Journal of Pediatric Genetics 2 (2013) 9–20
DOI 10.3233/PGE-13041
IOS Press

Review Article

Genetics and non-syndromic facial growth

James K. Hartsfield[a,*], Lorri A. Morford[a], Liliana M. Otero[b] and David W. Fardo[c]
[a]*Department of Oral Health Science, University of Kentucky College of Dentistry, Lexington, KY, USA*
[b]*Faculty of Dentistry, Pontificia University Javeriana, Bogotá, Colombia*
[c]*Department of Biostatistics, University of Kentucky College of Public Health, Lexington, KY, USA*

Received 11 September 2012
Revised 4 January 2013
Accepted 8 January 2013

Abstract. Just as pediatricians and endocrinologists are interested in understanding statural growth patterns and the prediction of adult height, pediatric dentists, orthodontists, and oral/maxillofacial surgeons need to be knowledgeable about a patient's facial growth patterns to effectively treat them. Some variations in facial growth have been clinically associated with a poor esthetic self-image, malocclusion formation and the development of physical and/or functional deformity. To understand how different genetic factors influence growth and development patterns, scientists and clinicians study developmental sequences, malformations and syndromes. While understanding this general information can be clinically valuable when making treatment decisions for an individual and their family, the greatest contribution of genetics in clinical practice may be in the form of personalized or "precision" medicine in the general population. Precision medicine takes into account knowing a portion or all of a patient's specific DNA code to estimate how their genetic makeup will influence growth and development patterns. Ultimately, the identification of key genetic variations at the level of the individual patient can improve growth predictions for that patient and may be indicative of how well they will respond to specific forms of treatment.

Keywords: Facial growth, oral facial genetics, genetics, malocclusion

1. Introduction

The "rediscovery" of Mendel's laws of inheritance in the early twentieth century led to the mistaken belief that all growth and development was, in essence, controlled by genetic factors. This presumption of genetic control was extended to facial growth and therefore the development of facial growth variation and malocclusion. As an outgrowth of the acceptance of this genetic predetermination philosophy, clinicians began to wrongly assume that environmental factors, including orthodontic treatment and appliance usage could not change facial growth patterns [1].

This absolute paradigm of the genetic control of facial growth was challenged by studies indicating that increases in malocclusion could occur when a population relocated to another geographic area and/or mixed with other populations. These findings supported the proposition that the formation of some forms of malocclusion could be due to changes in environmental rather than genetic factors. For example, Corruccini [2] suggested that the rapid increase in malocclusion among the indigenous Australian people was produced by dietary factors concurrent with industrialization. He emphasized the importance of environmental influences on occlusal variation and on the variability of apparent genetic determinants with respect to the environment or population in which they are measured [2–4].

*Corresponding author: James K. Hartsfield, University of Kentucky College of Dentistry, Department of Oral Health Science, 800 Rose Street, Lexington, KY 40536-0297, USA. Tel.: +1 859 323 5911; Fax: +1 859 257 8878; E-mail: James.Hartsfield@uky.edu.

Likewise, after studying the concordance of malocclusion in twins, Kawala et al. [5] showed the distribution of within-pair malocclusions depended upon the sex of the individuals, and supported the impact of environmental factors.

Siblings may often have similar malocclusions not just because of common genetic or environmental factors, but also because of how their shared genetic factors affect response to the shared environmental factors [6]. This is supported by studies in mice that showed that differences in shape of the mandibular condyles were "slightly greater" among four different inbred strains on a hard diet compared to those placed on a soft diet for 6 wk. When the environment changed sufficiently, the adaptive biological changes were different among animals with different genotypes even though there was not an observable difference before the environmental change [7].

Numerous studies have examined how genetic variation contributes to either or both occlusal and skeletal variation among family members [6,8–35]. It is difficult to estimate the influence of environmental treatment factors in facial growth because the heritability studies of occlusion are typically based on twins and siblings who did not receive surgery and/or orthodontic treatment. Even if family members had undergone 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, or there was no comparison of the facial changes before and after treatment to those not treated. Moreover, 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; i.e., 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 [36] and ascertainment bias [6]. 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 [37], variations in standardized lateral head radiographs studied through cephalometric analysis have shown that skeletal dimensions are associated in general with a moderate to high degree of genetic variation. By comparison, variation of occlusal or dental bite relationships, in general, has little or no association with genetic variation [38].

