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Genetic Factors Affecting Facial Growth

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1. Introduction

Malocclusion is the manifestation of complex genetic and environmental interactions on the development of the oral-facial region. Historically, orthodontists have been interested in genetics as a means to better understand why a patient has a particular occlusion, and to determine the best course of treatment for the malocclusion. The application of genetic information in treatment, however, has been hampered by several factors including: 1) the presumption that heritability studies have some clinical relevance to the individual patient, which they do not (Harris, 2008); 2) the presumption that whatever genetic factors may have contributed to the occlusion will also affect how the patient responds to treatment, which they may not; and 3) a lack of understanding to the extent at which genetic factors may interact with environmental factors (such as those created during orthodontic and dentofacial orthopedic treatments) to influence single gene (Mendelian) traits versus “Complex” traits which are more frequently observed in the clinic. (Hartsfield, 2011)

While it is essential to consider genetic factors when diagnosing the underlying cause for virtually all oral-facial anomalies and developmental variations, the importance of how genetic factors will affect the outcome of treatment is often not appreciated. Understanding the etiology of a malocclusion is important, e.g., if the patient is a thumb sucker, then that habit must stop. But in terms of etiology, the factors that influenced a malocclusion to develop may not be the same ones that will influence how the patient responds to treatment of that malocclusion. In addition, the patient’s developmental stage during treatment is typically a later stage than when the basis of the malocclusion first formed. 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.(Buschang & Hinton, 2005) As every orthodontist knows, the ability of the practitioner to affect a change is dependent both on the time of intervention (treatment) and the patient’s stage of development.

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), because of an intrinsic “predestination.” This is a misapplication of genetics to clinical practice since most malocclusions we treat appear to not be the result of a single dominant (Mendelian) gene.(Mossey, 1999b) There are inappropriate uses of

heritability estimates in the literature as a proxy for evaluating whether a malocclusion or some anatomic morphology is “genetic.” This however has no relevance to the question. Regardless of the heritability estimate, there is not a yes or no answer. Heritability estimates only apply to the group that was studied and the environmental factors that they were exposed to up to that time. They do not necessarily apply to an individual at the time of the study, and are not predictive for an individual or the group in the future.(Harris, 2008) How genetic factors will influence the response to environmental factors, including treatment, and the long-term stability of its outcome as determined by genetic linkage or association studies, should be the greatest concern for the clinician as they are the only way leading to a better understanding of the genetic background of the individual patient in terms of their malocclusion and response to treatment.(Hartsfield, 2008) It is of critical importance in clinical practice to understand how genetic factors and their interaction with environmental factors may affect facial growth. The aim of this chapter is to review what is known about the genetic factors that affect facial growth with an emphasis on human studies involving malocclusion.

2. Genome, genotype, phenotype, modes of inheritance and epigenetics

An individual’s **genome** is defined as the genetic information inherited from both of their parents. The information encoded in a patient’s genome can influence growth and development when the coded information is converted into the form of **protein** (and/or regulatory molecules such as microRNAs (miRNAs)). This information is encoded by ~3.2 billion nucleotide base pairs (bps), comprised of adenine (A), thymine (T), cytosine (C) and guanine (G) residues, that are organized into sequences on 23 pairs of chromosomes. Each individual has 22 pairs of **autosomal chromosomes** (chromosomes that exhibit the same copy number in both males and females) and 1 pair of **sex chromosomes** (XX or XY). One chromosome of each pair is inherited from the individual’s mother and the other pair from their father. Collectively this genetic information is often referred to as a person’s DNA or genetic code. Amazingly, the genetic sequences of all humans appear to be ~99.9% identical, and hence it is a mere 0.1% of the sequence information which codes for our individual differences.

It is estimated that the human genome is comprised of 25,000 genes (accounting for only ~2% of the entire genome), with the average gene length being ~3,000 bps of information. A **gene** is a specific sequence of information that provides the instructions for making a unique protein or set of related proteins. The location or “address” for any gene within a genome is called its **locus** (plural loci: i.e., referring to the physical location of more than one gene). A determination of the actual DNA code (A, T, C or G) for a specific location within a person’s genome describes their **genotype** for that location. Since there is natural variation in the sequence of DNA, a specific gene at a locus can still vary among individuals and homologous chromosomes in the same individual. These different forms of the “same” gene are called **alleles**. When the alleles on homologous chromosome pairs are the same, they are said to be **homozygous**. When the alleles on homologous chromosome pairs are different, they are said to be **heterozygous**. The **mode of inheritance** describes how the genetic information is passed down one generation to the next.

Within a single individual, the majority of cells in the body will contain a complete copy of the genome the individual inherited from their parents. Only a small number of specialized

cell types (e.g. mature erythrocytes, mature T- and B-cells of the immune system, sperm, and egg cells) eliminate a portion of inherited DNA to facilitate the cell's ability to perform a specialized function. Aside from these specialized cell types, most cells within an individual's body become (or differentiate into) a particular kind of cell (e.g. a muscle, nerve, or skin cell, etc...) or become part of a larger tissue or organ based upon the pattern of genes that are turned "on" or "off" within each cell. The process of turning a gene "on" is referred to as "gene expression" and most forms of gene expression lead to the production a protein or set of related proteins. Hence, a well differentiated cell like an osteoblast, does not become an osteoblast due to the presence of unique DNA codes found only in osteoblast cells or due to the loss of non-osteoblast related genetic information. An osteoblast becomes an osteoblast due to the genes and related proteins (or regulatory molecules) being expressed within the cell combined with the influence of any environmental factors that can alter these expression pattern(s).

