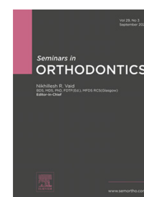
Seminars in Orthodontics 29 (2023) 260–263

Contents lists available at ScienceDirect

Seminars in Orthodontics

journal homepage:



Insights in orthodontic genetic and epigenetic knowledge and its translation in clinical practice

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ARTICLE INFO

Keywords:
Genetics
Epigenetics
Biomarkers
Phenotype
Biological variation

ABSTRACT

Applying genetic practice to current medicine has become more common and necessary in the prognosis, diagnosis and outcome of a myriad of diseases and disorders. Despite the general awareness of its importance, genetic knowledge still lacks direct application in daily orthodontic practice. The aim was to identify multiple genetic associations with orofacial phenotypes, highlight the importance of genetic influence in orthodontics, and describe challenges and gaps in integrating genetic knowledge in clinical practice. In the process, the influence of environmental factors on orofacial development and treatment is underscored, hence the role of epigenetics in regulating gene expression and tissue remodeling.

Introduction

Sequencing the human genome and the advancement of next generation sequencing (NGS) and novel technologies used for RNA, DNA, variant/mutation detection not only improved the diagnosis of diseases and malignancies but also assisted in efficient and effective intervention. Hence treatment outcomes and patient quality of life have improved. In addition, progress in sequencing technologies not only enabled the discovery of changes in genes and genomic loci that result in a specific phenotype, but also allowed the detection of gene expression, whether activation or repression during specific developmental time points, by analyzing DNA methylation and histone modification status. In this context, the term epigenetics has been defined to encompass the impact of environmental factors on gene activation at various times during development and treatment.

Therefore, combining the genetic and epigenetic code is necessary to capture the entire framework of a specific phenotype. The linked knowledge of genetics and epigenetics is valid and necessary in dental research and oral disorders. Although the field is at its infancy, it is growing in a fast pace because of the availability of relevant technologies and exponential expansion of knowledge.

Genetics and orofacial phenotypes

Malocclusions, discrepancies in jaw size, and irregular tooth alignment can be caused by genetic factors[1] that affect oral-facial phenotypes and their treatments. Representative studies are reported to illustrate this perspective.

Class III with mandibular prognathism and Class II malocclusions segregate mainly in an autosomal-dominant manner with variable expressivity and incomplete penetrance and have a polygenic inheritance.[2-4] Genetic linkage and association studies have identified genes and loci for Class II and mainly Class III phenotypes. Genes *FGFR2, MSX1, MATN1, MYOH1, ACTN3, GHR, KAT6B, HDAC4, AJUBA, NOGGIN, R577X* and *SNAI3* were found to be positively linked to skeletal Class II malocclusion.[5-8] In a recent study on mandibular micrognathism, eight additional potentially novel genes (*GLUD2, ADGRG4, ARSH, TGIF1, FGFR3, ZNF181, INTS7,* and *WNT6*) were disclosed.[9] Positive correlations have been found between mandibular prognathism and genes *MATN1, HSPG2, ALPL, EPB41, MYO1H, SSX2IP, PLXNA, COL2A1, TGFB3, LTBP2, ARHGAP21, ADAMTS1, FGF23* and *DUSP6.*[10-19] In a key study cohort from a Mediterranean population novel genes *C1orf167, NBPF8, NBPF9* were found to be associated with mandibular prognathism.[20]

Moderate to high heritability proportions (>60%) have been reported for many dental and facial features such as mid and lower facial dimensions, dental spacing, arch dimensions and Bolton type tooth size discrepancies. However, lower heritability rations have been revealed for overbite (53%) and overjet (28%) demonstrating an increased environmental component of variance.[21,22]

Regarding dental anomalies, numerous mutations in transcription factors and growth factor–related genes involved in dental development

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https://doi.org/10.1053/j.sodo.2023.06.003

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have been shown to have roles in human dental agenesis, including *PAX9, MSX1, EDARADD*, *AXIN2* and WNT10A.[23,24] The genetics of the less prevalent condition of supernumerary teeth is also under the control of a number of different loci[25] and tooth shape and size are largely determined by hereditary constitutional factors.[26] Genetic factors have also been involved in primary failure of eruption (including mainly the *PTHR1* gene), submerged primary molars, maxillary canines/1st premolar transposition and ectopic maxillary canines.[27-31]

