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Genetics and Orthodontics: Exploring the Link: A Review

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Abstract

Growth is the result of the interaction between the genetic factors and environmental factors over the time. Most of the data studied so far shows a great influence of genetic factors on the treatment of orthodontic patients with dental and skeletal malocclusions. Most of the literature in orthodontics about genetics had discussed the role the genetics factors in the growth and malocclusion. Knowledge of the genetic component influences the final outcome of the treatment and enhances the ability of the orthodontist to treat the malocclusions successfully. This review article thus aims to explore the link between role of genes in the development of dentofacial abnormalities and malocclusions.

KEYWORDS: *Genetics, malocclusion, orthodontics, dentofacial anomalies, craniofacial malocclusion.*

Introduction

Frederick Kussel, in 1836 in an extensive study reported that malocclusion, both skeletal and dental, could be transmitted from one generation to another and also stated that chromosomal defects account for approximately 10% of all malocclusions. (1) Since then the interaction between different genetic and environmental factors on malocclusion have studied with a confirmatory influence of environmental and genetic on the development of the orofacial area. The genetic factors, thus are considered very important in the diagnosis of dentofacial anomalies. (2)

Phenotyping is considered as an advancement in dentofacial diagnosis, which is the comprehensive characterization of hard-tissue and soft-tissue variation in the craniofacial complex, together with the acquisition of largescale genomic data have started to unravel genetic mechanisms underlying facial variation, in the field of orthodontics. Knowledge of the genetics of human malocclusion is still less even though the results attained thus far were encouraging, with promising opportunities for future research.3 This review article aims to explore the link between role of genes in the development of dentofacial abnormalities and malocclusions.

Genetic Influences on the Skeletal Malocclusion

Growth is the result of the interaction between the genetic factors and environmental factors. In general, heritability estimates of craniofacial skeletal structures are greater than those for dentoalveolar traits, such as tooth position, number and size. In other words, studies have shown that skeletal malocclusions are more influenced by genetics.

Mandibular Prognathism

Although mandibular prognathism has been said to be having a multifactorial origin (as its influenced by the interaction of many genes with environmental factors), and in most cases, there are families in which it appears to have autosomal dominant inheritance, such as in the European noble families. (4)

The genetic factors hence are likely to be heterogeneous, with monogenic influences in some families and multifactorial influences in others. (5) This contributes to the variety of anatomic changes in the cranial base, maxilla, and mandible that may be associated with "mandibular prognathism" or a Class III malocclusion. (6,7) When we consider this heterogeneity, it is not surprising that genetic linkage studies to date have indicated the possible location of genetic loci influencing mandibular prognathism trait in several chromosomal locations.

Genetic Influences on The Dental Malocclusion

According to Hughes,8 both mandible and maxilla have separate genetic controls. Moreover, there are certain positions of individual bones, for example ramus, body and symphysis of the mandible are under different genetic and environmental influences. Various studies have indicated that class II division 1 and class II division 2 malocclusions were influenced by multiple factors including genetic as well as environmental factors while class III malocclusion is mainly influenced by genetics. (8)

Class II division 1 malocclusion. This type of malocclusion appears to have a multifactorial inheritance. Extensive cephalometric studies have showed that in class II division 1, the mandible is significantly extended than in class I patients with the body of the mandible smaller and overall mandibular length reduced. (9) However, environmental factors, such as tongue pressure, digit sucking habit may also have a role to contribute to the development of class II division 1 malocclusion. (10)

Class II division 2 malocclusion. In this type of malocclusion, a high genetic influence was observed in different studies. (2.10) Familial occurrence of Class II division 2 malocclusion has been documented in several published reports such as Ckloeppel (1953), Markovic (1992) Korkhaus (1930), Peck (1998). In a cephalometric study conducted by Markovic (1992) on 48 twin pair and six sets of triplets showed that there was 100% concordance for class II division 2 malocclusion in monozygotic twin pairs. Thus, presenting strong evidence for genetics as main ethological factor in development of class II division 2 malocclusion. Results of various family pedigree studies suggest the possibility of autosomal dominant inheritance with incomplete penetrance. However, class II division 2 malocclusion also depends upon others factors such as High lip line, lip morphology and behavior. In general, simultaneous and synergistic influence of genetics and environment is attributed to the development of class II division 2 malocclusion, also it has a strong genetic influence.