The visible or measurable characteristics of an individual is their **phenotype**. A phenotype is determined based on the combination of: (1) the inherited genetic information being expressed by cells within the individual (e.g., the individual's genotype); (2) the environment in which the proteins (or regulatory molecules) are being expressed; and (3) any genotype-environment interactions that could influence protein (or regulatory molecule) expression or function. In contrast, a **trait** is a particular aspect or characteristic of the overall phenotype. An **inherited trait** is one that has the ability to be transferred from one generation to the next generation. A **syndrome** is a combination of traits that occur together in non random pattern that is different from the usual pattern. (Hartsfield & Bixler, 2011)

When the information in a single gene locus is essentially responsible for the development of a trait or syndrome, this trait or syndrome is said to be *monogenic*. If the gene locus is located on one of 22 autosomal chromosome pairs (chromosomes other than the X or Y sex chromosomes), and only one copy of a specific gene allele on the autosomal pair is sufficient to lead to the production of the trait or syndrome, then the individual is typically heterozygous for that allele and the effect on the inheritance pattern of the trait or syndrome is **autosomal dominant**. If the production of the trait or syndrome does not occur when only one copy of a particular allele is present at the locus on a paired set of autosomes, but does occur when two copies of that particular allele are present at the locus of a paired set of autosomes, then the inheritance pattern of the trait or syndrome is **autosomal recessive**. In this situation the "recessive" alleles are said to be homozygous. (Mossey, 1999a) This may be the case by having a common ancestor (inbreeding) in which the alleles are presumed to be identical, or by the random combination of alleles that although may not be of identical DNA sequence, still are operationally recessive.

The following are characteristic for **autosomal dominant inheritance**: (1) the trait or syndrome occurs in successive generations; (2) when an individual has the gene allele that results in the trait or syndrome, each child of theirs has a 50% chance of inheriting that gene allele; (3) males and females are equally likely to have the trait or syndrome; and (4) parents who do not have the trait or syndrome have offspring who do not have the trait or syndrome (see figure 1). However, there are notable caveats to these characteristics. Just because an individual has the "dominant" gene allele that would usually lead to the development of some particular trait or syndrome, such as Class III malocclusion, Treacher

Collins syndrome or Crouzon syndrome (a common craniosynostosis condition), the appearance of the trait or syndrome may “skip a generation” in what is called **non-penetrance** in the individual, or incomplete penetrance in a group of individuals who have the genotype but don’t manifest the trait or syndrome. (Cruz et al., 2008; Everett et al., 1999; Hennekam et al., 2010) In addition, traits and syndromes with autosomal dominant inheritance typically have **varying degrees of severity** in individuals who show any evidence of the condition, which is termed **variable expressivity** of the phenotype. Thus analyzing the genome/genotype of even traits or syndromes with autosomal dominant may not “precisely” predict the phenotype, but certainly can often indicate there will be a major effect on growth and development to some degree. Variable expressivity also may apply to the pleiotropic effect of a particular genotype: that is the expression of a gene resulting in seemingly disparate traits in an individual. Thus even dominant traits that are said to be due to a change in a single gene can be influenced by the proteins from other genes and environmental factors (see figure 2).

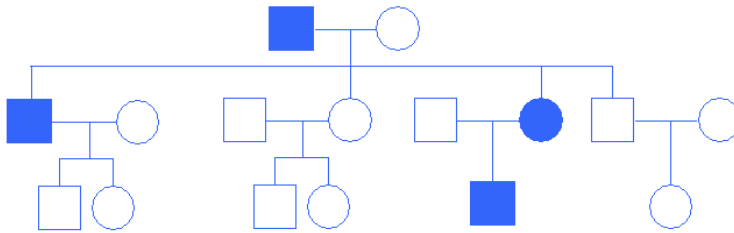


Fig. 1. Autosomal dominant Inheritance.

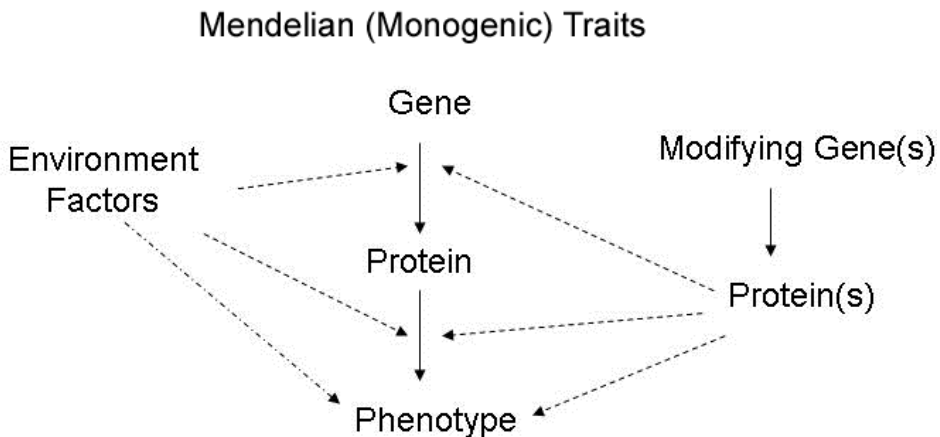


Fig. 2. Interaction of Genetic and Environmental Factors on an “Monogenic Dominant” Trait.

In **autosomal recessive inheritance** the transmission of the pedigree is typically horizontal (present only in siblings, see figure 3). Parents of a child with a trait or syndrome that has an autosomal recessive mode of inheritance are typically heterozygous ("carriers"). The heterozygous parents would then have a 25% of each child of theirs having the autosomal recessive trait or syndrome.

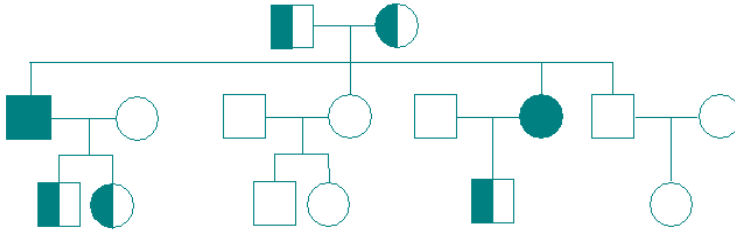


Fig. 3. Autosomal recessive inheritance.