Genetic factors have been shown to control growth of the maxilla and mandible and the dental developmental stages.[32-33] The morphology of all bones of the craniofacial complex is under rigid hereditary control with a high transmissibility rate for craniometric variables compared to a low to moderate rate for dentoalveolar variables.[34] A highly significant genetic variation was attributed to the anterior cranial base and mandibular body in comparison to the upper face height, which is reported as a more stable element in the facial profile contributing less significantly to the genetic variability of the face as a whole. Vertical skeletal variables (particularly total and lower anterior facial heights) seemingly are under a stronger genetic control, apparently expressed more anteriorly than posteriorly, compared with horizontal variables. The shape and sagittal position of the mandible is under stronger genetic control than its size and vertical relationship to cranial base.[35-37]

Epigenetic markers and potential applications in orthodontics

Epigenetics is a rapidly growing area of research that does not involve changes in the sequence of DNA but rather the addition or removal of chemical groups on the genetic material that turns genes on or off in different times throughout development. As such, epigenetic mechanisms are important in determining cell identity and tissue regeneration and remodeling. These modifications occur though different mechanisms that affect gene transcription, such as DNA methylation and demethylation,[38] histone modification[39] and non-coding RNA.[40]

In addition to the direct correlation of the genetic factors in dental phenotypes and orthodontic treatment outcomes, the role of the environment on these phenotypes and outcomes must be highlighted from the epigenetic perspective. Tissue remodeling is a fundamental mechanism in orthodontics whereby growth modifiers such as mouth breathing or orthodontic tooth movement as well as orthopedic appliances influence the shape and relative position of each bone. Thus, it is essential to understand how these changes may affect gene expression.

Forces acting upon the jaw may induce changes that potentiate gene activation through epigenetic mechanisms.[41] Class III malocclusion was thought to be mostly affected by genetic factors. However, research has shown that its etiology is multifactorial and involves both genetic and epigenetic layers. In fact, Class III malocclusion associated with mandibular prognathism and/or macrognathism has been mainly related to genetic factors but in Class III malocclusion associated with maxillary retrognathism, environmental factors are possibly predominant, as illustrated by the concept of developmental or “intragrowth orthopedics”, which stipulates that an early anterior cross bite sustained by mandibular forward positioning (caused by inherited macro and/or prognathic mandible, occlusal interferences, habits, or to improve breathing), may induce forces that inhibit maxillary forward growth and produce maxillary retrognathism that otherwise would not exist.[42,43] Epigenetic regulation in the determination of skeletal muscle fiber phenotypes and bone growth is instrumental, whereby chromatin acetylation/deacetylation plays an important role in muscle fiber composition and MHC gene expression during the development of malocclusion.[44]

Orthodontic tooth movement triggered a whole map of gene expression changes when tested in a time course manner in mice.[45] In this study, genes involved in tissue degradation, phagocytosis, leukocyte extravasation, innate and adaptive immune system responses were up-regulated initially and declined later post force application. Genes involved in cell proliferation and migration, cytoskeletal rearrangement, tissue homeostasis, angiogenesis were initially down-regulated and increased at day 14 post force application. Among countless other examples, this study underscores the need to understand changes in gene expression due to environmental factors for efficient clinical practice, including orthodontics.

The significance of genetic knowledge in orthodontics

In view of the technological advances that facilitated finding specific genetic markers linked to tooth and jaw abnormalities, genetic testing has the potential to impact the science and practice of orthodontics by helping recognize genes that might cause dentofacial problems.[46,47] Thus, orthodontists may be able to identify early warning signs of the aberrant condition by studying these markers in patients with malocclusions. Personalized, rational and effective treatment programs could then be tailored to specific individuals,[48] by determining borderline malocclusions between patients who can be treated non-surgically (orthopedically) and those in whom orthognathic surgery is necessary. By early forecasting the condition, orthodontists could either intervene before it worsens and possibly avoid later orthognathic surgery or, if the dentofacial malocclusion is primarily genetic, they would forego earlier interventions and plan with parents and patient for a later orthognathic surgery, thus also avoiding the side effects of a long treatment.[49] However, despite the promise of genetic testing for potential patient care, orthodontists cannot yet be seen incorporating its use in diagnostic and treatment planning procedures.

