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Genetics and Orthodontics

(A Review Study)

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Certification of the Supervisor

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

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Dedication

My success during my life is not only the result of my hard work. It also stems from my family's continued support, prayer, love, and guidance throughout life. You are indeed the best parents. You have always served as my source of motivation and given me all I needed to achieve my goals. Thank you for all that you have done for me.

I owe all good in my life to you (family)

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Table of contents

List of Figures

List of Tables

List of abbreviations

- **SNP** **single nucleotide polymorphism.**
- **VNTRs** **variable number tandem repeats.**
- **MP** **Mandibular Prognathism.**
- **PFE** **Primary Failure of Eruption.**
- **EARR** **External Apical Root Resorption.**
- **PDCs** **Plasmacytoid dendritic cells.**

Introduction

Orthodontists who gain a solid foundational understanding of genetics are best equipped to understand why some patients develop certain occlusions. The consideration of family history and known genetic factors in the diagnosis and treatment planning of malocclusion is essential, especially since there are genetic influences on virtually all aspects of dental/facial growth and development. (Morford, n.d.) Most problems in orthodontics (or any outcome of growth and development), unless acquired by trauma such as (postnatal injury: fracture of jaw and teeth, TMJ trauma) (Rapeepattana et al., 2019) are not strictly the result of only genetic or only environmental factors. (Proffit, 1986)

Growth is the result of the interaction of genetic and environmental factors over time.(J. E. Harris, 1975; Moss, 1997a) Knowing whether the cause of the problem is "genetic" has been cited as a factor in eventual outcome; that is, if the problem is genetic, then orthodontists may be limited in what they can do (or change). (Mossey, 1999a) (Manfredi et al., 1997) (Vanco et al., 1995)

How specific genetic factors will influence a patient's responsiveness to environmental factors (including orthodontic treatment and the long-term stability of its outcome) as determined by studies of genetic markers, or gene sequences, and their impact on the proteins that they encode or influence, should be the greatest concern for the clinician. (E. F. Harris, 2008a; Hartsfield Jr, 2008) A patient's biological responsiveness to a particular environmental factor (e.g., orthodontic treatment) does not necessarily depend on any prior interactions of genetic and environmental factors but rather on the individual's biological responsiveness to the orthodontic treatment. The final outcome of orthodontic treatment will be a function of the overall interactions between the gene products generated from genetic factors that are expressed (or not expressed) during the treatment time, combined with any other environmental factors present during the

treatment time, against the backdrop of the developmental maturity of the individual. (Buschang & Hinton, 2005a; Griffiths et al., 1999a; E. F. Harris & Potter, 1997; Vogel & Motulsky, 2013)

The aims of the study

Genetics explains a great deal of variation seen in the population when facial deformities and malocclusions are considered. However, genetics is not synonymous of a deterministic concept in which a single gene, segregating in families, determines malocclusion. These monogenic models explain very few cases of malocclusion and the other human diseases, as well as traits such as height, weight, amount of sugar in the circulating blood, blood pressure, intelligence, behavior, and sexual orientation. All these traits, as well as the majority of human diseases and congenital defects, have complex or multifactorial modes of inheritance, which can be influenced by the environment, and determine the presence of the majority of traits and diseases.

1 • Chapter one: Review of literature

1.1 BACKGROUND AND BASIC DEFINITIONS:

Before proceeding, a few basic genetic definitions and concept descriptions are required:

- Organism's genome is defined as the complete set of genetic instructions for that organism.
- Human genome is made up of a double helix of deoxyribonucleic acid (DNA) comprised of ~3.2billion chemical nucleotide base pairs. The genetic instructions, or DNA code(s), are created by the linear pattern, order, and number of adenine (A), thymine (T), cytosine (C), and guanine (G) bases along the paired double helix. This genetic information is normally organized into smaller units (ranging in length from ~50 to 250million base pairs each) called chromosomes primer11.pdf (ornl.gov)
- A chromosome is made up of a continuous stretch of the double helical DNA that is wrapped around proteins that are called histones.
- A gene which represent the smallest physical and functional unit of inheritance, can be defined as the complete DNA sequence that codes for the synthesis of a specific polypeptide via a messenger RNA intermediate or the synthesis of a specific RNA molecule (e.g., transfer RNA, ribosomal RNA, and noncoding regulatory RNA molecules such as microRNA or long noncoding RNA). (Hartsfield Jr & Bixler, 2010)
- The term locus is used when describing a single genetic region or location, and loci is plural. Genes at the same locus on a pair of homologous chromosomes are called alleles, One allele would be a copy of the maternal allele and the other a copy of the paternal allele.

- Altogether, we each inherit a total of 46 chromosomes; 22 homologous pairs of chromosomes called autosomes that are numbered by size and other characteristics, along with one pair of sex chromosomes that are homologous (X,X) in females and only partly homologous (X,Y) in males

There are an estimated 25,000 genes in the human genome, our genes only make up 2% of the whole genome, The average gene is 3000 nucleotide base pairs in length. the human genome is ~99.9% identical from one person to another. Thus, there is only an estimated 0.1% variation within the entire DNA code between two people that makes each individual unique.

