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Role of Genetics in Orthodontics- A Review

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Abstract

The formation of the craniofacial complex and dental structures is intricately controlled by specific genetic pathways. These pathways can be disrupted by various genetic and environmental influences, potentially causing developmental abnormalities. Over time, understanding of the genes and processes involved in orofacial and dental development has been enhanced through family pedigree analysis, twin studies, and experimental investigations using vertebrate models. These approaches have offered valuable insights into the underlying mechanisms that shape craniofacial and dental structures.In orthodontic practice, it is important to account for the genetic origins of skeletal anomalies when diagnosing patients. As a result, treatment plans should be carefully selected based on these genetic factors. However, more genetic research is needed to precisely identify the genes responsible for the wide range of skeletal variations, given the polygenic nature of craniofacial traits. This article reviews the current knowledge on the relationship between genetics and orthodontics, providing evidence-based insights into how heredity influences dentofacial development and examining the genetic causes of skeletal anomalies from an etiological perspective

Keywords: Genetics, twin study, malocclusion, agenesis, external root resorption, dental eruption problem.

Introduction

Malocclusion results from the interaction between genetic and environmental factors during orofacial development. Orthodontists may turn to genetics to gain a better understanding of the reasons behind a patient's specific occlusion. Considering genetic factors is a

crucial part of the diagnostic process, as these factors play a role in nearly all dentofacial anomalies. Understanding whether the cause of the issue is genetic is important before starting treatment, as a genetic origin may limit the extent of what orthodontic interventions can achieve. As our knowledge of the human genome expands, it is becoming essential for healthcare professionals to be well-versed in the genetic conditions they are likely to come across in their clinical practice.[1] Genetics, which originated from the study of heredity in the early 20th century, has advanced through distinct eras marked by significant conceptual and technical breakthroughs. As an etiological factor, genetics plays a critical role in the development of the jaws (both maxilla and mandible), dentition, and occlusion.[2] Understanding the genetic factors that influence variations in dentofacial morphology associated with malocclusion is crucial for accurate diagnosis, which ultimately aids in developing new treatment approaches. Progress in dentofacial phenotyping encompassing the detailed analysis of hard and soft tissue variations in the craniofacial complex combined with large-scale genomic data collection, has begun to reveal the genetic mechanisms that drive facial variation. While our knowledge of the genetics underlying human malocclusion is still limited, the findings to date are promising and indicate significant potential for future research.[3]

Role of Twins in Dentofacial Genetic Research:

Twins, as introduced by Galton, serve as a valuable resource for examining the interaction between genetic and environmental factors. The comparison of monozygotic (MZ) and dizygotic (DZ) twins is commonly employed to discern the influences of genetics and environment on quantitative traits. Over the past two decades, three significant advancements have been made in twin research:**Improved Analytical Methods**: 1-Enhanced techniques, primarily developed by Christian and colleagues, have refined the analysis of twin data, minimizing the risk of erroneous conclusions. These methods allow for the separation of genetic variance into additive and dominance components, as well as an assessment of how these elements affect heritability estimates.2-**Insights into Developmental Variations**: Boklage identified significant differences in development, growth, and behavior between families with twins and those without.3-**Development of the Twin Half-Sib Method**: This innovative approach increases research efficiency by leveraging the large pool of MZ twin families, as MZ twins share identical genetic makeup, effectively addressing the limitations associated with having fewer offspring from the same parents.[4]

Data on occlusal and dentofacial structure: The rising prevalence of malocclusions in modern societies underscores the importance of environmental factors in dental health. Research shows that populations like Australian Aborigines have a lower prevalence of malocclusions, suggesting modernization impacts dental health.Studies by Corruccini et al. indicate variable genetic variance for traits such as overbite among twins, while genetic factors significantly influence arch width and length. Additionally, research found that the maxillary arch is larger than the mandibular arch in South Australian twins. A study on Northwest Indian twins revealed substantial genetic variance in dental arch dimensions, with environmental influences being more crucial for occlusal traits. Lastly, findings by Sognnaes et al. showed significant differences in tooth positions among MZ twins, suggesting that even identical twins may have differing occlusions.[4]