Class III Malocclusion

The House of Habsburg, is the best-known example which produced kings and emperors of Bohemia (current Czech Republic), England, Germany, Croatia, Illyria (an Austria area Hungary, the Mexican second empire, Portugal, Ireland, Spain, and many principalities and directors of Denmark and Italy.4 This most famous example of a genetic trait in humans passing through several generations is probably the pedigree is so called “Hapsburg Jaw.” This was the famous mandibular prognathism demonstrated by several generations of the Hungarian/Austrian dual monarchy. The genetic component of malocclusion comes from monitoring mandibular protrusion. Although class III malocclusion could also result from various environmental factors, such as premature loss of permanent molars due to trauma, enlarged tonsils, nasal blockage, and posture, an autosomal dominant model is best suitable to the overall inheritance pattern.11 To date, to identify the genetic mutations effectively, they are thought to cause Class III malocclusion than the association studies of Class III are DNA sequencing technologies in conjunction with family linkage analyses. Therefore, it is necessary to sub classify patients according to their form with a combination of cephalometric or geometric morphometric information for outlook researches of many unrelated patients who have a Class III malocclusion and to better study the genetics of the dominant subtype of dental and skeletal Class III a cross families. (12)

Genetic Effects on Individual Tooth Variations

Genetic factors control the size of the tooth, tooth morphology

1. Hypodontia.

Genetic factors are supposed to play the main part in most cases, with autosomal recessive, X-linked, autosomal dominant, and multiple agent inheritance officially described. (13) One of the most prevalent examples of hypodontia includes the upper lateral incisors. This may be an autosomal dominant trait with imperfect penetrance and changeable meaningfully as proofed by the phenotype at some points being a peg-shaped lateral instead of agenesis, sometimes involving both sides or the other some points "skipping" generations. (14) It was proposed that multiple factors with polygenic influence on the teeth patterning and size, for existing hypodontia in some families, the apparent teeth may still small. (13)

2. Impacted/ Ectopic Canines

Various studies have reported a genetic tendency for ectopic maxillary canines. (16) Frequent displacement of canines is palatal, but not always, are found in dentitions with several anomalies. Such as hypodontia, including other teeth, small, missing maxillary lateral incisors or peg-shaped dentitions with delayed development, and dental spacing. (17) Peck et al concluded that palatally ectopic canines, as an inherited trait, is one of the anomalies in a complex of genetically related dental disturbances, often occurring in combination with missing teeth, tooth size reduction, supernumerary teeth, and other ectopically positioned teeth. (18) There is a relation between class II malocclusion and ectopic maxillary canines, as have to be seen by (Mossy, et al in 1994 and others),(19) and this has a strong basis. Commonly, the class position of maxillary canine/first premolar affected by tooth transposition and display a familial occurrence. However, there has been some discussion about the influence of genetic factors to some degree on palatally displaced canines themselves.

3. A supernumerary tooth.

According to the research studies, a supernumerary tooth, which is most frequently seen in the premaxillary region with a greater gender predilection for males, also has genetic factors involved. Niswander and Sujaku 20 in 1963 analyzed data from family studies, and concluded that the genetics of less prevalent condition of supernumerary teeth is under control of several genes in

different loci and may be associated with an autosomal recessive gene with less prevalence in females. The study done Galas and Garcia in 1999 was also in accordance with this. (21) However, Bruning et al suggested that the possibility of sex-linked heredity was present along with an autosomal dominant inheritance with incomplete penetrance. His study also resulted in the increased incidence in males. Although, this inheritance does not follow a simple Mendelian pattern, these are commonly present in parents and siblings of patients who present with this condition. Evidence from twins with supernumerary teeth also supports this theory. (22)

4. Tooth agenesis

Dental agenesis is also one of the most common developmental anomaly seen in humans. It is genetically and phenotypically a heterogeneous condition. According to the current knowledge of genes and the factors involved in the tooth development and morphogenesis, it is proposed that different phenotypic forms are caused by different genes involving different interacting molecular pathways. Tooth development involves more than 200 genes, which are expressed during tooth development, and mutations in these genes are well-known to cause arrested tooth development in mice.23 Population studies have shown that tooth agenesis can be manifested as an isolated trait or part of a syndrome. Isolated forms may be either sporadic or familial. Familial tooth agenesis can be the result of a single dominant gene defect or recessive or X-linked. Third molar agenesis cannot be explained in most of the cases with a simple model of autosomal dominant transmission. Besides, a polygenic mode of inheritance has also been reported in the literature.