A person's genotype cannot be seen with our eyes but must be determined with the use of a genetic test or analysis. In contrast to genotypes, phenotypes are the observable properties, measurable features, and physical characteristics of an individual.(Baltimore, 2001a) A phenotype is generated by the summation of the effects arising from an individual's genotype and the environment in which the individual develops over a period of time. (Baltimore, 2001b)

1.2 TYPES OF GENETIC EFFECTS AND MODES OF INHERITANCE

It is important to understand that it is the trait, and not the gene, that influences the trait, which can be described as having a specific mode of inheritance (e.g., dominant or recessive). When considering genetic influences on traits, it is convenient to think of two types of influences: monogenic and complex (referred to as multifactorial traits).(Lidral et al., 2008)

A single gene could be "turned on" (i.e., "expressed") to produce a protein that affects the development of one trait in a given tissue or area of the body. The same gene could also be "turned on" to produce the exact same protein, in a different area of the body, which affects the development of a very different trait in

another tissue. Any one gene or a specific gene allele, therefore, is technically not dominant or recessive; it is simply a set of instructions. The same gene allele in an individual can influence more than one trait in that person, and each trait may have a different mode by which it is inherited. For example, the melanocortin 1 receptor gene (MC1R, OMIM *155555) produces a protein that is involved in the pigmentation of our skin, hair, and eyes. This gene is known to play an important role in the development of two different traits: freckles and red hair. Freckles (ephelides) are inherited as a dominant trait because a person only needs to have one causative copy of the MC1R gene to develop them.(Flanagan et al., 2000) Red hair, on the other hand, can be inherited as an autosomal recessive trait, where you have two causative copies of the MC1R gene to develop red hair,(Flanagan et al., 2000) or as a compound heterozygous trait that acts similarly to a recessive trait.(Sturm et al., 2003)

Homologous genes that exhibit more than one allele will vary from one another at the DNA sequence level due to either normal inherited variations or sporadic mutations. The most common inherited variation or sporadic mutation in the human genome is called a single nucleotide polymorphism (SNP; pronounced "snip") (Fig. 2-4). SNP describes the occasion when more than one nucleotide base (A, G, T, or C) can be inherited at a specific location in the DNA code upon comparing the DNA codes at that same position among many individuals. There are over 10million SNPs that have been identified in the human genome to date; ~1 SNP occurs every 300 nucleotides.(Green et al., 2015) primer11.pdf (ornl.gov) Three basic categories of SNPs exist: (1) intergenic SNPs located in between genes; (2) intragenic SNPs located within the intron regions of a gene; and (3) gene coding region SNPs, which lie within an amino acid coding (exon) region of a gene. Different types of sporadic or inherited variations in the DNA code can also

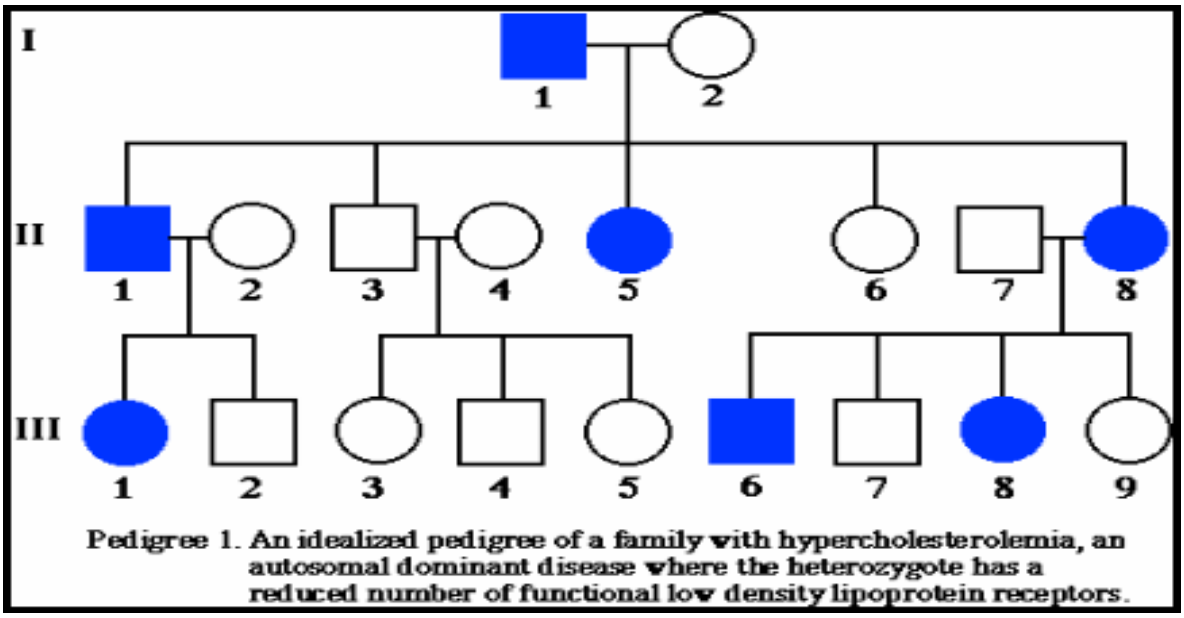
arise from variable number tandem repeats (VNTRs; i.e., microsatellites, simple sequence repeats, short tandem repeats), gene or region duplications, insertions or deletions of a small segment of DNA sequence, inversions of the DNA sequence, translocation of a segment of the DNA sequence, or base-pair changes. DNA variations are examined and analyzed using numerous methodologies. Large abnormalities in chromosome structure can be studied via karyotyping or genomic hybridization, which are methods that can detect insertions, deletions, translocations, and whole chromosome deletion or duplication.

1.2.1 Monogenic Traits:

Traits that develop primarily due to the influence of a single gene locus with the possibility of other smaller genetic and environmental factors. Sometimes are called mendelian traits. These types of traits also tend to be described as discrete or qualitative (dichotomous or yes/no) in occurrence. They can have autosomal recessive or dominant, or X-linked recessive or dominant, inheritance. a monogenic influence may be less amenable to environmental (treatment) intervention. (Graber et al., 2017a)

1.2.1.1 Autosomal Dominant Traits and Penetrance

When a trait is present as the result of only one copy of a particular allele (e.g., A) in a heterozygous allele pair (e.g., Aa), then the trait has an autosomal dominant inheritance. The nature of these family-based (familial) traits can be 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. This can be particularly useful for monogenic traits including Class III malocclusion, hypodontia, primary failure of eruption (PFE), and developmental dental dysplasias such as types of dentinogenesis and amelogenesis imperfecta.



