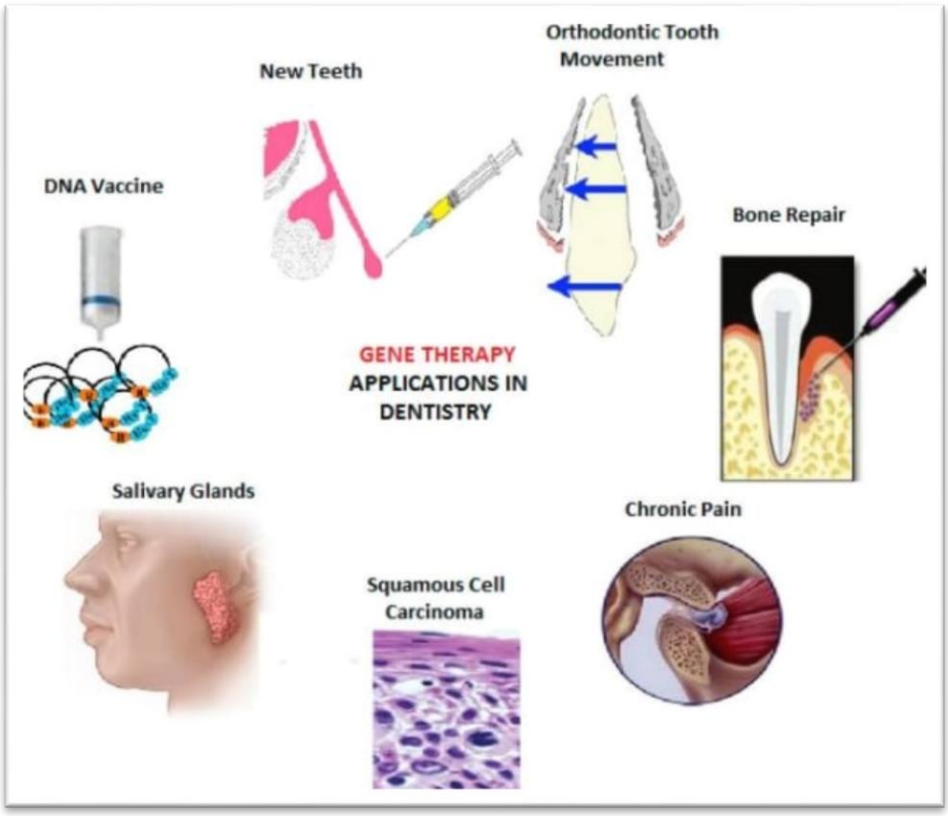

Figure 8: Applications of gene therapy in dentistry.

1.10.3 What is Precision Orthodontics?

Genetics, anatomy and past environmental exposure influence how each patient responds to treatment, either favorable response or unfavorable response. This phenomenon is known as heterogeneity of treatment effects. Precision medicine optimizes treatment for the individual rather than the average patient typically described in clinical trials **(Zanardi et al., 2012).**

Precision orthodontics (PO) refers specifically to the tailoring of medical treatment to the individual characteristics of each patient considering maturity, physical features, and genetic data as well. In other words, PO is the application of a specific type of treatment to an individual because that person belongs to a

subpopulation of patients who are expected to develop disease and/or respond to treatment differently than the rest of the overall population based on his/her genetic/genomic profile **(Vogenberg et al., 2010).**

Nevertheless, precise prediction of orthodontic treatment outcome is not tenable because of the heterogeneous complexity of facial and dental development, the physiology of tooth movement and the occurrence of EARR. Investigations are ongoing on many genetic factors and how they may relate to orthodontic treatment outcome **(Zanardi et al., 2012).**

1.10.4 Role of Gene Therapy in Achieving Precision Orthodontics:

Gene therapy as a genetic engineering technique has the potential to make possible the prevention of many antenatal, congenital, and postnatal genetically induced dentofacial anomalies, including dental malocclusion. The gene therapy experiments in orthodontic treatment are still emerging and limited to cell cultures or animal experiments **(Abraham and Maliekal, 2017).**

1.10.4.1 Gene Therapy for Tooth Movement Modulation:

Orthodontic tooth movement has its foundation laid upon remodeling of periodontal ligament and alveolar bone. This requires the relay of mechanical loading to biological signals by alveolar bone cells such as osteoblasts, osteocytes and osteoclasts and periodontal ligament (PDL) **(Atsawasuwan and Shirazi, 2018).**

The remodeling process has its reins handled by osteoclasts and osteoblasts. Precursors of osteoclasts and osteoblasts are hemopoietic cells and stromal cells respectively. Osteoclastic maturation and activation require interaction with cells from the osteoblastic lineage. The molecular mediators for such interactions are the receptor activator of the nuclear factor kappa B (RANK) or

receptor activator of nuclear factor kappa-B ligand (RANKL) **(Boyce and Xing, 2007b; Yamaguchi, 2009).**

Gene therapy has been implicated to be beneficial in tooth movement. Two experimental studies **(Kanzaki et al., 2006; Kanzaki et al., 2004)** were conducted by using gene therapy with Osteoprotegrin (OPG) and RANKL to decelerate and accelerate orthodontic tooth movement respectively.