For X linked traits, recessive genes on the one male X chromosome express themselves phenotypically as if they were dominant genes because a male usually only has one X chromosome (hemizygous). In this case the males with the genotype are affected in the pedigree, although in some cases the females can be affected as well. Females who are heterozygous for the gene associated with the X linked recessive phenotype may show some expression of the phenotype. This is because most of the genes on one of the X chromosomes in each cell of a female normally will be inactivated by a process called **lyonization (or X chromosome inactivation)**. Early in fetal development (at approximately the 16-cell morula stage), each cell of the developing female fetus inactivates almost all the genes on one of her two X chromosomes, and all cells that develop from that cell will show the inactivation of the same X chromosome. Depending on the ratio of cells with the X chromosome that has the recessive gene on it versus the X chromosome that does not have the recessive gene, the female may show some variable manifestation of the condition.

Most traits do not adhere to patterns of Mendelian inheritance. These traits are referred to as complex or common diseases and traits, and reflect their complex interaction between genes from more than one locus and environmental factors. Polygenic traits infer the effect of multiple genes on the phenotype, but can be affected by environmental factors also (see figure 4). The distinction between polygenic traits and multifactorial traits (both are traits influenced by environmental and multiple genetic factors) has been made for some multifactorial traits that are discrete (dichotomous) and that occur in an individual once a developmental threshold of genetic and environmental factors to produce the phenotype has been reached.

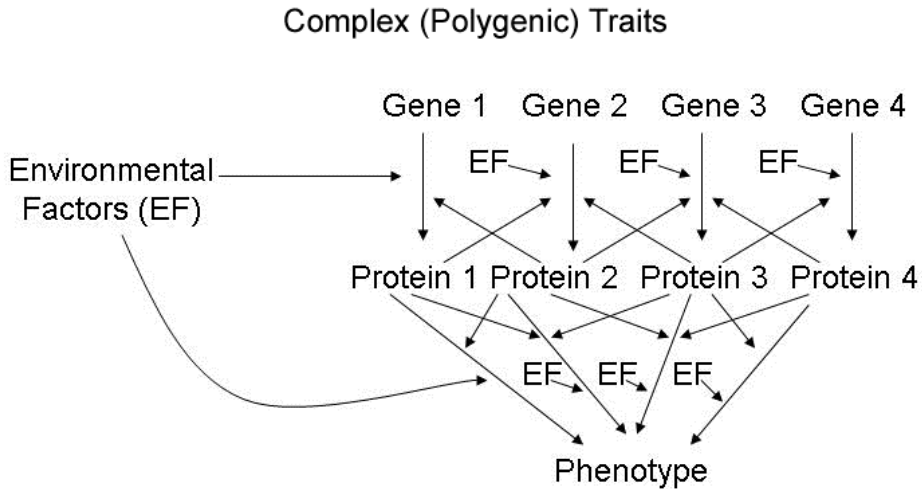


Fig. 4. Interaction of Genetic and Environmental Factors on a Complex Trait.

Epigenetics is the study of acquired and heritable changes in gene function that occur without a change in the DNA sequence. Environmental factors can influence epigenetic mechanisms such as DNA modification (i.e., methylation), histone modification (e.g., lysine and arginine methylation, acetylation, ubiquitination, phosphorylation, sumoylation, ADP ribosylation, deamination and proline isomerization)), and post-transcriptional silencing by RNA interference (microRNA, miRNA). All of these processes can result in gene activation and inactivation. (Lambert & Herceg, 2011) Epigenetic mechanisms can mediate the effect of the environment (e.g., dietary, hormonal and respiratory factors) on the human genome by controlling the transcriptional activity of specific genes, at specific points in time in specific organs. (Gabory et al., 2009; Schwartz, 2010) Malocclusion is a trait than can be greatly influenced by environmental factors. Corrucini suggested that the rapid increase in malocclusion in indigenous Australian people was produced by dietary factors concurrent with industrialization, and emphasized the importance of environmental influences on occlusal variation and the variability of apparent genetic determinants with respect to the environment or population in which they are measured. (Corruccini, 1984, 1990; Corruccini et al., 1990) Likewise Kawala et al. after studying the concordance of malocclusion in twins showed the distribution of within-pair malocclusions depended upon the gender of the individuals, and supported the impact of environmental factors. (Kawala et al., 2007)

In the consideration of environmental effects upon the development of malocclusion, it should not be forgotten that one's genome may influence the response to environmental factors. This is supported by the differences in shape of the mandibular condyles being "slightly greater" among four different inbred strains of mice on a hard diet than on a soft

diet for six weeks. When the environment changed sufficiently, the response was different among animals with different genotypes that were not different before the environmental change.(Lavelle, 1983) Siblings may often have similar malocclusions not just because of common genetic or environmental factors, but also because of their shared genetic factors affecting how they respond to the shared environmental factors.(King et al., 1993) However, none of these studies on the effect of environmental factors were focused on epigenetic modifications as a result of environmental factors influencing malocclusion. As the exploration of epigenetics continues throughout biology and medicine, it may also be an interesting area to explore in facial growth.