Pedigree 1. An idealized pedigree of a family with hypercholesterolemia, an autosomal dominant disease where the heterozygote has a reduced number of functional low density lipoprotein receptors.

Fig(1)

If the mode of inheritance is autosomal dominant, the following characteristics may be present in a pedigree:

1. the trait occurs in successive generations.
2. on average, 50% of the offspring of each parent who has the trait will also have the trait.
3. if an individual has the gene allele that results in the trait, each of his or her children has a 50% chance of inheriting the gene allele that leads to the expression of the trait.
4. males and females are equally likely to inherit the trait.
5. parents who do not have the trait have offspring who do not have the trait. An exception to this occurs when the trait shows non-penetrance in a particular offspring.

When a person inherits a gene allele or genotype that characteristically is associated with a specific trait, yet the trait is not evident in that person, then the trait is said to show non-penetrance in that individual and incomplete penetrance in

any group of individuals who have the genotype.If some of the individuals do not manifest the trait in a sample of individuals with the trait-associated genotype, then the trait is said to have a penetrance of whatever percentage of the trait-associated genotype that the group actually manifests. Incomplete penetrance is a condition most commonly observed with dominant traits such as hypodontia, Class III malocclusion, and Treacher Collins syndrome, to name a few. Exceptions to this may include (1) when a new (sporadic) mutation is introduced into the DNA of the sperm or egg that will form the offspring or (2) when a germinal mosaicism arises because one of the parents was mosaic at the germ cell level (Taylor et al., 2014)

1.2.1.2 Variable Expressivity

If the trait is present, it may vary in its severity or degree of expression. Thus, not all individuals with the trait may have it to the same extent and they may express varying degrees of effect or severity. Variable expressivity also may apply to the pleiotropic effect of a particular genotype; that is, the expression of the same gene may result in seemingly disparate traits in an individual. Variable expressivity, even in the same family with presumably the same segregating primary genetic determinant, may be observed with a large number of dominantly inherited traits, syndromes, and conditions, including Class III malocclusion, (Cruz et al., 2008) hypodontia, (McDonald et al., 2010) osteogenesis imperfecta involving type I collagen abnormalities, (Hartsfield Jr et al., 2006; Retrouvey et al., 2014) and craniosynostosis syndromes. (Escobar & Bixler, 1977; Everett et al., 1999; Mulvihill, 1995)

This phenomenon is presumably due to the variable interaction(s) of different proteins encoded by modifying genes plus environmental/epigenetic factors occurring in each individual. Simply discovering the likely causal gene

mutation may indicate a future effect on craniofacial growth and development, but it will not necessarily predict the precise effect.

1.2.1.3 Autosomal Recessive Traits

An autosomal recessive trait requires the inheritance of two causal allele copies to see an observable phenotype (i.e., homozygous aa). The concept of having a "gene carrier" is used regularly with autosomal recessive traits. Sometimes, however, the carrier status can be detected, greatly improving the precision of genetic counseling, even before a child is born with the recessive trait. The rarer the recessive gene allele, the more likely it is that the unaffected parents who have an affected child will be blood relatives—that is, a consanguineous mating. A study on inbreeding in Japan by Schull and Neel that was cited by Niswander (Niswander, 1975a)found that malocclusion occurred 6% to 23% more often (depending on the sample and the sex) in children of first cousins compared with children of nonrelated parents, indicating the potential for the effect of recessive genes when homozygous. Given that both parents who produce a child with an autosomal recessive trait are presumed to be heterozygotes, only one of the four possible gene combinations from the parents will result in the homozygous genotype associated with the autosomal recessive trait. Hence, the recurrence risk for an affected child in this case is 25% (i.e., Aa×A*a* would yield offspring with an approximately equal distribution of the genotypes: AA*, Aa*, aA*, or aa*, where only the aa* genotype can manifest the recessive trait). Transmission of the phenotype in a pedigree is horizontal (typically present only in siblings) and not vertical, as with a dominant trait.

1.2.2 X-Linked Traits and Lyonization (X Inactivation)

Most genes located on the X and Y chromosomes are not homologous and are unequally distributed between males and females. This inequality occurs because males inherit only one copy of the X chromosome along with one copy of the Y chromosome, compared to females who inherit two X chromosomes. Many of the unique genes found only on the Y chromosome influence the development of the male reproductive system e.g., SRY gene stimulate testis development and repress the development of female structures (Jiang et al., 2013). Since females inherit two X chromosomes, it is possible for them to be either homozygous or heterozygous at each X-linked gene locus. By comparison, however, males only inherit one X chromosome normally, and while some loci on the males' X chromosome do have a homologous locus on the Y chromosome, most loci on the males' X chromosome do not have a homologous locus in the males' genome. The term hemizygous is used to describe the fact that men inherit only half of the number of X-linked genes (one copy) that females inherit, a condition that can lead to interesting genetic phenotypes that are possible only in men. Accordingly, recessive genes located on the one male X chromosome express themselves phenotypically as if they were dominant genes. In females, both X-linked recessive genes must be present at a homologous locus to express the recessive phenotype. Consequently, full expression of rare X-linked recessive phenotypes is almost entirely restricted to males, e.g., in X-linked hypohidrotic ectodermal dysplasia (HED), although occasionally it is seen with variable severity in females. Females who are heterozygous for the gene associated with the X-linked recessive phenotype may show some expression of the phenotype because most of the genes on one of the X chromosomes in the female will normally be inactivated by a process called lyonization.

