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GENETICS IN ORTHODONTICS- A REVIEW

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ABSTRACT

Genetics is derived from the Ancient Greek word genetikos. Genetic mechanisms predominate during development and therefore genetic factors must be considered in the etiology of malocclusions. Genetic factors playing a predominant role in the etiology of malocclusion is backed up by population studies, especially family and twin studies. Orthodontists maybe interested in genetics to help understand why a patient has a particular occlusion and consideration of genetic factors is an essential element of diagnosis that underlines virtually all the dentofacial anomalies.

KEYWORDS: Genetics, syndromes, malocclusion.

INTRODUCTION

Genetics is derived from the Ancient Greek word *genetikos*. It is the science of genes, heredity and variation in living organisms. Genetics deals with the molecular structure and function of genes, gene behavior in the context of a cell or organism (e.g. dominance and epigenetics), patterns of inheritance from parent to offspring, gene distribution, variation and change in populations.Genetics provides an insight into what makes us humans and what distinguishes each of us as individuals.[1]

Genetics began with the study of how the characteristics of organisms are passed from parents to offspring- that is how they are inherited. Humans have a mere 30,000 genes rather than the 100,000 predicted earlier. However, it is also known that by alternative splicing, 30,000 genes can give rise to greater than 100,000 proteins. Genetics has revealed that any two individuals share 99.9% of their DNA sequences.[2]

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HISTORY

William Bateson a British geneticist was the first person to use the term “genetics” (from the Greek genno, i.e. to give birth) to describe the study of inheritance and the science of variation. He first used the term "genetics" publicly at the Third International Conference on “Plant Hybridization” in London in 1906.

Gregor Johann Mendel (1822-1884) often called the “father of genetics” for his study of the inheritance of traits in pea plants.

Mendel was the one who showed that the inheritance of traits follows particular laws, which were later named after him.

Ray E Stewart, a medical geneticist, listed malocclusion as the most common hereditary deviation in dentistry followed by periodontal disease and dental caries.

In 1836 Frederick Kussel reported that malocclusion both skeletal and dental can be transmitted from one generation to another. He also reported that chromosomal defects account for about 10% of all malocclusions.

MALOCCLUSION

Malocclusions may be defined as a significant deviation from what is defined as an ideal or normal occlusion. Malocclusion is a manifestation of both environmental and genetic interaction on the development of the craniofacial complex.[3] Environmental factors known to contribute to malocclusion include trauma, hormonal imbalances, muscle dysfunction, poor nutrition, illness, pituitary gland diseases, mandibular posture habits, caries experience, premature loss of primary teeth, history of prolonged sucking or resting tongue habits, mouth breathing, enlarged tonsils, atypical swallowing, and low socioeconomic status.[4]

Edward H Angle classified malocclusion into three types based on the assumption that the position of maxillary first molar and canine were stable in the maxilla and corresponding lower teeth/jaw showed deviations in antero-posterior positions. Based on this assumption he classified all malocclusions into class I, class II and class III malocclusion.

Class I: Mesiobuccal cusp of the maxillary first permanent molar occludes in the buccal groove of the mandibular first permanent molar.

Most cases fall into one of three categories:
(1) Local abnormalities:
a) Crowding of the upper and/or lower incisors,
b) Labial inclination of the upper anterior teeth,
c) Anterior crossbite
d) Posterior crossbite
e) Local abnormalities due to premature loss of deciduous molars

(2) Vertical malrelationships:
Excessive overbite (deep bite) or deficient overbite (open bite)
Class II: Distobuccal cusp of the upper first permanent molar occludes in the buccal groove of the lower first permanent molar. It is subdivided into.

(i). **Class II division I**: This is usually characterized by:
• Proclination of the maxillary incisors
• Increased overjet
• Short upper lip and failure of the anterior lip seal
• V- shaped upper arch (narrow in the canine and premolar region and broad between the molars)
• Deficient mandible and underdeveloped chin.

(ii). **Class II division II**: This is usually characterized by:
• Lingual inclination of the maxillary central incisors and may be overlapped by the maxillary lateral incisors.
• Broad maxillary arch
• Deep overbite with the maxillary and mandibular incisors in apparent supraocclusion.
• Normal length upper lip contacting the lower lip but deep mental groove may be present.
• The mandible is frequently of good size.