To date, any aspect of orthodontic practice cannot be exactly predicted or explained by only one mutation in one gene. Genetics is expected to significantly aid clinical practice through the discovery of specific genetic factors and factor variations that can influence the identified craniofacial traits within an individual. Hartsfield et al[50] adequately summarized such influencing factors in the development of disease and response to treatment that have been investigated and published regarding orthodontics (Table 1). They include areas covering growth and development, individual constitution, disease or condition, and factors related to orthodontic methods and rate of tooth movement. Considering one of those conditions, the primary failure of eruption (PFE), genetic innovations may not only aid in the identification of individuals who are at risk of or already afflicted by PFE, but they may also enable the molecular manipulation of specific tooth eruption rates to improve treatment regimens on an individual basis. Although monogenic disorders like PFE and Class III malocclusion show promise as knowledge and technology develop, the daily use of genetic testing is not yet ready for practice.[51]

Hartsfield et al[50] recommend that the most important “genetic test” is to collect and factor in the diagnosis and treatment planning of malocclusion the patient’s individual and family history. This practice will help recognize family traits (with variable severity) that may be useful in future clinical research encompassing the role of genetic and environmental factors. Since orthodontic treatment is viewed as an environmental influence, the authors underscore the need for studies that depict specific clinical responses, such as the contribution of genetics in slow and late growers with or without growth modification treatment (e.g., functional appliances in Class II patients, TAD or plate-assisted restriction of mandibular growth in Class III patients). The outcome of these studies would determine when and in whom growth modification would enhance or limit growth.[50]

Current wide gap between genetics and orthodontic practice

The review of existing evidence on the impact of genetic knowledge and advancement underscores their distant application in clinical practice, certainly including gene therapy, which is being investigated as a potential treatment option for orofacial conditions.[51] Although the fundamental causes of many malocclusions and craniofacial anomalies are better understood thanks to advances in genetic investigations, much research must be invested to arrive at translating genetic findings into

Table 1
Genetic factors influencing the development of disease and response to treatment related to orthodontics.

Area of interest	Investigated condition*
Growth and development	- Differences in rate of annualized sagittal growth of the jaws - Primary failure of eruption (PFE) - Variation in Muscle and its Influence on Malocclusion
Individual constitution	- Facial hair - Facial scan morphology - Micrognathia, macrognathia
Disease/condition	- Skeletal variation and malocclusions - Dental crowding in Class I malocclusion - Arch form - Facial morphology associated with obstructive sleep apnea - Dental agenesis (anodontia, hypodontia, oligodontia) - Palatally displaced canines (PDC) - Canine impaction - Cleft lip and palate - Dental dysplasias (dentinogenesis/amelogenesis imperfecta) - Pain perception - Multiple (cluster phenomenon) dental implant failure
Treatment related factors (orthodontic methods and rate of tooth movement)	- External apical root resorption (EARR)

* Most listed conditions adapted from Hartsfield et al[50].

clinical practice. Even though orthodontists already have a basic grasp of this subject, and awareness is increased about the biological underpinnings of orthodontic therapy, demand is rising for education and training programs that keep orthodontists abreast of genetic research and its potential impact on clinical analysis and treatment.[52] A primary example of this process is the understanding of the genetic impact on the most severe Class II and Class III malocclusions with underlying skeletal discrepancies.[20,53]

The recognized gaps are exacerbated in countries with low resources at least in identifying conditions affected by the environment and possibly eligible for genetic and epigenetic study. Limited funding and resources in these countries limits access to treatment and benefit from the latest developments in practice notwithstanding major limitations in genetic technologies pertaining to accessibility and affordability.[54] Moreover, global research is needed covering genetics data and insights from individuals of various ethnicities. Medical professionals can leverage community outreach programs in genomics to discuss genetic findings, verify diagnoses, and collaborate on patient care across borders. In this context, practitioners and scientists should ensure that patients receive proper medical care, regardless of geography or available resources.

Conclusion

1. Genetics influence both the development and the management of dentofacial problems, but present genetic knowledge has not yet found direct application in daily orthodontic practice.
2. The current state of genetic science is focused on identifying hereditary traits for proper diagnosis and possibly prediction of growth and treatment outcome, particularly the potential and limitations of recognizing the inherited components of malocclusion.
3. In a farsighted vision that approaches present fiction, gene therapy could be foreseen as eliminating phenotypical expressions of dentofacial dysmorphologies. Until then, research on epigenetic markers of environmental and developmental modifiers seems within closer reach to widen the scope of understanding the interaction between genes and clinical practice as inducer of environmental change.

Declaration of Competing Interest

None.

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