1.2.3 Complex Traits

Complex or common diseases, phenotypes, or traits, reflecting their complex etiologic interaction among genes from more than one locus and environmental factors, as well as their greater incidence/more common occurrence when compared with monogenic phenotypes. Historically, each gene involved in creating the trait was thought to have a minimal effect by itself but that the effect of all genes involved was additive. The associated phenotype is rarely discrete and is most commonly continuous or quantitative. Environmental factors can play a variable and generally greater role in complex traits than in monogenic traits. A change in phenotype depends on the result of the genetic and environmental factors present at a given time. Thus, one may expect that compared with monogenic traits, complex traits will be more amenable to change (or a greater change) following environmental/treatment modification. Although an environmental/treatment 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 or function.(Buschang & Hinton, 2005b)

1.3 NATURE VERSUS NURTURE

Growth and development, however, are not simply the results of genetic (nature) or environment (nurture) working in complete absence or independence of other. Genetic factors refer to the actual DNA code that is inherited. Environmental factors, in contrast, can include such things as diet, living conditions, stress, and learned behaviors that may influence a person's mindset, perception, and/or epigenetic landscape. The term epigenetic is used to describe heritable changes to the structure of chromatin (DNA packaged around histones) that directly influence how genes are turned on and off. This type of regulation occurs in the absence of

any code changes within the actual DNA sequence and can be reversible. While our DNA code provides the necessary instructions for how to make a polypeptide, a person's epigenetic landscape helps to determine what polypeptides will be made, when they will be made, and where they will be made. Modification of the DNA double-helix backbone by methylation, combined with various amino acid modifications on histone proteins specifically acts to "open" or "close" the regional chromosome structure to enhance or shut down gene expression.(Graber et al., 2017b)

Monozygotic (MZ) twins are identical at the level of their actual DNA code, differences in their epigenetic landscapes can still generate phenotypic differences between them. Thus, environmental factors may not only cause a change in the DNA sequence through mutations, but they may also alter gene expression (short term and long term) through epigenetic regulation. Genetic mutations, as well as epigenetic patterns located on the DNA backbone and histone protein complexes, can be inherited.(Golbabapour et al., 2011; Williams et al., 2014)

Full siblings share, on average, half of their genes, and studies have shown that siblings can have similar occlusions. Developing similar occlusions, however, is influenced in some part by environmental factors (e.g., influenced by having dietary and respiratory factors in common) and in some part by genetic factors that influence development.(Beecher et al., 1983; Corruccini & Potter, 1980a) (Garn et al., 1979)For example, malocclusion is less frequent and less severe in populations that have not been industrialized (i.e., nonurbanized) and that tend to be isolated. Typically, an increase in the occurrence of malocclusion has been noted as these populations become more "civilized" or increasingly urbanized. Increase in malocclusion within populations that have moved recently into an industrialized lifestyle occurred too quickly to be attributed to genetic change caused by

evolutionary fitness pressure. (Chung et al., 1971) The most likely explanation for the observed increase in the occurrence of malocclusion in “civilization” is environmental change, such as the types of foods being consumed and airway effects. (Corruccini, 1984)

Neither genetic nor epigenetic factors alone are sufficient, and only their integrated (interactive) activities provide the necessary and sufficient causes of growth and development. Moss (Moss, 1997b) considered factors as intrinsic, while prior causes and epigenetic causes were extrinsic and proximate. The phrase form follows function has been used to explain that skeletal development is secondary to muscle function, airway requirements, and other causes extrinsic to the bone. Variations in masseter muscle fiber type, gene expression in masseter muscle, and epigenetic changes are associated with anterior open versus deep bites, mandibular retrognathism versus prognathism, and mandibular asymmetry. (Rowlerson et al., 2005a; Sciote et al., 2013a) (Huh et al., 2013a; Raoul et al., 2011a)

Interestingly, differences in muscle fiber composition have been noted in masseter muscle tissue obtained from patients with a mandibular asymmetry. 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., 2011b)

Additional studies have shown, 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. (Huh et al., 2013b; Rowlerson et al., 2005b; Sciote et al., 2013b) And, gene expression at both

KAT6B and HDAC4 loci were elevated in masseter muscle from patients with Class III malocclusions compared to individuals diagnosed with Class II.(Desh et al., 2014; Huh et al., 2013b) It has been proposed that the KAT6B protein could play a potential role in MP through its ability to activate the runt-related transcription factor 2 gene (RUNX2), which encodes an osteogenic transcription factor.(Desh et al., 2014)

1.4 Heritability and Its Estimation

Heritability estimates can range from 0 to 1. A trait with a heritability estimate of 1 would be expressed with complete positive correlation to genotypic factors theoretically, as measured by comparing the concordance of the phenotype to the percentage of genes in common—for example, among twins or other siblings. By comparison, a trait with a heritability of 0.5 would have half its variability of concordance (from individual to individual) positively correlated with the percentage of genes in common.

One must remember some important aspects of heritability studies, first, hereditary estimates are just that, estimates of genetic and environmental contributions that may have been affected by not accounting for a common environmental effect and ascertainment bias. They only include additive genetic influences and do not take into account genetic and environmental interactions.(Corruccini & Potter, 1980b; L. King et al., 1993) In addition, heritability estimates refer to a specific sample and do not necessarily pertain to the situation of a given individual, even from within the sample. Thus, they do not allow one to tell to what degree a particular trait was determined by genetic or environmental factors in a single individual. Finally, heritability estimates are descriptive of variances within a sample at a given time; they are not predictive.(LaBuda et al., 1993) It is important to understand that heritability

estimates can change with age. This was demonstrated in a longitudinal analysis of 30 sets of siblings, none of whom had undergone orthodontic treatment, which showed a significant increase overall in median heritability estimates between the ages of 4 and 14 years for 29 craniofacial skeletal variables. The affected variables included increases for total anterior face height, upper anterior face height, total posterior face height, and upper posterior face height. Still, despite the general increasing trend in heritability estimates for the craniofacial skeletal variables, a decrease was noted for lower posterior face height. The median estimates of heritability for craniofacial skeletal variables increased from 0.6 at age 4years of age to 0.9 at age 14 and 20 years of age. This is in contrast to the heritability estimates of arch and occlusal variables that decreased from 0.5 at age 4 years to 0.2 and 0.1 at ages 14 and 20, respectively.(E. F. Harris & Johnson, 1991) because craniometric variables, have high heritabilities, and almost all of the occlusal variability is acquired rather than inherited. 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 relationships. Still, arch size and shape are associated more with environmental variation than with genetic variation.(Cassidy et al., 1998a)

longitudinal analysis of	Age	heritability estimates	Age	heritability estimates	**Heritability**
craniofacial skeletal variables	4 years	0.6	14 and 20 years	0.9	high heritabilities
occlusal variability	4 years	0.5	14 year 20 year	0.2 0.1	low heritabilities