2. Familial correlations and predictions

Siblings have often been noted as sharing similar facial features and types of malocclusion. Malocclusions are fundamentally categorized by the sagittal relationship of the first permanent molars as described by Edward Angle, whose name is affixed to the classification system. Although the Angle classification focuses on the sagittal relationship and arch forms of the upper (maxillary) and lower (mandibular) teeth, the sagittal relationship of the jaws often (but not always) corresponds to a relative change in the sagittal position of the teeth.

In an Angle class I malocclusion, the first molars are in the appropriate sagittal position, as are typically the jaws, but there is dental crowding or some other deviation from an ideal occlusion present. In an Angle class II malocclusion, the mandibular molars are positioned posterior to their usual relationship with the maxillary molars, and often the lower jaw (mandible) is also set back or retrognathic relative to the upper jaw (maxilla).

After Angle formulated his classification, type II malocclusions were subdivided into separate categories: class II division 1 and class II division 2. Both categories have the mandibular first molars set back relative to the maxillary first molars, and the lower jaw tending to be retrognathic.

However, the class II division 2 patients often have a very deep bite and retroclined maxillary central incisors, while the class II division 1 patients do not have the retroclined maxillary central incisors, and variably have an overbite that may range from being open to deep. Finally, the Angle class III subjects have the mandibular molars anterior to their usual relationship with the maxillary molars, and often the lower jaw (mandible) is also set forward or prognathic relative to the upper jaw (maxilla). Thus it is the Angle class II and III malocclusions that are most likely to show a deviation in jaw growth, at least one jaw relative to the other in the sagittal plane.

Examination of parents and older siblings has been suggested as a way to gain information regarding the treatment needs for a child, including early treatment of malocclusion [39–42]. Niswander [41] noted that the frequency of malocclusion is decreased among siblings of index cases with normal occlusion, whereas the siblings of index cases with malocclusion often tend to have the same type of malocclusion. There are high correlation coefficient values between parents and their offspring for class II and class III malocclusions [43]. It has been shown that the craniofacial skeletal patterns

of children with class II division 1 malocclusions tend to be familial, and that a high resemblance to the skeletal patterns occurs in their siblings with class I occlusion [22]. Although this was ascribed to the class II division 1 malocclusion as 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 division 1 malocclusion, although it was acknowledged that, the current morphology of the patient is the primary source of information about future growth [39].

When looking at parents with differing skeletal and/or dental occlusal "bite" morphology, the combined influence on the child of the inherited parental developmental genes is difficult to know until the child's phenotype matures under the continuing influence of environmental factors. With 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 full 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 [44].

Squaring the correlation between two variables determines the amount of variation predicted for one variable in correlation with the other variable. Therefore, at best, using mid-parent values (i.e., 0.7), only 49% of the variability of any facial dimension in an adult offspring can be predicted by consideration of the average of the same dimension in the parents. Because varying effects of environmental factors interact with the multiple genetic factors, the usual correlation for facial dimensions between parents and their offspring is about 30%, yielding even less predictive power [44]. Only 25% of the variability of any facial dimension in an adult offspring at best can be expected to be predicted by considering the same dimension in a sibling or one parent. Family patterns of resemblance frequently seem obvious, but predictions must be made cautiously because of the genetic and environmental variables and their interaction, which are largely unknown [45].

3. Heritability estimates in clinical practice

There is the common perception that knowing a trait's heritability should affect how a patient is to be treated. This is a misconception. The ability of the patient to respond to changes in the environment (including treatment), which has nothing to do with estimates of heritability for the trait, will define this. 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 [46].

Heritability estimates by themselves, in fact, imply nothing about trait size or treatment limits based upon some presumed genetic "predetermination". Heritability estimates only apply to the population that was studied and the environmental factors to which they were exposed up to that time. They are not predictive for an individual or the group in the future [38]. On the other hand, the estimation of heritability can provide an indication of the relative importance of genetic factors on a trait in a group at that time under certain circumstance. Conformation that there is a certain degree of genetic influence on a particular trait is only a preliminary but necessary step prior to performing further genetic studies using deoxyribonucleic acid to identify specific genomic regions associated with the characteristics of that given trait [47].

