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UNDERSTANDING MALOCCLUSION: A DETAILED GUIDE TO GENETIC FACTORS

Orthodontics

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ABSTRACT

The development of the craniofacial complex and dental structures is a complex process regulated by genetic factors and environmental influences. The majority of cases of malocclusion have a polygenic or multifactorial etiology. Genetics plays a significant role in the etiology of malocclusion, making its understanding essential for accurate diagnosis, effective treatment planning, and successful orthodontic outcomes. Advances in genetic research, including twin studies, pedigree analysis, and experimental models, have improved insight into the genes and molecular processes involved in orofacial and dentofacial development. Genetic factors should be taken into account in order to identify the root cause of existing problems, as this may influence how well treatment works. Treatment options for genetically caused malocclusions are typically regarded to be less effective than those from environmental factors. This review article provides information on the role of genetics and the effect of genetic factors on various malocclusions.

KEYWORDS

Genetics, Epigenetics, Inheritance Pattern, Malocclusion, Dentofacial Deformities.

INTRODUCTION

The development of the craniofacial complex and dental structures is a highly regulated and complex process governed by genetic predisposition and environmental modulation; disruption of these factors may lead to dentofacial abnormalities and malocclusion[1]. Genetics plays a major role in the etiology of malocclusion and understanding the etiology of malocclusion is essential for accurate diagnosis, effective treatment planning, and successful orthodontic outcomes. Advances in genetic research have significantly enhanced orthodontist's understanding of dentofacial characteristics and their inheritance patterns[2]. Twin studies, pedigree analyses and experimental studies on vertebrate models have proven to be some of the most effective methods for investigating genetically determined variables and genetic mechanisms involved in the development of orofacial and dental structures[3]. A comprehensive understanding of the molecular and cellular processes and genes regulating craniofacial growth is crucial for the development of novel and improved treatment strategies[4].

Along with dental cavities, gingival diseases, and dental fluorosis, malocclusion is one of the most prevalent dental issues in the world. An irregularity of the teeth or a mal-relationship of the dental arches that goes beyond what is considered normal is called a malocclusion[5]. Malocclusion can raise the risk of dental trauma, impair masticatory function, cause deformed facial appearance, and lower the quality of life. The development of jaws, the maxilla and mandible, as well as dental and occlusion, are all significantly influenced by genetics as an etiological factor. In 1836, Frederick Kussel suggested that chromosomal abnormalities are responsible for about 10% of all malocclusions and that both skeletal and dental malocclusions might be passed down from one generation to the next[2]. Since the 19th century, when Gregor Johann Mendel's pioneering findings created interest in the field, genetics has played a crucial role in research conducted in various categories of biological and medical sciences. Through a number of conceptual advances based on the 20th century, this field of study has developed. Inadequate understanding of genetic inheritance principles in the past resulted in an unclear perspective on genetics and malocclusion[6]. This review article focuses on summarising the role of genetics and genetic factors involved in the development of orofacial and dental structures and their effect on various malocclusions.

Genetics and Malocclusion

Malocclusion represents a variation of normal craniofacial development influenced by both genetic factors and environmental modifiers like habits, nutrition, and muscle function [7]. Twin studies support the genetic basis even more by demonstrating that monozygotic twins have higher concordance rates for malocclusion, especially Class III, than dizygotic pairings[8]. Familial studies suggest that mandibular prognathism is inherited. Autosomal dominant with incomplete penetrance, simple recessive, and variable expressivity and penetrance are among the suggested inheritance patterns, which may vary among ethnic groups[8]. Strohmayer originally described the familial character of mandibular prognathism, which Wolff et al. found in their pedigree analysis of the Habsburg family lineage[9]. The Habsburg jaw is linked to European royalty, where mandibular prognathism was common over several generations. Genetic influences are heterogeneous, with some families having a monogenic influence (typically autosomal dominant with imperfect penetrance and variable expression) and others having a polygenic complex influence[10].

Mutations in genes involved in dental development, particularly the transcription factor, paired box 9 (PAX9) and muscle segment homeobox 1 (MSX1), contribute to human dental agenesis. MSX1 mutations can cause hypodontia or oligodontia and affect gene bone morphogenetic protein 4 (BMP4) signalling, while a specific MSX1 point mutation leads to agenesis of second premolars and third molars[11]. Various twin studies have shown that genetic variables control tooth size, shape, number, position, and inheritance[12]. HOX genes, a subset of homeobox genes are essential for oral and dental development, exhibit site-specific anteroposterior expression patterns. Butler's field hypothesis is confirmed by molecular genetics of tooth morphogenesis, which shows that the homeostatic Hox 7 and Hox 8 (now MSX1 and MSX2) genes involved in stability in dental patterning[11]. There are currently around 200 genes known to be expressed during tooth development, and mutations in a number of these genes have been shown to disrupt tooth development in mice[13].

Dental crowding results from inadequate arch space for erupting permanent teeth, and genetics may contribute to its cause. A study by Ting et al found significant associations between crowding and the genes ectodysplasin A (EDA) and X-linked ectodermal dysplasia receptor (XEDAR), which are involved in developmental signalling pathways, in the Hong Kong Chinese population[14]. There are also some association studies that have documented agenetic tendency for ectopic maxillary canines. A study conducted by Peck et al. concluded palatally ectopic canine as an inherited characteristic, frequently occurring in conjunction with other ectopically positioned teeth, missing teeth, tooth size reduction, and supernumerary teeth as one of the abnormalities in a complex of genetically related dental disturbances[15].