TABLE (1)

The heritability of a trait cannot necessarily be extrapolated from one sample and set of environmental conditions to another.(Griffiths et al., 1999b) For example, heritability estimates of lower anterior face heights change more than upper anterior face heights in a group of subjects who have a change in their breathing pattern.(Hartsfield Jr, 2002) Therefore, a high heritability cannot measure if a trait can be influenced substantially by subsequent changes in environmental/treatment conditions.(Griffiths et al., 1999b; E. F. Harris, 2008b) Still, confirming a certain degree of genetic influence on a trait for a particular sample in a particular environment at a particular time is a preliminary step to further specific genetic studies to determine areas of the genome that appear to be associated with the characteristics of a given trait.(LaBuda et al., 1993)

1.5 Use of Family Data to Predict Growth

Siblings have been noted as often showing similar types of malocclusions. Examination of parents and older siblings has been suggested as a way to gain information regarding the treatment need for a child, including early treatment of malocclusion.(J. E. Harris & Kowalski, 1976; Litton et al., 1970a; Niswander, 1975b; Saunders et al., 1980) Niswander (Niswander, 1975b) noted that the frequency of malocclusion is decreased among siblings of index cases with normal occlusion, whereas the siblings of index cases with malocclusion tend to have the same type of malocclusion more often. Harris and colleagues(J. E. Harris et al., 1975) showed that the craniofacial skeletal patterns of children with Class II malocclusions are heritable and that a high resemblance to the skeletal patterns occurs in their siblings with normal occlusion. From this it was concluded that the genetic basis for this resemblance was probably due to multiple genetic factors, and family skeletal patterns were used as predictors for the treatment prognosis of the child with a Class II malocclusion, although it was acknowledged that the

current morphology of the patient is the primary source of information about future growth.(J. E. Harris & Kowalski, 1976) Although each child receives half of his or her genes from each parent, they are not likely the same combination of genes in each sibling, unless the children are MZ twins.

When looking at parents with a differing skeletal morphology, it is difficult to know which of the genes, in what combination from each parent are present in the child until the child's phenotype matures under the continuing influence of environmental factors. Therefore, at best, using mid-parent values, only 49% of the variability of any facial dimension in a child can be predicted by consideration of the average of the same dimension in the parents. Only 25% of the variability of any facial dimension in a child can be predicted, at best, by considering the same dimension in a sibling or one parent. Because varying effects of environmental factors interact with the multiple genetic factors, the usual correlation for facial dimensions between parents and their children is about 30%, yielding even less predictive power.(Hunter, 1990) Unfortunately, orthodontists usually do not have sufficient information to make precise and accurate predictions about the complex development of occlusion simply by studying the frequency of its occurrence in parents or even siblings.

1.6 FACIAL GROWTH

The pubertal growth spurt response is mediated by the combination of sex steroids, growth hormone, insulin-like growth factor, and other endocrine, paracrine, and autocrine factors. The administration of low doses of testosterone in boys with delayed puberty not only accelerates their statural growth rate but their craniofacial growth rate as well. (Verdonck et al., 1999) In addition to testosterone, estrogens are also a group of hormones involved in growth and development.(Moss, 1972) Aromatase (also known as estrogen synthetase) is a key

cytochrome P450 enzyme involved in estrogen biosynthesis by catalyzing the final rate limiting step of converting testosterone and androstenedione to estradiol and estrone, respectively.(Guo et al., 2006) CYP19A1 is the gene that encodes aromatase; therefore, regulation of this gene's transcription is critical for the testosterone/estrogen (T/E) ratio in the body. Some studies have shown that the T/E ratio is critical in the development of sex-indexed facial characteristics such as the growth of cheekbones, the mandible and chin, the prominence of eyebrow ridges, and the lengthening of the lower face. (Schaefer et al., 2005, 2006)

A significant difference in the average sagittal jaw growth was observed between the groups of Caucasian males examined who inherited different CYP19A1 alleles/genotypes, with the greatest differences in growth per year just over 1.5 mm per year during treatment for the maxilla, and 2.5 mm per year for the mandible. There was no statistical difference for the particular CYP19A1 alleles in females. This is particularly impressive since at the beginning of treatment there was no significant difference among the males based upon the CYP19A1 genotype. The significant difference only expressed itself over the time of treatment during the cervical vertebral stage associated with increased growth velocity.(Hartsfield Jr et al., 2010).

Further investigation of this and other genetic factors and their interactions with each other and with environmental factors will help to explain what has up to now been an unknown component of individual variations in pubertal facial growth.

1.7 Skeletal Variation and Malocclusions:

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

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.

1.7.1 Mandibular Prognathism/Class III Malocclusion

Class III malocclusion represents a growth-related dentofacial deformity with mandibular prognathism in relation to the maxilla and/or cranial base.(Zere et al., 2018) Perhaps the best known example is the familial "MP" referred to as the Hapsburg jaw. Although MP has been said to be a polygenic (Litton et al., 1970b) or multifactorial trait, in the majority of cases, there are families in which the trait (and possibly some other associated findings) appears to have autosomal dominant inheritance, such as in the European noble families.