3. Heritability and malocclusion

Most problems in orthodontics (or any outcome of growth), unless acquired by trauma, are not strictly the result of only genetic or only environmental factors. The ideal occlusion condition shows a proportional growth between the cranial base, the maxilla and the mandible; and involves the harmonious relation between skeletal bases and soft tissues (perioral musculature, lips and tongue).(Mossey, 1999b) The general morphology of craniofacial bones and teeth are largely genetically determined, although clearly variation is partly attributable to environmental factors.(Corruccini et al., 1990; Harris, 2008; Klingenberg et al., 2004; Kraus & Lufkin, 2006; Thesleff, 2006; Townsend et al., 2003) Genetic mechanisms predominate during embryonic craniofacial morphogenesis and in the etiology of many craniofacial abnormalities, therefore genetic factors must be considered in the etiology of malocclusion. However environment is also thought to influence dentofacial morphology postnatally, particularly during facial growth. In response to the presumption of the genome being the predetermining force for facial development and by inference skeletal malocclusion, the Functional Matrix Hypothesis by Moss theorized the primary role of function in craniofacial growth and development. Still, Moss did conclude that both genomic and environmental/epigenetic factors are necessary causes, that neither alone is a sufficient cause and that only the two interacting together furnish both the necessary and sufficient cause(s) of growth and development.(Moss, 1997b, 1997a)

One method employed to estimate this relative contribution of genetic and environmental factors is by calculating the heritability of a trait. Heritability in the broad sense (H^2) includes all additive, interactive and other types of genetic and environmental influences. This is impossible to derive, since all the factors and how they interact is not known. Therefore heritability estimates in the literature are in the narrow sense (h^2), and represent the proportion of the total phenotypic variance in a sample that is contributed by additive genetic variance. However, the estimated ratio of genetic variation does not take into account gene-gene or gene-environment interaction.(Hartsfield, 2011) Numerous studies have examined how genetic variation contributes to either or both occlusal and skeletal variation among family members. It is difficult to estimate the influence of environmental (treatment) factors in craniofacial growth because the heritability studies of occlusion are typically based on twins and siblings who did not receive orthodontic treatment. Twin pairs and other groups of siblings containing one or more treated patients (with moderate to severe malocclusion) may have been excluded from most studies. Moreover the twin studies have not included extensive analysis of the parents, nor familial, and nutritional habits; and usually have not compared the twin group with a control group to ascertain environmental

covariance (similarity due to twins and other siblings being in a common environment). Therefore, estimates of genetic and environmental contributions may have been affected by lack of accounting for a common environmental effect (Corruccini & Potter, 1980) and ascertainment bias. (King et al., 1993)

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. (Arya et al., 1973; Boraas et al., 1988; Byard et al., 1985; Cassidy et al., 1998; Chung & Niswander, 1975; Corruccini et al., 1986; Devor, 1987; Fernex et al., 1967; Gass et al., 2003; Harris et al., 1973; Harris et al., 1975; Harris & Smith, 1980; Harris & Johnson, 1991; Hauspie et al., 1985; Horowitz et al., 1960; Hunter et al., 1970; Johannsdottir et al., 2005; King et al., 1993; Kraus et al., 1959; Litton et al., 1970; Lobb, 1987; Lundstrom & McWilliam, 1987; Manfredi et al., 1997; Nakata et al., 1973; Nikolova, 1996; Proffit, 1986; Saunders et al., 1980; Susanne & Sharma, 1978; Watnick, 1972) In most studies (particularly those that try to account for bias from the effect of shared environmental factors, unequal means, and unequal variances in monozygotic and dizygotic twin samples), (Harris & Potter, 1997) variations in cephalometric skeletal dimensions are associated in general with a moderate to high degree of genetic variation, whereas in general, variation of occlusal relationships has little or no association with genetic variation. (Harris, 2008)

Although the heritability estimates are low, most of the studies that looked at occlusal traits found that genetic variation is positively correlated with phenotypic variation for arch width and arch length more 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. They will vary because of their own variation in position and those of the basilar structures. (Harris & Johnson, 1991) Heritability studies must be supplemented and to some degree superseded by studies linking or associating specific traits with variation in genetic markers such as single nucleotide polymorphisms (SNPs), variable number of tandem repeats, or other types of specific DNA variation.

For example, SNPs in the *EDA* gene and the gene for its receptor *XEDAR*, were found to be associated with dental crowding greater than 5 mm in a Hong Kong Chinese Class I malocclusion sample. It was thought that this may at least be due in part to variation in tooth size as the gene product of *EDA* is involved in tooth development, and mutations in *EDA* cause X-linked Hypohydrotic Ectodermal Dysplasia. (Ting et al., 2011) A possible affect on tooth size is consistent with the findings that in skeletal Class I crowding cases tooth size variation may more often play a role than skeletal growth. (Bernabe & Flores-Mir, 2006; Hashim & Al-Ghamdi, 2005; Poosti & Jalali, 2007; Ting et al., 2011) Although these genes are located on the X chromosome, the associations remained after adjustment for sex. This type of investigation is thought to help get around the problem of confounding environmental factors, although an increased analysis of epigenetic markers may show this is not that simple. Still these studies are the only way in which possible predictive data will be collected and tested.

4. Use of family data to predict growth

Siblings have been noted as often showing similar types of malocclusion. 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. (Harris & Kowalski, 1976; Litton et al., 1970; Niswander, 1975; Saunders et al., 1980) Niswander 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. (Niswander, 1975) There are high correlation coefficient values between parents and their offspring for Class II and Class III malocclusions. (Nakasima et al., 1982) It has been shown that the craniofacial skeletal patterns of children with Class II (division 1) malocclusions are familial (i.e., occur more often in multiple members of some families), and that a high resemblance to the skeletal patterns occurs in their siblings with normal occlusion. (Harris et al., 1975) Although this was ascribed to the Class II (division 1) being "heritable," common environmental factors were not taken into account. From this it was concluded that the genetic basis for this resemblance is probably polygenic, 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. (Harris & Kowalski, 1976)