5. Crowding of teeth

Crowding of teeth is a complex dental anomaly that severely affects facial esthetics, and indirectly the quality of life. It's usually caused by lack of arch space where all erupting permanent teeth cannot be accommodated. Genetics has a great role in the etiology of crowding. A study conducted by Ting et al suggested a significant association for the genes ectodysplasin A (EDA) and X-linked ectodermal dysplasia receptor (XEDAR), which are important in the signaling pathway that plays a role in the development of dental crowding among the Hong Kong Chinese population. (24)

Genetic Implications on The Orthodontic Tooth Movement

Genes plays a major role in the effectiveness in inflammation and remodelling of extracellular matrix, in directing angiogenesis, osteoblast formation occur due to the primary response to the thorough forces.22 Recent studies have concluded that various molecular paths that influence the orthodontic

movement of the teeth are identified. There are two ways that effect on both external apical root resorption and orthodontic tooth movement involve the RANKL/RANK/ OPG pathway of bone modelling and remodeling and the ATP/ P2XR7/IL-1B inflammatory signaling pathway. Different studies have concentrated on determining how fundamental changes in non-syndromic genetic factors corresponded with the actual clinical results observed during OTM in humans, although this comprehension of key pathways affecting the orthodontic movement of teeth. (23) The outcome of orthodontic treatment is by the osteopontine protein that is thought to be a strong biomarker because it plays a part in periodontal and bone remodeling. (25) Many studies have been done with genetic variation markers depend on the part of the ATP/P2RX7/ IL-1B pathway, the genes related cytokine interleukin 1 α IL-1α the genes (IL1B and IL1A, respectively), for IL-1β and another and the gene (IL1RN) for another molecular pathway (IL-1 receptor antagonist, IL-RA) that assist the regulation of their action biologically. Interleukin 1 β-IL-1β is the most powerful for inhibiting the bone formation and bone resorption of these two types. Therefore, orthodontic tooth movement needs an equilibrium between IL-1β and IL-1RA formation for the bone remodeling and modelling procedures.

The Heritability Studies of Dentoalveolar Occlusal and Craniofacial Skeletal Disorders

The evidence for the heritability of various types of malocclusions comes from familial and twin studies. The methods to estimate heritability are based on correlation and measurements of the traits between various kinds of pairs of individuals in families, including:

- Monozygotic Twins
- Dizygotic Twins
- Parent-Child
- Sib-Sib (Sibling Pairs).

Familial studies/Pedigree studies

To best study the nature of inheritability of traits, family trees called pedigrees can be studied, in which males are denoted by squares and females by circles and by noting who in the family has the trait and who does not. (26) A particular trait is observed in successive generation to assess its mode of inheritance. Autosomal recessive traits are best studied in consanguineous marriages where interbreeding is permitted. (2)

Twin Studies

Twin studies, another type of studies on twins, offer the best evidence in establishing the relative contribution of genes and environment in the development of malocclusion.27 It's of two types Monozygotic twins and Dizygotic twins.

Monozygotic Twins:

The identical twins develop from single fertilized egg that later divides into two zygotes at an early stage of development. They are identical in genetic makeup and sex, i.e. genotype is identical. (2)

Dizygotic Twins:

Dizygotic twins develop from two separately fertilized eggs at the same time. Dizygotic twins share only 50% of their total gene complement. The underlying principle of twin studies is that the observed difference within a pair of monozygotic twins is due to environmental factors, however, the differences observed within a pair of dizygotic twins are due to both environment and genetic makeup. (10)

Conclusion

Orthodontist should be aware of the role of genetics in orthodontics so that treatment can be planned accordingly. This kind of awareness regarding the genetic expression of the dentofacial maldevelopment is an essential because 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 passing on to the future generations. In present the malocclusions of genetic origin are being detected in growing period, and are also being successfully treated with the help of orthopedic and functional appliances, except in extreme cases where surgical intervention is required. Moreover, the detection of genetic components and their role in dental anomalies and malocclusions is very challenging till date because of its polygenic nature. Therefore, further evaluation is very important to reach to proper conclusion.

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