Also noted was that some of the members of the European noble families had, in addition to varying degrees of MP, 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.(Thompson & Winter, 1988)

Apparent maxillary hypoplasia, as well as malar flattening and downward eversion of the lower eyelids, may indicate that although the trait is referred to as MP, the overall clinical effect may be at least in part due to hypoplasia of the maxilla. Clinically, we observe a variety of anatomic changes in the cranial base, maxilla, and mandible that may be associated with "MP" or a Class III malocclusion. (Bui et al., 2006; Singh, 1999)

Understanding the concept of phenotypic and genetic heterogeneity is critical to understanding the genetic influences on all types of

phenotypes.(R. A. King et al., 2002) For example, although orthodontists often first classify a malocclusion as Angle Class I, II, or III, we also know that a number of different subtypes of occlusions have varying genetic and environmental influences. A rationale for further subtypes is based on statistical cluster analysis of cephalometric variables, Most of the studies have sought to delineate Class III subtypes, finding either five or seven of them as separate clusters.(Otero et al., 2014) Still, the clustering effect based on cephalometric morphology could have clinical importance as the subtypes may be treated differently, or have different outcomes, or retention concerns.

The prevalence of Class III malocclusion varies and can show different anatomic characteristics among different ethnic groups. Considering this heterogeneity and possible epistasis (the interaction between or among gene products on gene expression), it is not surprising that genetic linkage studies to date have indicated the possible location of genetic loci influencing this trait in several chromosomal locations.(Hartsfield et al., 2013; Otero et al., 2014)

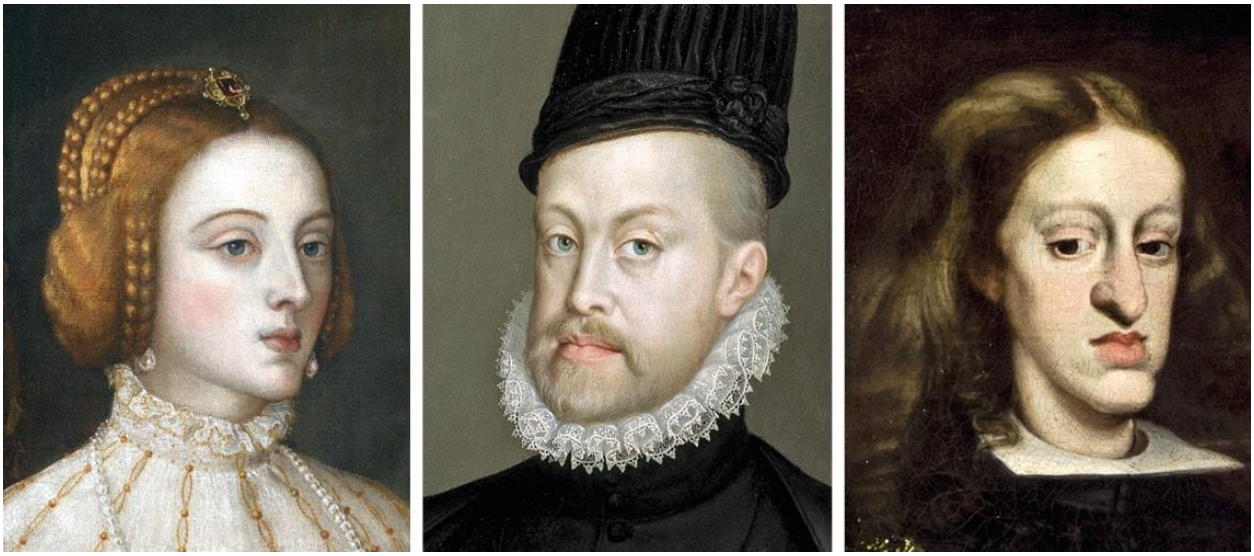


Fig (2)

1.7.2 Class II Division 2 (II/2) Malocclusion

The Class II division 2 (II/2) malocclusion is a relatively rare type of malocclusion, representing between 2.3% and 5% of all malocclusions in the western Caucasians.(Ast et al., 1965; Mills, 1966)

There is evidence that Class II/2 can have a genetic component based upon a twin study in which all 20 MZ twin pairs were concordant for Class II/2, while only 10.7% of 28 DZ twin pairs were concordant.(Markovic, 1992) The much lower concordance for DZ twins suggests that more than one genetic factor contributes to Class II/2.

There is a strong association of Class II/2 with dental developmental anomalies, more so than for other Angle malocclusion classes. Dental agenesis excluding third molars was at least three times more common in Class II/2 subjects than in the general population.(Basdra et al., 2000, 2001) In addition, there is a statistically significant reduction in permanent maxillary incisor mesial-distal width associated with Class II/2, (Peck et al., 1998) which could influence anterior Bolton discrepancies.

1.8 TOOTH SIZE AND AGNESIS

1.8.1 Dental Crown Morphology

Investigation of the genetic and environmental factors that affect dental crown morphology, especially mesial-distal dimensions, is important since tooth size variation may more often play a role in skeletal Class I crowding than skeletal growth variation. (Bernabé & Flores-Mir, 2006; Hashim & Al-Ghamdi, 2005; Poosti & Jalali, 2007; Ting et al., 2011)

Additive genetic variation for mesial-distal and buccal-lingual crown dimensions of the permanent 28 teeth (excluding third molars) ranged from 56% to 92% of phenotypic variation, with most over 80%. (Dempsey & Townsend, 2001)

Estimates of heritability for a number of variables measuring overall crown size of the primary second molars and permanent first molars were moderate to high. Yet, less genetic variation was associated with distances between the cusps on each tooth, implying that phenotypic variation for overall crown size was associated more with genetic variation than was the morphology of the occlusal

surfaces.(Townsend et al., 2003a) Based on studies of epithelial–mesenchymal interactions during tooth generation, cell proliferation in a specific spatiotemporal pattern along with sonic hedgehog (SHH) gene expression appears to have a major influence on crown width and cusp number. (Ishida et al., 2011) Thus, SHH may be a candidate gene for Class I malocclusion with dental crowding.