Each child receives half of his or her genes from each parent, but not likely the same combination of genes as a sibling unless the children are monozygotic twins. When looking at parents with a differing skeletal morphology, knowing which of the genes in what combination from each parent is present in the child is difficult until the child's phenotype matures under the continuing influence of environmental factors. When considering polygenic traits, the highest phenotypic correlation that can be expected based on genes in common by inheritance from one parent to a child, or between siblings, is 0.5. Because the child's phenotype is likely to be influenced by the interaction of genes from both parents, the "mid-parent" value may increase the correlation with their children to 0.7 because of the regression to the mean of parental dimensions in their children. Squaring the correlation between the two variables derives the amount of variation predicted for one variable in correlation with another variable. 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)

In most patients, the mode of inheritance for the craniofacial skeleton is polygenic (complex). However, in some families (e.g., with a relatively prognathic mandible compared with the maxilla), the mode of inheritance is not polygenic. Future research may investigate the genetic factors that do not fit a polygenic mode that may be present in some families. Identification of those factors will increase the ability to predict the likelihood of a particular resulting morphology. Unfortunately, orthodontists do not have sufficient information to make accurate predictions about the development of occlusion simply by studying the frequency of its occurrence in parents or even siblings. Admittedly, family patterns of resemblance are frequently obvious, and observed family tendencies should not be ignored.

Nonetheless, predictions must be made cautiously because genetic and environmental factors and their interaction are unknown and difficult to evaluate and predict with precision.(Hartsfield, 2011)

5. Genetic markers associated with variations in growth of complex etiology

5.1 Growth hormone receptor

Growth hormone is an important factor in craniofacial and skeletal growth. A variant in the growth hormone receptor and its gene (*GHR*), when there is a proline amino acid instead of threonine at the 561st residue in the protein, is referred to as the *GHR* P56IT allele. Of a normal Japanese sample of 50 men and 50 women, those who did not have the *GHR* P56IT allele had a significantly greater mandibular ramus length (condylion-gonion) than did those with the *GHR* P56IT allele. The average mandibular ramus height in those with the *GHR* P56IT allele was 4.65 mm shorter than the average for those without the *GHR* P56IT allele. This significant correlation between the *GHR* P56IT allele and shorter mandibular ramus height was confirmed in an additional 80 women.(Yamaguchi et al., 2001) Interestingly, the association was with the mandibular ramus height but not mandibular body length, maxillary length, or anterior cranial base length. This suggests a site-, area-, or region-specific effect. The study concluded that the *GHR* P56IT allele may be associated with mandibular height growth and can be a genetic marker for it. Still, whether the effect is directly on the mandible or some other nearby tissue or on another matrix is not clear. It has been suggested that *GHR* variants P561T and C422F are associated with mandibular ramus height in Japanese population and that the SNPs of the *GHR* gene associated with differences in mandibular ramus height in the Japanese are likely to be different in other ethnic groups. (Tomoyasu et al., 2009)

This is supported by the finding that although there is a possible association between the *GHR* polymorphisms P561T, C422F and “haplotype 4” in a Korean population, there was not significant association between these markers and mandibular height in African-Americans, European-Americans, and Hispanics.(Kang et al., 2009) This group suggested that this finding might partly explain the differing craniofacial morphology among different ethnicities. Analysis of the possible association between the P561T variant in the *GHR* gene and mandibular growth during early childhood did not find a difference between mandibular protrusion and normal occlusion. (Sasaki et al., 2009) To see what effect different diets would have on individuals with and without the *GHR* P56IT allele would be interesting as a means of looking at genetic and environmental factor interaction. Undoubtedly many other genes that may influence craniofacial structure, including ramus height, could be identified, and their variation could be studied along with different environmental factors (e.g., orthodontic treatment) and the resulting phenotype.

5.2 Growth differences during puberty

Increased accuracy in the estimation of pubertal facial growth would be of great benefit prior to the utilization of different therapeutic modalities including orthodontics, orthopedic growth modification and surgery. Research and discussion about facial growth and treatment in the literature have focused either on the timing of the greatest amount of facial growth, particularly for the mandible(Gu & McNamara, 2007; Hunter et al., 2007; Verma et

al., 2009); or the estimated extent of facial growth to be attained.(Chvatal et al., 2005; Turchetta et al., 2007) As useful as average facial growth predictions based upon expected growth curves may be, more valid prediction must incorporate and account for the variation associated with individual genetic factors, particularly those that are highly pertinent to the pubertal growth spurt. The pubertal growth spurt response is mediated by the combination of sex steroids, growth hormone, insulin-like growth factor (IGF-I) and other endocrine, paracrine and autocrine factors. Testosterone and estradiol in mice have a direct, sex-specific stimulatory activity on male and female derived chondroprogenitor cell proliferation. Testosterone stimulated growth and local production of IGF-I and IGF-I-R in chondrocyte cell layers of an isolated organ culture of mice mandibular condyle.(Maor et al., 1999) Investigation into the effects of neonatal surgical castration and prepubertal chemical castration on craniofacial growth in rats showed that craniofacial growth was related to testosterone concentration. 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., 1998; Verdonck et al., 1999)

Ovariectomized and orchietomized mice that sex hormone levels influenced condylar morphogenesis changed the internal structure of the mandibular condyle.(Fujita et al., 2001) It has been suggested that the suppression of sex hormone secretion in the growth phase might inhibit craniofacial growth and result in poor craniofacial development, particularly nasomaxillary bone and mandible, in new born and pubertal rats.(Fujita et al., 2004; Fujita et al., 2006) It has been demonstrated using administration of sex hormone specific receptor antagonists that growth of the mandible and femur is induced in response to the stimulation of the estrogen receptor beta ($ER\beta$) in chondrocytes before and during early puberty in mice. In late and after puberty, the growth is induced by the stimulation of estrogen receptor alpha ($ER\alpha$) in male and female mice. From this it was proposed that a screen of sex hormones could be used as an indicator of bone maturity to accurately predict the beginning and end of growth in orthodontic treatment.