Role of genetics in various malocclusion:

Class II div 1- Extensive cephalometric studies have investigated the heritability of craniofacial parameters in Class II division 1 malocclusions. Findings indicate that the mandible is significantly more retruded in Class II patients compared to Class I, with a smaller mandibular body and reduced length. The studies also show a stronger correlation between affected individuals and their immediate family members than among randomly paired unrelated unrelated siblings, supporting polygenic inheritance.Environmental factors also contribute to Class II division 1 malocclusions. Soft tissues can influence the position and inclination of incisors; for example, the need for lip and tongue contact during swallowing can lead to retroclination of lower incisors and proclination of upper incisors, affecting overjet severity. Additionally, digit sucking can create a Class II incisal relationship even with a Class I skeletal base, while lip incompetence may promote upper incisor proclination due to imbalanced labial and lingual pressures.[5]

Class II div 2- Class II division 2 malocclusion is a distinct syndrome characterized by a combination of deep overbite, retroclined incisors, Class II skeletal discrepancy, high lip line with strap-like activity of the lower lip, and an active mentalis muscle. It also presents specific dental features such as poorly developed cingula on the upper incisors and smaller-than-average teeth, as noted by Peck et al. (1998) and earlier studies. Research indicates a tendency for forward mandibular rotation, contributing to deep bites, chin prominence, and reduced lower facial height, while also affecting the position of the lower lip. Genetic factors play a significant role in Class II division 2 malocclusion, with studies showing 100% concordance in monozygotic twins and nearly 90% discordance in dizygotic twins, suggesting a likely autosomal dominant inheritance pattern. While genetic influences are emphasized, the interaction of genetics and environmental factors is crucial in understanding facial morphology. Some researchers highlight the role of lip morphology and behavior as etiological factors, while others stress the importance of genetic contributions. Recent evidence suggests that certain aspects of masticatory muscle behavior are also strongly influenced by genetics.[5]

Class III malocclusion- Probably the most famous example of a genetic trait in humans passing through several generations is the pedigree of the so-called Hapsburg jaw. This was the famous mandibular prognathism demonstrated by several generations of the Hungarian/Austrian dual monarchy.

Strohmayer (1937) concluded from his detailed pedigree analysis of the Hapsburg family line that the mandibular prognathism was transmitted as an autosomal dominant trait. This could be regarded as an exception and, in itself, does not provide sufficient information to predict the mode of inheritance of mandibular prognathism. Suzuki (1961) conducted an extensive study involving 1,362 individuals from 243 Japanese families and found that, although the index cases exhibited mandibular prognathism, there was a notably higher prevalence of this trait among other family members (34.3%) compared to those in families with normal occlusion (7.5%).Schulze and Weise (1965) also explored mandibular prognathism by examining monozygotic and dizygotic twins, reporting that concordance rates for monozygotic twins were six times higher than those for dizygotic twins. Both studies support the notion of a polygenic inheritance model as the primary mechanism behind mandibular prognathism (Litton et al., 1970).The interplay between genetic and environmental factors in the development of Class III malocclusion has been a

subject of multiple investigations. This type of malocclusion arises from a skeletal imbalance between the maxillary and mandibular bases, which may be due to insufficient growth of the maxilla, excessive growth of the mandible, or a combination of both factors. Furthermore, research has indicated that distinct cranial base morphologies—characterized by a more acute cranial base angle and a shortened posterior cranial base—are associated with a more anterior positioning of the glenoid fossa, further influencing the development of Class III malocclusion.[5]

Tooth size and Agenesis:

Additive genetic variation for mesial-distal and buccal-lingual crown dimensions of the permanent 28 teeth ranged from 56% to 92% of phenotypic variation, with most over 80%. Estimates of heritability for a number of variables measuring overall crown size of the primary second molars and permanent first molars were moderate to high. Yet less genetic variation was associated with distances between the cusps on each tooth, implying that phenotypic variation for overall crown size was associated more with genetic variation than was the morphology of the occlusal surfaces. Hypodontia may occur without a family history of hypodontia, although it is often familial. Hypodontia also may occur as part of a syndrome, especially in one of the many types of ectodermal dysplasia, although it usually occurs alone.[1]

Genetic factors are believed to play a major role in most of these cases with autosomal dominant, autosomal recessive, X-linked, and multifactorial inheritance reported. Still, only a couple of genes MSX1 and PAX9 involved in dentition patterning so far have been found to be involved in some families with nonsyndromic autosomal dominant hypodontia, as well as the LTBP3 gene, which may also involve short stature and increased bone density in autosomal recessive hypodontia, although there are other chromosomal locations that nonsyndromic hypodontia has been mapped to and candidate genes, including 10q11.2 and KROX26.A general trend in patients with hypodontia is to have the mesial-distal size crowns of the teeth present to be relatively small (especially if more teeth are missing). 1 The mesial-distal size of the permanent maxillary incisor and canine crowns tends to be large in cases with supernumerary teeth. Relatives who do not have hypodontia still may manifest teeth that are small. This suggests a polygenic influence on the size and patterning of the dentition, with a multifactorial threshold for actual hypodontia in some families. A single maxillary incisor can be mistaken for fusion; however, if it appears normal and symmetric, it may indicate the solitary median maxillary central incisor syndrome, often linked to mutations in genes like SHH or SIX3. Genetic influences account for 43% of dental age variation, while shared environmental factors contribute 50%. In extreme Class II, Division 2 malocclusions, incisor sizes are typically smaller due to significant vertical mandibular growth.[1]

Class II, Division 2 malocclusion likely follows an autosomal dominant inheritance pattern with incomplete penetrance, although polygenic inheritance is also a possibility. Hypodontia frequently affects maxillary lateral incisors and may also be inherited as an autosomal dominant trait. Maxillary canines are predominantly impacted palatally (85%) rather than buccally (15%), often linked to dental crowding. The occurrence of palatally displaced canines is more common in families and associated with dental anomalies, suggesting a multifactorial cause involving genetic factors like MSX1 and PAX9, along with environmental influences. [1]

Dental eruption problem:

Maxillary canine impaction or displacement occurs buccally in 15% of cases, often associated with dental crowding. Conversely, palatally displaced canines (PDCs) are seen in 85% of cases and usually do not correlate with crowding. PDCs frequently occur alongside various dental anomalies, including small, peg-shaped, or absent maxillary lateral incisors, hypodontia, spacing issues, and delayed dental development. The prevalence of PDCs is higher within families, indicating a potential genetic influence.[1]

Additionally, PDCs are more likely to occur on the same side as a missing or small lateral incisor, suggesting a local environmental effect. However, some PDC cases can arise without any visible anomalies in the lateral incisors, while in other instances, lateral incisors may be absent without PDCs. This situation is further complicated by the variability observed in cases of buccally displaced canines and PDCs. Although the canine eruption theory suggests that the roots of lateral incisors guide the positioning of canines, it does not account for all cases of PDCs. The underlying causes appear to be multifactorial, stemming from the interaction of genetic influences—either direct or indirect—with environmental factors. Some examples may demonstrate how genetic factors impact dental development within specific local conditions, such as the relationship between the lateral incisor and the developing canine. Candidate genes, such as MSX1 and PAX9, are believed to play a role in the occurrence of PDCs and hypodontia.[1]

Genetic factors and external root resorption:

The genetic basis of individual responses to orthodontic treatment, specifically concerning external apical root resorption (EARR), has been thoroughly analyzed. EARR, a significant complication during orthodontic therapy, results from a complex interplay of genetic, host, and environmental factors. It is often associated with conditions such as missing teeth, increased probing depths, and reduced crestal bone heights in individuals who have not undergone orthodontic treatment. Additionally, factors like bruxism, chronic nail-biting, and anterior open bites with tongue thrusting may predispose individuals to higher EARR levels prior to orthodontic intervention.