While the genetic factors that influence a trait's formation may also influence the response to intervention aimed at altering that trait, other genetic factors may also be involved in the response. The possibility of altering the environment to gain a more favorable occlusion therefore theoretically does exist, even in individuals in whom the malocclusion does have a high estimation of heritability. The question of how environmental and genetic factors interact is most relevant to clinical practice, because it may explain why a particular alteration of the environment (treatment) may be successful in one compliant patient and not in another [48].

In terms of genetics, clinicians are interested in knowing whether there are genetic factors that will affect or limit what we can treat. These are most clearly defined for those traits whose genetic influence is to the degree that a clear pattern of Mendelian inheritance is present.

These patterns or modes of inheritance are not to be confused with estimates of heritability previously mentioned. The modes of inheritance are secondary to the primary effect of single genes, or more accurately, the effect of the variations of the gene at the same locus. However, most traits, including almost all of the developmental variation we deal with clinically, do not follow

a Mendelian pattern of inheritance. Instead, they are the result of some combination of multiple genetic and environmental factors that is now commonly referred to as complex inheritance. For these complex traits, we do not have sufficient information to make accurate predictions about the development of facial morphology or occlusion simply by studying its correlation, the frequency of its occurrence, or the estimation of heritability, in family members.

4. "Personalized" facial growth prediction

There are everyday clinical questions of how much will a patient's jaw(s) grow either closer to (or deviate from) what will be or is an esthetically pleasing and harmonious relationship, affecting decisions regarding when and how to treat the patient. The understanding of the combination and interaction of genetic and environmental factors, including treatment modalities that influence the variation in facial growth and treatment response of our patients is fundamental to evidence-based practice [49]. This is the idea of understanding how nature and nurture work together.

Research and discussion about facial growth and treatment in the literature has focused on either the timing of the greatest amount of facial growth, particularly of the mandible [50–52], or the estimated extent of facial growth to be attained [53,54]. In order to best diagnose and treat an adolescent patient, the clinician needs to know as much as possible about their growth potential. Although useful, current methods of growth predictions are solely based on non-genetic growth models. Improved predictions must incorporate genetic variation, especially those genetic factors related to the pubertal growth spurt.

5. Facial growth and the CYP19A1 gene

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 the local production of IGF-I and IGF-I receptor in chondrocyte cell layers of an isolated mouse mandibular condyle organ culture [55–57].

Changes in the internal structure of the mandibular condyle occur in ovariectomized and orchiectomized mice secondary to changes in sex hormone levels [58]. It has been suggested that the suppression of sex hormone secretion in the growth phase might inhibit craniofacial growth, particularly nasomaxillary bone and mandible, in new born and pubertal rats [59,60]. 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 in chondrocytes before and during early puberty in mice. In the later stage of puberty and after, growth is induced by the stimulation of estrogen receptor 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.

Aromatase (also known as estrogen synthetase and encoded by the CYP19A1 gene) is a key cytochrome P450 enzyme involved in estrogen biosynthesis [61]. This steroidogenic enzyme catalyzes the final and rate limiting steps of estrogen biosynthesis by converting testosterone and androstenedione to estradiol and estrone, respectively [62]. Estrogens are a group of hormones involved in growth and development [63]. 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 [64]. Since aromatase plays an important role in the conversion of androgens to estrogens, the regulation of CYP19A1 expression is critical for the testosterone/estrogen ratio in the body. Studies have shown that the testosterone/estrogen 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 [65,66].

In strong support this finding, differences in the average sagittal jaw growth of Caucasian males during orthodontic treatment have been associated with specific allelic variations in the CYP19A1 gene, where the greatest differences in growth due to allele variation approached over 1.5 mm per yr for the maxilla and 2.5 mm per yr for the mandible [67]. There was no statistical difference for the particular CYP19A1 alleles tested in females. This is particularly impressive since there were no significant differences in sagittal dimensions among the males based upon the CYP19A1 genotype at the beginning of treatment. The significant difference only expressed

itself over the time of treatment during the cervical vertebral stage associated with increased growth velocity [68].