1.8.2 Dental Agenesis

Dental agenesis may occur within the context of having a family history of dental agenesis (familial) or due to a newly introduced mutation (sporadic), although it is most often familial in origin and usually observed as an "isolated" trait (i.e., non-syndromic). Dental agenesis, however, may also occur as part of a syndrome, especially in one of the many types of ectodermal dysplasias. however, epigenetics and environment can also be involved in the etiology. (Brook, 2009) A general trend in patients with dental agenesis is to have the mesial-distal size crowns of the teeth present to be relatively small (especially if more teeth are missing). The mesial-distal size of the permanent maxillary incisor and canine crowns tends to be large in cases with supernumerary teeth. (Brook et al., 2002) 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, sometimes being a peg-shaped lateral instead of agenesis, and sometimes involving one or the other or both sides. (Woolf, 1971)

Numerous mutations in transcription factor and growth factor–related genes involved in dental development have been shown to have roles in human dental agenesis, including paired box 9 (PAX9; OMIM 167416) and muscle segment homeobox 1(MSX1; OMIM 142983). Mutations in PAX9 typically show a nonsyndromic autosomal dominant mode of inheritance for oligodontia with variable expressivity within families. (Frazier-Bowers et al., 2002; Kapadia et al., 2006; Klein et al., 2005; Nieminen et al., 2001; Suda et al., 2011) The characteristic pattern of dental agenesis caused by PAX9 mutations largely affects molars in both dental arches and second premolars most often in the maxilla arch than the mandibular arch, (Bergendal et al., 2011; Nieminen et al., 2001) occasionally presenting with missing or peg-shaped mandibular central incisors

and/or maxillary lateral incisors. (Bergendal et al., 2011; Frazier-Bowers et al., 2002; Klein et al., 2005; Liu et al., 2022; Nieminen et al., 2001; Suda et al., 2011) MSX1 gene mutations can lead to hypodontia or oligodontia, (Bergendal et al., 2011; Chishti et al., 2006; Kim et al., 2006; Kimura et al., 2014; Lidral & Reising, 2002; Pawlowska et al., 2009; Yamaguchi et al., 2014) (De Muynck et al., 2004; Mostowska et al., 2006; Xuan et al., 2008) as well as variations in the downstream signaling gene BMP4. (Antunes et al., 2012)

In addition to the association of dental agenesis with many syndromes, mutations in tooth development genes have been associated with other medical conditions, such as cancer. In 2004, Lammi et al.(Lammi et al., 2004) reported on a Finnish family with multiple members who manifested oligodontia early in life and colon cancer later in life. While some studies have begun to examine connections between dental tooth agenesis and epithelial ovarian cancer, (Chalothorn et al., 2008; Fekonja et al., 2014, 2015) other studies have connected dental agenesis with a self-reported family history of cancer;(Küchler et al., 2013a) however, the causal genes are yet to be determined.(Küchler et al., 2013b)

1.9 DENTAL ERUPTION PROBLEMS

1.9.1 Canine Impaction and/or Displacement

Maxillary canine impaction or displacement is labial/buccal to the arch in 15% of the cases of maxillary canine impaction and often is associated with d ental crowding. The canine impacted or displaced palatally occurs in 85% of the cases and typically is not associated with dental crowding.(Mcsherry, 1998)

PDCs frequently, but not always, are found in dentitions with various anomalies. In addition, the occurrence of PDCs does occur in a higher percentage within families than in the general population.(Pirinen et al., 1996) A greater likelihood exists of a PDC on the same side of a missing or small maxillary lateral incisor, emphasizing a local environmental effect.(Becker et al., 1999) Also, in some cases, a canine is displaced palatally without an apparent anomaly of the maxillary lateral incisors; in some other cases, lateral incisors are missing without palatal displacement of a canine. Adding to the complexity is the heterogeneity found in studies of cases of buccally displaced canines(Chaushu et al., 2003) and PDCs.(Becker et al., 2002) With apparent genetic and environmental factors

playing some variable role in these cases, the cause appears to be multifactorial.(Peck et al., 1994) Candidate genes that are proposed possibly to influence the occurrence of PDCs and hypodontia in developmental fields include MSX1 and PAX9. (Peck et al., 2002)

1.9.2 Primary Failure of Eruption

Presently, this is clearest in cases of PFE, in which all teeth distal to the most mesially involved tooth do not erupt or respond to orthodontic force. The familial occurrence of this phenomenon in approximately one-quarter of cases facilitated the investigation and discovery that the parathyroid hormone 1 receptor (PTHR1) gene is involved.(Decker et al., 2008; Proffit & Frazier-Bowers, 2009) Advancements in this area could not only help to define patients who are likely to develop or have PFE but also potentially result in the molecular manipulation of selective tooth eruption rates to enhance treatment protocols on an individual basis. (Wise et al., 2002)

1.10 ENVIRONMENTAL AND GENETIC INFLUENCES ON BILATERAL SYMMETRY

Unlike structures that have directional asymmetry when development of one side is different from that of the other during normal development, facial and dental structures lateral to the midline are essentially mirror images of each other, with the same genetic influences affecting both sides. The conditions are theoretically identical for the trait on both sides of the body because they are developing simultaneously and therefore should develop identically. Fluctuating asymmetry occurs randomly when a difference exists between right and left sides. This reflects the inability of the individual to develop identical, bilaterally homologous structures.(Cassidy et al., 1998b) Fluctuating asymmetry has been observed in the primary and permanent dentitions,(Black, 1980; Corruccini & Potter, 1981) as well as in the craniofacies.(Cassidy et al., 1998b) The greater amount of fluctuating asymmetry for the distance between cusps on each tooth than for the overall crown size of primary second molars and permanent first molars indicates that the occlusal morphology of these teeth is influenced more by environmental factors than the overall crown size.(Townsend et al., 2003b)

1.11 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 EARR.