(iii). **Class II subdivision**: Class II molar relation on one side and class I on the other side.[4]
The ideal occlusal condition shows a proportional growth between the cranial base, the maxilla and the mandible; and involves the harmonious relation between the skeletal bases and soft tissues (perioral-musculature, lips and tongue). Genetic mechanisms predominate during development and therefore genetic factors must be considered in the etiology of malocclusions.

GENETICS IN MALOCCLUSION

Genetic factors playing a predominant role in the etiology of malocclusion is backed up by population studies, especially family and twin studies. A literature review carried out by Lauweryns in 1993 concluded that 40% of the dental and skeletal variations that lead to malocclusion could be attributed to genetic factors.[5] Hughes and Townsend in 2001 quantified the extent of variation in different occlusal features such as interdental spacing, overbite, overjet and arch dimensions of Australian twins and indicated a moderate to relatively high genetic contribution to the observed variation.[6] Ting Wong et al in 2011 suggested an association for the genes EDA and XEDAR in dental crowding present in Class I patients by identifying 5 SNPs that were significantly different in a genotype or allele frequency distribution in the Hong Kong Chinese case-control population.[7] While these studies provide evidence for the heritability of dental occlusal characteristics that contribute to malocclusion, other studies have come to the opposite conclusion. For instance, Corruccini, Sharma et al could not demonstrate significant heritability for occlusal traits among Indian twins suggesting that dental patterns are environmentally based.[8] Harris and Johnson also noted almost all of the occlusal variability within their sample of untreated subjects was acquired rather than inherited.[9] These conflicting data suggest that dental variation is more dependent upon environmental factors. In a study of the association of the Pro561Thr (P56IT) variant in the growth hormone receptor (GHR) gene with craniofacial measurements on lateral cephalometric radiographs by Yamaguchi et al, those who did not have the GHR P56IT allele had a significantly greater mandibular ramus length (condylion-gonion) than did those with the GHR P561T allele in a normal Japanese sample of 50 men and 50 women. 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 P561T allele. This significant correlation between the GHR P56IT allele and shorter mandibular ramus height was P56IT allele and shorter mandibular ramus height was confirmed in an additional 80 women.[10]

Theoretically, there are two general ways in which predisposing or causative factors formalocclusion could be due to heritable characteristics. One would be inheritance of adisproportion between the size of the teeth and the jaws resulting in crowding or spacing, whereas the other would be inheritance of a disproportion in the position, size, or shape of the mandible and maxilla. However genetic influences on each of these traits are rarely due to a single gene, which would be necessary for malocclusion to be due to the simple inheritance of discrete skeletal and dental characteristics. Instead they are often polygenic with the potential for environmental influence.

Twin studies by Lundstrom showed that heredity played a significant role in determining the following characteristics: tooth size, width and length of the dental arch, height of the palate, crowding and spacing of teeth and degree of overbite.[11] Kraus, Wise and Frei's

cephalometric study of triplets showed that the morphology of an individual bone is under strong genetic control but that the environment plays a major role in determining how various bony elements are combined to achieve a harmonious or disharmonious craniofacial skeleton.[12]

CLASS II DIVISION 1 MALOCCLUSION

Cephalometric studies by Harris suggested the concept of polygenic inheritance for Class II division 1 malocclusions showing that the craniofacial skeletal patterns of children with class II malocclusions are heritable and that there is a high resemblance to the skeletal patterns in their siblings with normal occlusion.[13]

Environmental factors can also contribute to the etiology of class II division 1 malocclusion. Soft tissues can exert an influence on the position or inclination of upper incisors. Digit sucking habit can produce class II division 1 malocclusion even if the underlying skeletal base relationship is class I. Lip incompetence also can lead to this type of malocclusion by virtue of imbalance in labial and lingual pressures on the teeth. In addition, any factor disrupting the nasopharyngeal pathway, including allergies or enlarged adenoids can possibly affect the occlusion adversely. To aid in the prevention of malocclusion it is crucial to begin identifying and correcting the environmental factors that contribute to a disharmony in the face and jaws.[14]