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 [69]. 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.

6. Facial growth and the growth hormone receptor (GHR) gene

Growth hormone is an important factor in craniofacial and skeletal growth. A variant in the GHR and its gene, when there is a proline amino acid instead of threonine at the 561st residue in the protein, is referred to as the GHR Pro561Thr (P561T) allele. Of a normal Japanese sample of 50 men and 50 women, those who did not have the GHR P561T allele had a significantly greater mandibular ramus length (condylion-gonion, CoGo) than did those with the GHR P561T allele. The average mandibular ramus height in those with the GHR P561T allele was 4.65 mm shorter than the average for those without the GHR P561T allele. This significant correlation between the GHR P561T allele and shorter mandibular ramus height was confirmed in an additional 80 women [70]. 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 P561T 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 functional 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 single nucleotide polymorphisms of the GHR gene associated with differences in mandibular ramus height in the Japanese are likely to be different in other ethnic groups [71]. This is supported by the finding that although there is a possible association between the GHR polymorphisms P561T, C422F and "haplotype 4" in Korean population, there was not significant association between these markers and mandibular height in African-Americans, European-Americans, and Hispanics [72,73].

7. Class II division 2 malocclusion

There is evidence that class II division 2 (class II/2) and, particularly, class III malocclusions have strong genetic influences. The class II/2 malocclusion is a relatively rare type of malocclusion, representing between 2.3% and 5% of all malocclusions in the western white population [74,75]. In one study 100% of 20 monozygotic twin pairs were concordant for class II/2 malocclusion, while only 10.7% of 28 dizygotic twin pairs demonstrated concordance for the class II/2 malocclusion [76]. These findings suggest the effect of common genetic or environmental factors; however, the much lower concordance for dizygotic 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 and Pancherz [77] concluding that the etiology of class II/2 malocclusion was unclear, with neither form nor function the sole controlling factor.

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 [78]. 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 [79,80].

Further evidence for a polygenic complex etiology for class II/2 was found in a study of 18 probands and 50 of their first-degree relatives. Each proband had a minimum of 2 first-degree relatives in the study. Of the total 68 subjects, 67 were self-reported as white, while a child of one of the probands was reported as white/African-American. 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 comparisons of the percentage affected in the probands and first-degree relatives for dental agenesis and small size compared to general population values are

Table 1
Dental agenesis (hypodontia) and small tooth size in probands with class II division 2 malocclusion, and incidence of class II division 2 malocclusion in first-degree relatives of probands

	Class II division 2 proband [74]	First degree relatives of the proband [74]	Incidence in the general population [75]
Number of subjects	18	50	
Number of subjects with class II division 2 malocclusion	18/18 (100%)	6/36* (16.7%)	2.3–5.0% [81,82]
Agenesis of one or more permanent teeth (excluding 3rd molars)	2/18 (11.1%)	7/50 (14.0%)	3.0–7.5%
Agenesis of one or more 3rd molars	4/18 (22.2%)	12/50 (24.0%)	2.5–35.0%
Agenesis of one or both permanent maxillary incisors	0/18 (0.0%)	2/50 (4.0%)	1.0–2.0%
Presence of one or more small permanent teeth (excluding 3rd molars)	4/18 (22.2%)	15/50 (30.0%)	No data found
Presence of one or both small permanent maxillary incisors	0/18 (0.0%)	4/50 (8.0%)	1.0–2.0%
Agenesis of one or more teeth (including 3rd molars) and small teeth together	2/18 (11.1%)	7/50 (14.0%)	No data found

*Information was available for only 36 of the 50 first-degree relatives.

in table 1 [74,75,81,82]. These results indicate that first-degree relatives of class II/2 probands have an increased risk of having a class II/2 malocclusion as compared with individuals from the general population. If the class II/2 malocclusion were 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 complex etiology for class II/2 malocclusion. It is unclear as to whether 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 are needed to address that question and possible common etiological factors, including genes associated with tooth development and hypodontia.

A start on this was made when single nucleotide polymorphisms in 2 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 [83,84]. 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 statistical 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 deoxyribonucleic acid markers should be investigated in a larger Caucasian and other ethnic groups [85–87].