CYP19A1 is the gene that encodes aromatase. This enzyme catalyzes the rate limiting step in estrogen biosynthesis by converting androgens. In order to best diagnose and treat the child or adolescent patient, the orthodontist needs to know as much as possible about the patient's growth potential. As useful as predictions based upon expected growth models starting from early in the patient's life may be, prediction must incorporate and account for the variation associated with individual genetic factors, especially those that are highly pertinent to the pubertal growth spurt.

Estrogens are a group of hormones involved in growth and development.(Honjo et al., 1992) Estrogen stimulates chondrogenesis, promotes the progressive closure of the epiphyseal growth plate, has an anabolic effect on the osteoblast and an apoptotic effect on the osteoclast, and increases bone mineral acquisition in axial and appendicular bone during adolescence and into the third decade.(Grumbach, 2000) Aromatase (also known as estrogen synthetase) is a key cytochrome P450 enzyme involved in estrogen biosynthesis.(Bulun et al., 2003) This steroidogenic enzyme catalyzes the final step of estrogen biosynthesis by converting testosterone and androstenedione to estradiol and estrone, respectively.(Guo et al., 2006) Regulation of this gene's transcription is critical for the testosterone/estrogen (T/E) ratio in the body since aromatase plays an important role in the conversion of androgens to estrogens. 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; Schaefer et al., 2006)

The difference in the average sagittal jaw growth between the two groups of Caucasian males with different *CYP19A1* alleles with the greatest differences in growth per year was just over 1.5 mm per year during treatment for the maxilla, and 2.5 mm per year for the mandible. (Hartsfield Jr. et al., 2010) 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 et al., 2010) Interestingly the same result was found in a group of Chinese males and females, strongly suggesting that this variation in the *CYP19A1* gene may be a multi-ethnic marker for sagittal facial growth. (He et al., 2011) Although the difference in average annual sagittal mandibular and maxillary growth based upon this *CYP19A1* genotype were significant, as one factor in a complex trait (sagittal jaw growth), they account for only part of the variation seen, and therefore by itself has little predictive power. Further investigation of this and other genetic factors, 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 facial growth.

5.3 Class II division 2 (Class II/2) malocclusion

There is evidence that Class II division 2, and particularly Class III malocclusions, can have a strong genetic component. 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 white population. (Ast et al., 1965; Mills, 1966) In one study 100% of 20 monozygotic (MZ) twin pairs were concordant for II/2 malocclusion, while only 10.7% of 28 dizygotic (DZ) twin pairs demonstrated concordance for the Class II/2 malocclusion. (Markovic, 1992) These findings suggest the effect of common genetic or environmental factors; however, the much lower concordance for DZ twins would suggest that multiple genetic factors rather than a single gene contribute to the risk for Class II/2. This was reinforced by Ruf et al. concluding that the etiology of Class II/2 malocclusion was unclear, with neither form nor function the sole controlling factor. (Ruf & Pancherz, 1999)

From a developmental viewpoint it is interesting that there is a strong association of Class II/2 malocclusion with dental developmental anomalies, more so than for other Angle malocclusion classes. (Basdra et al., 2001) Excluding 3rd molars, agenesis of other teeth was at least three times more common in Class II/2 subjects than in the general population. In addition, there were a significantly greater number of dental developmental anomalies present in Class II/2 subjects as compared to the general population. They found 56.6% of Class II/2 patients exhibited developmental tooth anomalies including hypodontia as compared to as many as 35% of the general population having agenesis of one or more third molar. (Basdra et al., 2000) In addition Peck et al. showed a statistically significant reduction in permanent maxillary incisor mesial-distal width associated with Class II/2. (Peck et al., 1998)

Further evidence for a polygenic complex etiology for Class II/2 was found in a study of 68 subjects (67 self reported as white and 1 white/African-American who was a child of one of the 18 probands). (Morrison, 2008) A proband is the affected individual through whom a family is first seen or studied for a genetic trait, syndrome or disorder. In this study, researchers included 50 reported first-degree relatives of each proband, with a minimum of 2 first-degree relatives of each proband. The findings showed a marked increase in the number of females affected with Class II/2 in both the probands and their first-degree relatives than affected males. Of the 36 first-degree relatives whose occlusion was analyzed, 6 (16.7%) were found to be Class II/2. The relative risk (RR) of first-degree relatives to have a Class II/2 was found to be 3.3 – 7.3. The confidence interval (CI) was 1.1-10.3 if the RR was 3.3 and 1.7-31.6 if the RR was 7.3.

Agenesis of one or more permanent teeth (excluding 3rd molars) was found in 2 (11.1%) of the 18 probands and 7 (14.0%) of the 50 first-degree relatives. Agnesis of one or more 3rd molars was found in 4 (22.2%) of the 18 probands and 12 (24.0%) of the 50 first-degree relatives. Agnesis of one or both permanent maxillary incisors was found in none of the 18 probands and 2 (4.0%) of the 50 first-degree relatives. One or more small teeth (excluding 3rd molars) were found in 4 (22.2%) of the 18 probands and 15 (30.0%) of the 50 first-degree relatives. Small maxillary permanent incisors were found in none of the 18 probands and 4 (8.0%) of the 50 first-degree relatives. Agnesis of one or more permanent teeth in combination with the presence of one or more small permanent teeth was found in 2 (11.1%) of the 18 probands and 7 (14.0%) of the 50 first-degree relatives. Of the 36 first-degree relatives evaluated for malocclusion, 6 (16.67%) were found to be Class II/2. The RR for first-degree relatives of the probands to have a Class II/2 malocclusion was 3.3 – 7.35.(Morrison, 2008)

These results indicate that first-degree relatives of Class II/2 probands have a significantly increased risk of having a Class II/2 malocclusion as compared with individuals from the general population. Were Class II/2 malocclusion to be the result of variation in a single gene, acting in either a dominant or recessive fashion, the relative risk would be expected to be much higher. Rather, the modest, albeit significant increase in risk appears consistent with results from previous studies, which suggest a multifactorial etiology for Class II/2 malocclusion.