CLASS II DIVISION II MALOCCLUSION

Class II division 2 malocclusion is characterized by a well-developed mandibular basal bone, prominent chin, decreased lower facial height with anterior rotation of the mandible and smaller mesiodistal tooth size. Class II division 1 malocclusion and class II division 2 malocclusion both have polygenic inheritance in common. Class II division 2 is relatively rare type of malocclusion, representing between 2.3% and 5% of all malocclusions.[15] Twin studies showed that the identical twins demonstrated 100% concordance for Class II division 2 malocclusion, indicating a strong genetic influence in the development of Class II division 2 deep-bite malocclusions. Marcovic's clinical and cephalometric study of intra and inter pair comparisons of 114 Class II division 2 malocclusions, 48 twin pairs and six sets of triplets showed complete penetrance and variable expressivity of autosomal dominant genetic impression.[16] In addition to these studies in a polygenic model rather than being the effect of a single gene for entire occlusal malformation, a simultaneous expression of a number of genetically morphological traits are determined. Furthermore, the presence of strong masticatory muscle pattern in Class II division 2 cases is explained by the genetically determined muscular and neuromuscular system.

A mild impact of PAX9 on the development of class II division 2 with hypodontia and that of RUNX2 on the development of class II division 2 but not occasionally associated hypodontia has been seen.

CLASS III MALOCCLUSION

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 a Greek **pro: forward** and **gnathos: jaw**).

The familial nature of mandibular prognathism was first reported by Strohmayer (1937) as noted by Wolff et al (1993) in their analysis of the pedigree of the Hapsburg family. The Hapsburg jaw was seen in European royalty in which mandibular prognathism recurred over multiple generations.

McNamara and Carlson hypothesized that class III malocclusion might be precipitated underthese biomechanical conditions by the inheritance of genes that predispose to a class III phenotype.[17] Rabie et al indicated that forward positioning of the mandible triggered the expression of Ihh and Pthlh, which promote mesenchymal cell differentiation and proliferation, respectively and that these proteins acted as mediators of mechanotransduction to promote increased growth of the cartilage. An increase in transcription factors like sex-determining region Y and Runx2 was noted during mechanical loading of mandible. These factors induce differentiation of chondrocytes.

Human studies support an autosomal-dominant mode of inheritance in two independent studies of the Class III phenotype. The Hox families of genes play a definitive role in patterning the hindbrain and branchial regions of the developing head, up to and including structures derived from the second branchial arch. The HOX3 region contains at least 7 genes in a 160-Kb stretch of DNA, including Hoxc4, Hoxc5, Hoxc6, Hoxc8, Hoxc9, Hoxc10, Hoxc11, Hoxc12 and Hoxc1346.

The COL2A1 (collagen, type II, alpha 1) gene, located between positions 12q13.11 and 12q13.2, encodes the alpha-1 chain of type II collagen found in cartilage. Though heterogeneity exists in the Class III phenotype, since different populations (Japanese/Korean and Hispanic) reveal that differing subtypes of the Class III phenotype share linkage to loci on chromosome 14, this may point to a common upstream regulator that affects both maxillary and mandibular development. In addition, the gene EPB41 was also determined to be associated with mandibular prognathism.[4]

The genetic factors appear to be heterogeneous with monogenic (usually autosomal dominant with incomplete penetrance and variable expressivity) influence in some families and multifactorial (polygenic complex) influence in others.

MALOCCLUSIONS ASSOCIATED WITH GENETIC SYNDROMES

In some cases, the malocclusions with severe skeletal discrepancies might be accompanied by a genetic syndrome. Some of the genetic syndromes are known to influence the development of craniofacial complex. Chromosomal aberrations, deficiencies, transpositions, breakage, deletions or enlargements usually lead to abnormal development of the first branchial arch. This genetic situation results in micrognathia, malocclusions, facial asymmetry, facial and oral clefts, oligodontia and other dentofacial disorders accompanied by different types of deformities anddeficiencies in other parts of the body. Syndrome is defined as a set of signs or a series of events occurring together that often point to a single disease or condition as a cause. Syndromes occurring commonly with malocclusions are classified as:[18]

1. Malformation syndromes associated with mandibular deficiency.
2. Malformation syndromes associated with mandibular prognathism.
3. Malformation syndromes associated with problems of facial height.
4. Malformation syndromes associated with facial asymmetry

MALFORMATION SYNDROMES ASSOCIATED WITH MANDIBULAR DEFICIENCY

• Robin complex.
• Treacher Collins syndrome. (Mandibulo facial dysostosis; Franceschetti syndrome).
• Wilder Vanck Smith syndrome.
• Goldenhar syndrome (Hemifacial Microsomia).
•Hallermann – Streiff syndrome.