RANKL gene was transferred locally to the periodontal tissue. It gave results that point towards accelerated orthodontic tooth movement by approximately 150% after 21 days, without evoking any systemic effects, thereby reducing the time of treatment **(Kanzaki et al., 2006).** It was suggested that local RANKL gene transfer might be a useful tool not only for abbreviating the duration of orthodontic treatment, but also for treating ankylosed teeth. In contrast to RANKL, local OPG gene transfer inhibited tooth movement by about 50% after 21 days of application of force **(Kanzaki et al., 2004).**

These findings with gene therapy could cause a paradigm shift in orthodontic treatment by reducing treatment time with improved results **(Iglesias-Linares et al., 2011)**

1.10.4.2 Gene Therapy in Repair of Root Resorption and Retention Stability:

Using viral envelope packaging and delivery system, **(Kanzaki et al., 2004)** performed the OPG gene transfer experiment to investigate the inhibition of orthodontic relapse in rats.

The investigators suggested that local OPG gene therapy to periodontal tissues could inhibit relapse after orthodontic tooth movement via an inhibitory effect on osteoclastogenesis **(Zhao et al., 2012).**

Kanzaki et al. (2006) further investigated the effect of local OPG gene therapy on orthodontic root resorption with the same design of experiment by utilization of a microcomputed tomogram and histological analyses. The result showed no

difference between root resorption at the beginning and the end of tooth movement in the OPG gene therapy group.

However, they were able to conclude that repair of root resorption in the gene therapy group was higher than other control groups **(Zhao et al., 2012)**

1.10.5 Limitations and Challenges of Gene Therapy:

At present, the application of gene therapy in clinical practice is limited by its biosafety concerns **(VandenDriessche et al., 2003).**

The success expected from gene therapy depends on its delivery system. For the delivery of the gene, either viral or nonviral vectors may be used as carriers. Viral vectors provide efficient gene delivery to the targeted tissue cells and longer duration of gene expression. Nevertheless, use of viral vectors for transgenesis is still doubted to be hundred percent safe and free of adverse side effects. Due to safety concerns associated with viral vectors such as immunogenicity and oncogenicity **(Hacein-Bey-Abina et al., 2003).**

Despite these challenges and biosafety issues, some promising successful stories of gene therapy are emerging in the field of dentistry. Ongoing research in the gene therapy field provide an optimistic future for dentistry field especially for precision orthodontics. The application of gene therapy in orthodontics has just seen the beginning of an era of immense potential and possibility **(VandenDriessche et al., 2003).**

2 Chapter two: Discussion

The effect of genetics on the development of malocclusion and also on patient response to treatment is a fact that is accepted by all. However, the extent of that effect is not well defined. As there is an interaction between genetic and epigenetic factors. Understanding the relative roles of these two factors during the processes and mechanisms that cause and control the craniofacial growth and development are both necessary.

The development of bones, muscles, and teeth need a multilevel interaction of cells and molecules so any disturbance in these interactions will result in teeth abnormalities and dental arch shape and size variations i.e., malocclusion.

The pattern of growth and development is typically the result of an interaction between multiple genetic and environmental factors over time, and the malocclusion seen in most patients is of polygenic/multifactorial cause but this does not mean that specific malocclusions are not influenced heavily by single genes that have large effects.

Gene therapy is a promising technique, and may aid in some aspects of orthodontic treatment. However, replacing defective genes with their correct analogue for gene expression it is still doubted to be safe and free of adverse side effects.

3 Chapter Three : conclusions and suggestions

Conclusions:

1. The growth and development of bone, muscles, or teeth, is mostly attributed to a multifactorial polygenic inheritance.
2. Different individuals could have different response to treatment as a result of having different genetic makeup.
3. The application of gene therapy in clinical practice could be limited by its biosafety concerns.

Suggestions :

Investigate the latest gene therapy application in orthodontics.

Performing a more extensive review on the role of genetic and epigenetic factors on the development of bone, muscle, and teeth.

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