The degree and severity of EARR associated with orthodontic treatment are complex, involving host and environmental factors. An association of EARR exists in those who have not received orthodontic treatment, with missing teeth, increased periodontal probing depths, and reduced crestal bone heights.(E. F. 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.(E. F. Harris & Butler, 1992) EARR is also increased as a pathologic consequence of orthodontic mechanical loading in some patients.(Brezniak & Wasserstein, 1993a, 1993b) The amount of orthodontic movement is positively associated with the resulting extent of EARR.(DeShields, 1969; Parker & Harris, 1998; Sharpe et al., 1987)

Orthodontic tooth movement, or "biomechanics," has been found to account for approximately one-tenth to one-third of the total variation in EARR.(Baumrind et al., 1996; Horiuchi et al., 1998; Linge & Linge, 1991) Owman-Moll and coworkers(Owman-Moll et al., 1995) showed that individual variation overshadowed the force magnitude and the force type in defining the susceptibility to histologic root resorption associated with orthodontic force. The reaction to orthodontic force, including rate of tooth movement, can differ depending on the individual's genetic background.(Abass & Hartsfield Jr, 2007; E. F. Harris et al., 1997; Hartsfield Jr et al., 2004; Iwasaki et al., 2008) There is considerable individual variation in EARR associated with orthodontic treatment, indicating an individual predisposition and multifactorial (complex) etiology. (E. F. Harris et al., 1997; Massler, 1954; Massler & Malone, 1954; Newman, 1975; Reitan, 1957; Sameshima & Sinclair, 2001)

Heritability estimates have shown that approximately half of EARR variation concurrent with orthodontia, and almost two-thirds of maxillary central incisor EARR specifically, can be attributed to genetic variation.(E. F. Harris et al., 1997; Hartsfield Jr et al., 2004) A retrospective twin study on EARR found

evidence for both genetic and environmental factors influencing EARR. (Ngan et al., 2004) In addition, studies in a panel of different inbred mice supported a genetic component involving multiple genes in histologic root resorption.(Abass et al., 2008; Al-Qawasmi et al., 2006) More recently studies are including multiple treatment and genetic factors in models to explain the occurrence of EARR concurrent with orthodontics. For example, 30% of the EARR variability in one study were explained by variation in or the presence of treatment duration, a Hyrax appliance, premolar extractions, sex, and the P2RX7 gene rs1718119 SNP, while age, overjet, tongue thrust, skeletal Class II, and other genetic polymorphisms made minor contributions.(Pereira et al., 2014) Likewise in another study looking at the relative influence of multiple parameters on the occurrence of EARR including treatment duration, extraction of maxillary premolars, and numerous cephalometric measurements (pretreatment values and post-treatment change in values), as well as genotypes for multiple DNA polymorphisms, found that a longer length of treatment and specific genotypes for P2RX7 SNP rs208294 together explained 25% of the total variation associated with EARR concurrent with orthodontics in the sample tested.(Sharab et al., 2015)

These studies are interesting in that they (1) emphasize the possible effect of longer treatment times on EARR concurrent with orthodontics and

(2) support the involvement of a biological pathway since the P2RX7 protein is an upstream regulator of the activation of IL1B that was a focus of initial studies (Hartsfield Jr, 2009) and an inbred mouse model with the mouse version of the P2RX7 gene knocked out showed an increase in histological root resorption with orthodontic force,(Viecilli et al., 2009) as did a previous inbred mouse model with the mouse version of the IL1B gene knocked out.(Al-Qawasmi et al., 2004)

While these more recent studies are helping us to investigate the complexity of EARR occurring with orthodontics, they are insufficient for clinically useful prediction. The use of a nonbiased whole exome or whole genome sequencing approach when possible instead of the current candidate gene models could aid in identifying additional genetic factors that may be involved in orthodontic patient EARR. Even if all the factors were known, their number and complexity may only yield a general high, medium, or low risk of EARR concurrent with orthodontics.

2 Chapter two: Discussion

While the field of oral and craniofacial genetics expands to learn more about the genetic factors that would help to better treat individual patients, it should not be overlooked that today the practitioner in their practice could start to take and consider family history in the diagnosis and treatment planning of malocclusion. This can be used to help understand the approximate likelihood that the patient or a sibling may also develop the same trait, which still may vary in its severity even within the same family. This can be particularly useful for monogenic traits including Class III malocclusion, hypodontia, PFE, and developmental dental dysplasias such as types of dentinogenesis and amelogenesis imperfecta. A family history may also be useful for complex traits such as skeletal Class III and Class II/division 2 malocclusions, EARR, PDC, or any trait that occurs in more than one member of the family.

3 Chapter three: Conclusions and Suggestions

- Uncovering the genetic factors that correlate with a clinical deviation helps to diminish the unknown variation influencing the phenotype.
- Clinical studies, particularly those that consider the effects of an appliance or treatment , need to be a part of these types of genetic investigations in the future.
- Genetic testing for monogenic traits such as Primary Failure of Eruption (PFE) and Class III malocclusion is showing more promise as knowledge and technology advances.
- Although the heterogeneous complexity of such things as facial and dental development, the physiology of tooth movement, and the occurrence of External Apical Root Resorption (EARR) make their precise prediction untenable, investigations into the genetic factors that influence different phenotypes, and how these factors may relate to or impact environmental factors (including orthodontic treatment) are becoming better understood.
- The most important "genetic test" the practitioner can do today is to gather the patient's individual and family history. This would greatly benefit the patient, and augment the usefulness of these families in future clinical research in which clinical findings, environmental, and genetic factors can be studied.

However, further genetic studies are required to clearly determine all the specific genes leading to a particular skeletal variability. The rapid development in this field could lead to the genetic correction of the genetically controlled dentofacial anomalies and malocclusions, perhaps in near future.

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