The question could be raised as to whether or not anomalous maxillary lateral incisors are associated with the Class II/2 malocclusion phenotype, and therefore share common etiological factors. Basdra et al. showed that 13.9% of Class II/2 subjects had agnesis of maxillary lateral incisors and 7.5% had peg-shaped or small maxillary lateral incisors. In contrast, Morrison found none of the probands had agnesis of or small maxillary lateral incisors, although first-degree relatives of the Class II/2 probands showed similar frequencies of hypodontia and microdontia of other teeth as the II/2 probands. However, the frequencies of these dental anomalies in the probands and first degree relatives were not significantly greater than those in the general population.(Morrison, 2008) Thus it is unclear if Class II/2 probands and their first-degree relatives are at an increased risk of developing hypodontia and/or microdontia. Investigations of a larger sample of Class II/2 subjects and relatives to address that question and possible common etiological factors, including genes associated with tooth development and hypodontia, are needed.

A start on this was made when DNA markers (single nucleotide polymorphisms, also referred to as SNPs) in two genes associated with dental development and or hypodontia, *MSX1*, *PAX9*, *AXIN2*, *RUNX2* and *RUNX3* were investigated in 94 Class II/2 Caucasian subjects (31 with hypodontia) compared to 89 non-Class II/2 Caucasian subjects without hypodontia. (Morford et al., 2010b; Morford et al., 2010a) A borderline-association of all Class II/2 subjects with the *PAX9* SNP (rs8004560) was identified ($p=0.06$). A borderline-association of the same rs8004560 *PAX9* SNP was also identified for subjects with Class II/2 with hypodontia of any permanent tooth, excluding third-molars, when compared to non-Class II/2 without hypodontia ($p=0.08$) but not when compared to Class II/2 without hypodontia ($p=0.46$). No associations of Class II/2 with the *PAX9* rs1955734, *MSX1* rs3821949, *RUNX2* (rs1406846), *RUNX3* (rs6672420), or *AXIN2* (rs7591, rs2240308) genotypes were identified. There was a significant association ($p=0.0286$) for Class II/2 subjects (with or without hypodontia) and the *RUNX2* rs6930053 SNP. However, there was no association of *RUNX2* rs6930053 for subjects with Class II/2 that had hypodontia of any permanent tooth, including third-molars, when compared to Class II/2 subjects without hypodontia ($p=0.3858$). This suggests a mild impact of *PAX9* (or a locus in linkage-disequilibrium with it) on the development of Class II/2 with hypodontia, and that *RUNX2* (or genetic loci in linkage-disequilibrium with *RUNX2*) plays a role in Class II/2 development but not in the occasionally-associated hypodontia. These findings and other DNA markers should be investigated in a larger Caucasian and other ethnic groups. (Malinowski, 1983; Strohmayr, 1937; Suzuki, 1961)

5.4 Class III malocclusion

Although all Angle occlusion types a Class III malocclusion were initially only based on the sagittal relationship of the permanent first molars, it has generally been recognized that this dental relationship is often observed with a corresponding skeletal relationship as well. Thus, the Class III malocclusion is a complex disorder characterized by a combination of dental and skeletal features that characteristically result in the appearance of a prominent lower jaw. Often referred to as mandibular prognathism (taken from the Greek pro =forward and gnathos =jaw), skeletal aspects of this disorder can be a result of pure mandibular prognathism, maxillary hypoplasia/retrognathism, or a combination of the two. These phenotypic variations create a significant heterogeneity among Class III subjects that can vary according to sex and ethnicity, and account for some of the difficulty encountered when investigating the condition. (Singh, 1999) The familial nature of mandibular prognathism was first reported by Strohmayr (1937) as noted by Wolff et al (1993) in their analysis of the pedigree of the Hapsburg family. (Wolff et al., 1993)

The highest prevalence of Class III malocclusion is observed in East Asian populations such as Korean, Chinese, and Japanese (8%-40%). (Allwright, 1964; Ishii et al., 2002) By comparison, African populations exhibit a reduced prevalence rate (3-8%) compared to Asian samples (Emrich et al., 1965; Garner & Butt, 1985), as do individuals of European or European-American (Caucasian) decent (reports varying between 0.48%-9.5%, with most in the 3-5% range) (Davidov et al., 1961; Emrich et al., 1965; Goose et al., 1957; Helm, 1968; Horowitz, 1970; Ingervall, 1974; Laine & Hausen, 1983; Luffingham & Campbell, 1974; Massler & Frankel, 1951; Solow & Helm, 1968; Tipton & Rinchuse, 1991) While the prevalence in a sample of Native American Chippewa Indian children is relatively low (2.6-3.1%), (Grewe et al., 1968) North American Eskimos in Labrador, Canada have a class III prevalence of approximately 16%. (Zammit et al., 1995) (Zammit, Hans, et al. 1995)

Populations in South America are often a mixture of Caucasian/European, African and Amerindian descent. While the percentage of children in Bogotá, Colombia with Class III has been reported as 3.7%, Brazilian children exhibited a frequency between 4 -10%.(Grando et al., 2008; Martins Mda & Lima, 2009; Thilander et al., 2001) In areas of the Middle East, the prevalence of class III also displays variation with the highest prevalence in Egypt at 10.6%,(El-Mangoury & Mostafa, 1990) followed by 7.8% in Iran,(Borzabadi-Farahani et al., 2009) and 5.1% in Lebanon.(Saleh, 1999)