MALFORMATION SYNDROMES ASSOCIATED WITH MANDIBULAR PROGNATHISM

• Klinefelter syndrome.
• Marfan syndrome.

MALFORMATION SYNDROMES ASSOCIATED WITH PROBLEMS OF FACIAL HEIGHT

• Beckwith Weidemann syndrome.

MALFORMATION ASSOCIATED WITH FACIAL ASYMMETRY

• Hemifacial Microsomia, Goldenhar syndrome, Hemifacial Hypertrophy.
• Mobius syndrome.

Neurofibromatosis (Von Recklinghausens disease):
• Parry- Romberg syndrome.
• Crouzons syndrome.
• Aperts syndrome.
• Cleido cranial dysostosis.
• Down's syndrome.
• Pfeiffer syndrome.

Pierre Robin sequence is an etiologically heterogeneous disorder and shows autosomal recessive inheritance. An X-linked form also exists.[18]

Treacher Collins syndrome is an autosomal dominant monogenic disorder caused by mutation in the treacle gene (TCOF1) mapped to the long arm of chromosome. It affects the craniofacial development and expresses itself as micrognathia, hypoplastic zygomatic bones and frequently cleft palate.[19]

Goldenhar Syndrome is associated with anomalous development of the first branchial arch and second branchial arch. It is thought to be multifactorial, although there may be a genetic component, which would account for certain familial patterns. It is characterized by incomplete development of the ear, nose, soft palate, lip and mandible on usually one side of the body.[20]

Hallermann-Streiff Syndrome is also known as the François Dyscephalic Syndrome, Hallermann-Streiff-François syndrome, Oculomandibulodyscephaly with hypotrichosis and Oculomandibulofacial syndrome. It is a congenital disorder associated with gene GJA1. It affects growth, cranial development, hair growth and dental development. Patients with this syndrome are shorter than the average person and may not develop hair in many places, including in the facial, leg and pubic areas.[21]

Marfan syndrome is fibrous connective tissue heritable disorder. Increased height, disproportionately, long limbs and digits, mild to moderate joint laxity, increased overjet, retrognathia, micrognathia, narrow and highly arched palate with dental crowding and dentinogenesis imperfecta-like tooth conditions are frequent skeletal and dental features of this syndrome. Westling et al reported that about 70% of the patients with Marfan syndrome had been referred for orthodontic treatment because of crowding and large overjet.[22]

Human craniofacial malformations such as Crouzon, Apert and Pfeiffer syndromes have craniosynostosis, maxillary hypoplasia, relative mandibular prognathism and related dental problems and malocclusions in common and these syndromes are caused by discrete point mutations in the fibroblast growth factor receptor-2 (FGFR-2) genes which are known to affect suture development.

Hemifacial microsomia is known as one of the most common syndromes resulting in facial asymmetry, hypoplasia of facial musculature and mandibular deficiency. Hemifacial microsomia is a common birth defect involving first and second branchial arch derivative. Its phenotype is highly variable. Although most cases are sporadic there are also familial cases exhibiting autosomal dominant, autosomal recessive or X-linked inheritance.[23]

Crouzon's Syndrome

The craniosynostosis syndromes constitute a group of conditions each characterized by premature craniosynostosis (closure of cranial sutures) occurring in association with a variety of other abnormalities. Underdevelopment of the maxilla is seen more in the premaxillary area, causing crowding of teeth and V shape to the arch. Cross bite or open bite with either high narrow arched palate or complete cleft palate, bifid uvula and partial anodontia are also seen.[24]

CLINICAL IMPLICATIONS

In clinical orthodontics each malocclusion occupies its own distinctive slot in the genetic /environmental spectrum. The greater the genetic component to the malocclusion, the worse the prognosis for a successful outcome by means of orthodontic intervention. The difficulty, of course is that it is seldom possible to determine the precise contribution from hereditary and environment in a particular case.

For example- In case of mouth breathing where the influence of habit and posture is very much dependent on the genetically determined craniofacial morphology on which it is superimposed and the reason for the habit developing may well be dependent on the morphology in the first place. This is a classic example of the interaction of genes and environment and ultimately success of treatment will depend on the ability to ascertain the relative contribution of each.

There is also, currently a lack of evidence to show that orthopedic appliances can influence the growth of skeletal bases significantly beyond their innate genetic potential. Human studies to date tend to support the genetic determination of craniofacial form with a lack of evidence to show any significant long term influence on maxillary and mandibular dental bases using orthopedic appliances.