The relationship between orthodontic force application and the extent of EARR is noteworthy, as approximately 10% to 33% of the variation in EARR can be attributed to the amount of tooth movement achieved. However, individual variation appears to have a more significant impact than the magnitude or type of force applied. Studies demonstrate considerable individual differences in both the extent and depth of histological root resorption, showing that these variations are not directly correlated to the amount of tooth movement.[1]

Genetic factors account for a substantial portion of EARR variability; approximately 50% of EARR associated with orthodontic treatment and about 66% of EARR specifically in maxillary central incisors can be attributed to genetic differences. A twin study focusing on EARR highlighted the influence of both genetic and environmental factors. Research involving various inbred mouse strains further supports the involvement of multiple genes in the mechanism of histological root resorption. While mechanical forces are crucial in EARR development, they do not fully explain the individual differences observed. Therefore, there is increasing interest in understanding the genetic determinants that influence susceptibility to EARR. Notably, variations in the interleukin-1β gene (IL-1B) have been linked to approximately 15% of the variability in EARR among orthodontically treated patients. Specifically, individuals

who are homozygous for the IL-1B +3953 SNP allele "1" have a significantly increased likelihood (5.6 times) of experiencing EARR of 2 mm or greater compared to those with different genotypes. Similar associations with EARR have been observed in studies conducted in Brazil, where different radiographic techniques were utilized for measuring changes pre- and post-treatment.[1]

Genetic implication on orthodontic tooth movement:

Despite identifying multiple molecular pathways that influence orthodontic tooth movement (OTM), such as the ATP/P2XR7/IL-1B inflammatory signaling pathway and the RANKL/RANK/OPG bone remodeling pathway, few studies have investigated how variations in nonsyndromic genetic factors relate to clinical outcomes during OTM in humans. Research has primarily focused on genetic markers associated with the ATP/P2RX7/IL-1B pathway, including the genes for interleukin 1 beta (IL-1β) and interleukin 1 alpha (IL-1α), as well as the gene for the interleukin-1 receptor antagonist (IL1RN), which helps modulate their biological functions.[6]

Among these, IL-1β is particularly potent in promoting bone resorption and inhibiting bone formation. Effective OTM requires a balanced synthesis of IL-1β and IL-1 receptor antagonist (IL-1RA) to facilitate the necessary bone modeling and remodeling processes. This balance is crucial for optimizing the orthodontic treatment outcomes, highlighting the importance of understanding the genetic influences on these pathways.[5]

Conclusion

Understanding the genetic influences in orthodontics is crucial for clinicians, as it sheds light on the reasons behind specific occlusions in patients. Malocclusion arises from a complex interplay between genetic and environmental factors throughout the development of the orofacial complex. A thorough comprehension of the genetic factors contributing to dentofacial mal development is vital for effectively addressing malocclusion. This understanding allows orthodontists to differentiate between inherited malocclusions and those resulting from environmental effects, facilitating more accurate diagnoses and treatment plans, and potentially preventing malocclusions in future generations.

Significant advancements have been made in the field of genetically informed orthodontics. While identifying the genetic components of most malocclusions and dental anomalies remains challenging due to their polygenic nature, insights gained from the Human Genome Project have made it possible to map inherited conditions associated with dentofacial development. Nonetheless, further genetic investigations are necessary to identify the specific genes responsible for various skeletal variations. Genome-wide association studies will be instrumental in enhancing this understanding and developing a comprehensive database that supports evidence-based orthodontic practices.

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