8. Class III malocclusion

Although all Angle occlusion types including the 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 in the sagittal plane. 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.

It has been demonstrated that both prevalence rates and anatomical characteristics of the class III malocclusion vary largely according to ethnic background, and may represent the effects of cultural differences at least to some degree. The highest prevalence rates worldwide have been observed in certain African populations (10–16.8%), Eskimo populations (10–16%) and East Asian populations such as the Korean, Chinese, and Japanese (8%–40%) [88–111]. Overall, however, the frequency of class III formation remains relatively low worldwide and across most ethnic groups (1.6 to 10.0%) (Fig. 1).

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 [112] 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. Although they did not find significant sex differences, Baccetti et al. [113] showed a significant degree of sexual dimorphism in craniofacial features in subjects with class III malocclusion. 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

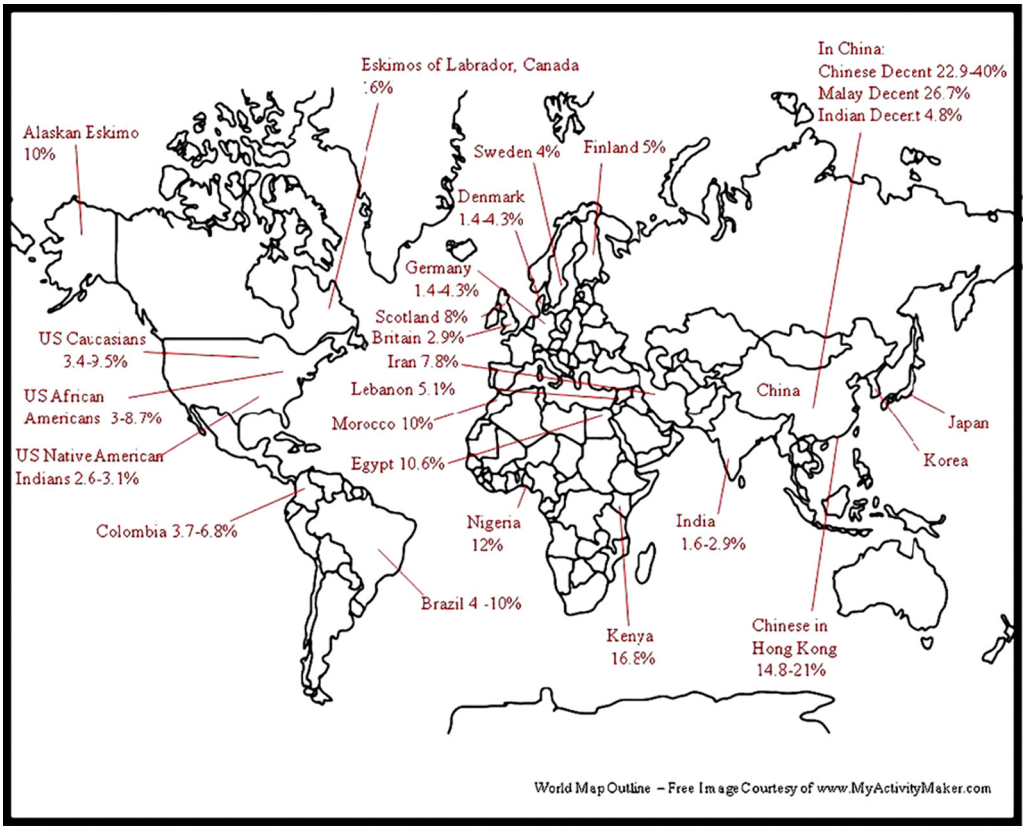

Fig. 1. Worldwide prevalence of class III malocclusion as reports in the literature. Depicted on the world map is the percentage of individuals diagnosed with class III malocclusion based on geographic region and/or ethnicity. The highest prevalence rates have been observed within Asian, Eskimo and African populations. The lowest prevalence rates have been recorded among populations originating from India, US Native American Indians and people of European decent.

greater in males with class III than in subjects with normal occlusion [114].