Several studies have suggested the existence of multiple patterns or sub-phenotypes of the Class III malocclusion based on anatomical appearance. For example, Ellis and McNamara reported considerable variation among class III patients. The most common combination of variables was a retrusive maxilla, protrusive maxillary incisors, retrusive mandibular incisors, a protrusive mandible, and a long lower facial height.(Ellis & McNamara, 1984) Although they did not find significant sex differences, Baccetti et al. showed a significant degree of sexual dimorphism in craniofacial features in subjects with class III malocclusion.(Baccetti et al., 2005) The female Class III subjects presented smaller linear dimensions in the maxilla, mandible, and anterior facial heights when compared with male subjects. The increase in mandibular growth was three times greater in males with class III than in subjects with normal occlusion.(Baccetti et al., 2007) Martone and colleagues suggested that craniofacial growth generates several head form types resulting in anatomic sub-groupings of Classes III.(Martone et al., 1992) Mackay et al (1992) identified five Class III subgroups, all of which exhibited mandibular prognathism.(Mackay et al., 1992) English children with Class III malocclusions divided into groups (normal anteroposterior positioned mandibles and protruded mandibles) according to their SNB angle were found to have significant differences in both groups relating to sagittal position of the maxilla and mandibular rotation.(Hashim & Sarhan, 1993)

Bui et al (2006) found five clusters representing distinct subphenotypes of class III malocclusion. The groupings of variables reflected anteroposterior and vertical dimensions rather than specific craniofacial structures, suggesting that different genes are involved in controlling dimension versus structure. The five subgroupings or "Prototype Clusters" were described as follows: (1) prognathic mandible with long face, (2) maxillary deficiency with decreased vertical dimension (low angle), (3) maxillary deficiency with increased vertical dimension (high angle), (4) mild prognathic mandible with normal vertical dimension, and (5) a combination of prognathic mandible and maxillary deficiency with normal vertical dimension.(Bui et al., 2006) Further studies of the variation of the subtypes of the Class III phenotype within families should facilitate increased understanding of the genetic and non-genetic factors involved.

The genetic factors appear to be heterogeneous, with monogenic (usually autosomal dominant with incomplete penetrance and variable expressivity) influences in some families and multifactorial (polygenic complex) influences in others.(Cruz et al., 2008; Downs, 1927 ; El-Gheriani et al., 2003; Krauss et al., 1959; Litton et al., 1970; Niswander, 1975; Stiles & Luke, 1953; Strohmayer, 1937; Thompson & Winter, 1988; Wolff et al., 1993) This contributes to the variety of anatomical changes in the cranial base, maxilla, and mandible that may be associated with "mandibular prognathism" or a Class III malocclusion.(Bui et al., 2006; Singh, 1999) The prevalence of Class III malocclusion varies among races and can show different anatomic characteristics between races.(Ishii et al., 2002) Considering this

heterogeneity, and possible epistasis (the interaction between or among gene products on their expression) and even epigenetics, it is not surprising that genetic linkage and candidate gene studies to date have indicated the possible location of genetic loci influencing this trait in several chromosomal locations (see figure 5). (Falcão-Alencar et al., 2010; Frazier-Bowers et al., 2009; Jang et al., 2010; Li et al., 2010; Li et al., 2011; Tassopoulou-Fishell et al., 2011; Xue et al., 2010; Yamaguchi et al., 2005)

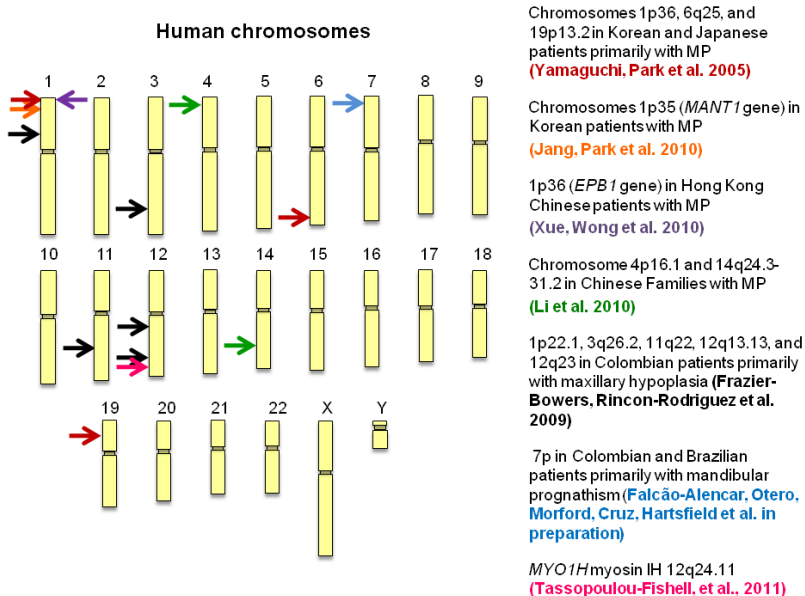


Fig. 5. Chromosome location of markers linked or associated with Class III malocclusion in humans.

6. Personalized orthodontics

In summary, “Personalized Medicine” is a new buzz phrase, based initially upon pharmacogenetics and now exploding as genome-wide association and pathway studies are undertaken. The understanding of the combination and interaction of genetic and environmental (including treatment) factors (nature and nurture together) that influence the growth treatment response of our patients is fundamental to the evidence based practice of orthodontics. Conclusions from retrospective studies must be evaluated by prospective testing to truly evaluate their value in practice. Genome-wide association studies, metabolic pathway analysis and candidate gene studies are necessary to further the evidence base for the practice of orthodontics to determine what the best treatment plan is for each patient in the era of truly personalized orthodontics. (Hartsfield, 2008)

7. References

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