PERSONALIZED ORTHODONTICS, THE FUTURE OF GENETICS IN PRACTICE

"Personalized medicine" is a new buzz phrase, based initially on pharmaco-genetics and now exploding as genome-wide association studies are undertaken. However, it still remains to be seen how much this will really affect daily practice. The same may be projected for the future of orthodontics. What would personalized orthodontics be based on, how would the studies be undertaken and then validated in practice? How will this be funded?.

The understanding of the combination and interaction of genetic and environmental (including treatment) factors (nature and nurture together) that influence the treatment response of our patients is fundamental to the evidence-based practice of orthodontics.

Your first patient of the day comes in for initial evaluation. It is a Class I "borderline" crowding case with good positioning of the incisors.Evaluation of the polymorphic variations of the major and modifying susceptibility to external apical root resorption genes indicate that this patient has a relatively high risk of external apical root resorption. Along with the expected tooth movement you anticipate depending on if you prescribed extraction of permanent teeth, as well as other factors such as root shape and anticipated length of treatment, you use this diagnostic data to decide on a treatment plan.

Your next patient, a 7-year-old, comes in with a negative anterior overjet. Cephalometric analysis indicates a relative retrusion of the maxilla involving certain anatomical structures. Evaluation of the polymorphic variations of the major and modifying Class III malocclusion genes, your examination and radiographic evaluation indicate a diagnosis of Class III malocclusion, type 3. Based on this you know what type of treatment, at what stage of development, will result in the greatest likelihood of successful treatment.

These are some of the possible scenarios that, although in the future, are now within our reach to work toward. The first is not at all improbable from where we are today and the second is probably not far behind. These discoveries are often milestone events and rightfully so. However, they are also just the beginning of a potentially long process of understanding. This is particularly true when a gene that contributes some increased likelihood of pathology or other trait developing is only one of several that may be involved referred to as susceptibility genes.

There are several shortcomings to this approach including the tedium of analyzing multiple polymorphic variants one or a few at a time, the difficulty in excluding a gene, or understanding the combination of a large number of polymorphic variants in an individual that may be contributory.

Rather than initially focusing only on "candidate" genes (which can still have use to further investigate genetic influence), it is now possible to search the genome in an unbiased manner for genes whose common variation contributes to the trait in the population.

The usefulness and impact of genetic research will be much more powerful when we can say that some combination of polymorphic variants in some number of genes, along with certain environmental (including treatment) factors, is associated with a much greater degree of the variation in the pathology or other trait.[25, 26]

GENOME-WIDE ASSOCIATION STUDIES (GWAS)

Association analysis is a method to determine if a particular polymorphic variant (marker allele) is more frequent in a group of subjects with the pathology or

other type of trait of interest compared with a control group. This initially was often done analyzing polymorphic variants in or close to a candidate gene, usually selected because of previous knowledge of the function of the gene and its possible effect on the development of trait of interest. This, of course, limits discovery of genes that may be important (you are not likely to find something if you do not know where to look for it), particularly ones that may play more of a cumulative or modifying role.

Practically all of these genome-wide association studies have more to do with etiology than response to treatment, although an increasing number of studies looking at the response of a variety of treatments—when there is a variable response in a population—is anticipated. Thus future studies may focus on etiological (diagnostic) factors, or response to treatment factors, or both.[27]

CONCLUSION

The knowledge of the role of genetics is essential for the orthodontists in helping to understand why a patient has a particular occlusion because malocclusion is basically a manifestation of genetic and environmental interaction on the development of orofacial complex.

Consideration of genetic factors is an essential element of diagnosis that underlies virtually all dentofacial anomalies. Thus it is important to recognize the genetic aberrations in the early stages before their full establishment.

For the orthodontist the awareness of the genetic expression of the dentofacial maldevelopment is an important aid in the correction of malocclusion as it helps to segregate the inherited malocclusions from those due to the effect of environmental factors and thereby helps to diagnose, treat and possibly even prevent a malocclusion from occurring in the next generation.

Orthodontists maybe interested in genetics to help understand why a patient has a particular occlusion and consideration of genetic factors is an essential element of diagnosis that underlines virtually all the dentofacial anomalies.

The outcome of treatment will be a function of the interaction of proteins from genetic factors that are expressed (or not) and the other environmental factors present at that time, against the backdrop of the developmental maturity of the individual.

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