Martone et al. [115] suggested that craniofacial growth generates several head form types resulting in anatomic sub-groupings of classes III. Mackay et al. [116] identified 5 class III subgroups, all of which exhibited mandibular prognathism. English children with class III malocclusions divided into groups (normal anteroposterior positioned mandibles and protruded mandibles) according to their sella-nasion-B point angle were found to have significant differences in both groups relating to sagittal position of the maxilla and mandibular rotation [117].

Similarly, Bui et al. [118] 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. 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 [33,41,85,119,120–125]. 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 [126,118]. The prevalence of class III malocclusion varies among races and can show different anatomic

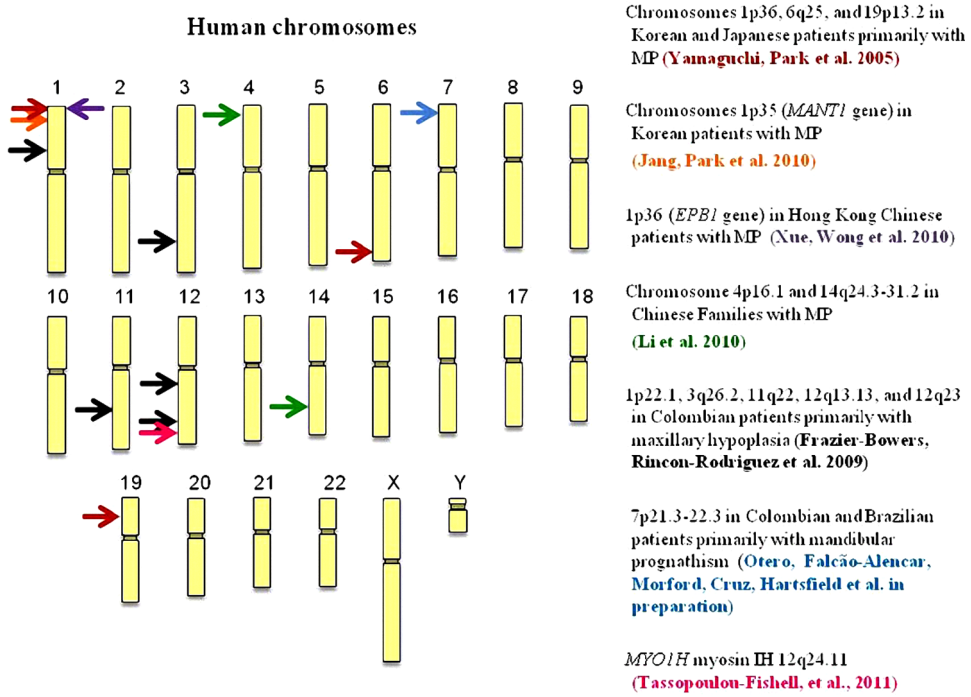

Fig. 2. Genetic Loci with a Putative Role in class III malocclusion formation based on Linkage and/or Association Analysis Results. Family-based linkage and population-based association analyses have been conducted by multiple research groups in an attempt to identify the genetic loci influencing class III formation. The loci influencing class III formation appear to vary by largely by ethnicity and class III subtype. Linkage and association studies of pure mandibular prognathism in Asians have implicated regions on chromosomes 1p35, 1p26, 4p16.1, 6q25, 14q24.3–31.2 and 19p13.2 in class III formation. In contrast, linkage analyses of South American populations with mandibular prognathism +/– maxillary hypoplasia have implicated chromosomal regions 1p22.1, 3q26.2, 7p21.3–22.3, 11q22, 12q13–13 and 12q13.13. In the only association analysis conducted with a US population having mandibular prognathism (consisting of 63.75% Caucasians, 26.25% African Americans, 6.25% Asian and 3.75% Hispanic individuals) implicated chromosomal region 12q24.11 in class III formation.

characteristics between races [90]. 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 (Fig. 2) [127–134].

9. Summary

Further investigation of these and other genetic factors, their interactions with each other and with environmental factors will help to explain what has, up until now, been an unknown component of individual variations in facial growth. Undoubtedly, many other genes that may influence craniofacial structure will be identified, and their variation could be studied along with different environmental factors (e.g., surgery and/or orthodontic treatment) and the resulting phenotype.

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