Recent genomic research has identified specific chromosomal loci (1p36, 1p22.1, 12q13.13, and 12q23) linked to Class III malocclusion, particularly affecting maxillary deficiency and mandibular

prognathism. Key growth-regulating genes such as insulin-like growth factor-1 (IGF1), Indian hedgehog (IHH), parathyroid hormone-like hormone (PTHLH), and vascular endothelial growth factor (VEGF) are involved in condylar growth and skeletal morphogenesis. They are responsive to mechanical strain and participate in key developmental signalling pathways, highlighting the interaction between genetic predisposition and functional environmental influences in determining craniofacial structure [16]. Additionally, research has indicated that different ethnic groups and malocclusion subtypes may have different genetic architectures. For example, Certain gene variants, such as those in CYP19A1, show sex-specific effects on jaw growth, particularly in males. Differences in patient responses to orthodontic appliances and growth modification therapy further suggest that individual genetic profiles influence treatment outcomes. A single gene does not cause a malocclusion; understanding gene-environment interactions and by applying genetic testing in conditions like primary failure of eruption (PFE) indicates promising potential for personalised orthodontic treatment planning[17].

Gene-association studies have identified variants in genes such as MSX1, ACTN3, and MYO1H that influence specific skeletal patterns. Gupta et al. (2017) in their study found nine single-nucleotide polymorphisms (SNPs), including two unique variations, in the MSX1 gene in people with Class I, II, and III malocclusions [18]. Cunha et al. (2019) clarified the connection between genetic variants in ACTN3 and MYO1H genes and how they are associated with different sagittal and vertical skeletal patterns in Brazilian population. Specific SNPs (rs678397, rs1815739 in ACTN3, and rs10850110 in MYO1H) were linked to skeletal Class II and dolichofacial patterns in Brazilian population. These findings support the role of muscle–skeletal interactions in craniofacial development[19].

Gullianne et al. (2022) investigated polymorphisms in the Myosin 1H (rs10850110) and P561T (rs6184) genes to be linked with Class I, II, and III skeletal malocclusions in an Indonesian cohort. They reported that the Myosin 1H (rs10850110) gene polymorphism was significantly associated with Class I, II, and especially Class III malocclusions in an Indonesian population. However, the P561T (rs6184) polymorphism showed no significant association with malocclusion[20].

Specific Genes Associated with Malocclusion

According to the study by Chaturvedi et al. (2026) [21], these are the particular genes linked to development of various malocclusions.

- Class I Malocclusion:
  Associated with MSX1 and MYO1H.
- Class II Malocclusion:
  - General sagittal and vertical patterns: ACTN3, MYO1H
  - Mandibular retrognathism: EGF, EGFR
  - Division 1 vs. Division 2 subtypes: PAX9
- Class III Malocclusion:
  - Mandibular prognathism (primary cause): MYO1H, MATN1, ADAMTS1, ARHGAP21, FGF23, PLXNA2, SSX2IP, RORA, C1orf167, NBPF9
  - Maxillary deficiency (primary cause): ADAMTS2, DUSP6
  - General/combined etiology: MSX1, ACTN3, FBN3, ERLEC1
- Mandible Size Variations (large or small):
  DLX5, DLX6, EDN1, HAND2, MSX1, PRRX1
- Other Malocclusions (arch discrepancies, crowding, transverse and vertical issues): VDR
- Muscle function-related malocclusion:
  MYO1C, KAT6B, RUNX2

Myo1H Genes

The incidence of craniofacial anomalies has been linked to variations in genes that are crucial during the craniofacial development process. The first unconventional myosin to be discovered is class 1 myosin, consisting 8 isozymes from MYO1A to MYO1H that are involved in a number of motile activities, such as cytoskeleton rearrangement, ion channel gating, and organelle translocation. Gene expression research and immunohistochemical labelling demonstrated that the masseter muscle has distinct combinations of myosin heavy chain isoforms. Single masseter fibers coexpress up to four distinct myosin heavy chain isoforms, whereas single orofacial and limb muscle fibers only contain one or two myosin heavy chain types[22]. The class 1 myosin MYO1H, which is localised at 12q24.11, belongs to a distinct protein group than the myosin heavy chain isoforms that are the foundation of fiber typing and are present in the skeletal muscle sarcomeres. The motor protein superfamily myosin is involved in force production and movement along actin filaments[23]. A few articles of research indicate that muscle influences skeletal development throughout the embryonic and postnatal stages as well as the homeostatic role in adulthood and the ageing process[24]. This means that alterations in the genes governing muscle function will also impact the formation of the skeleton.

According to a recent study by Sun et al. (2018), the zebrafish model's mandibular jaw showed MYO1H orthologous gene expression, and the MYO1H knockdown model showed jaw cartilage abnormalities. These functional and developmental investigations clearly show how crucial the MYO1H gene is for healthy jaw growth and development, as well as how it contributes to the pathophysiology of human mandibular prognathism and retrognathism[25].

Pax9 Genes

The gene family known as Paired Box 9 (PAX9 gene), which is found at chromosome 14 (locus 14q13.3), is in charge of both tooth and skeletal development[26]. According to Anne et al. (2015), the PAX9 gene controls cell division, migration, and proliferation in a variety of neural crest-derived lineages, including the cardiac, sensory, and enteric neural crest, pigment cells, glia, craniofacial skeleton, and teeth, as well as in organs that develop in close proximity to the neural crest, like the parathyroids and thymus[27].

Peter et al. (1998) and Nakatomi et al. (2010), by conducting animal studies, found that mutation or absence of PAX9 gene results in poor skeletal development and odontogenesis, along with a lack of coronoid process formation, this specific gene was highly expressed in the area of developing tooth buds, the mesenchyme of the nasal processes, the maxillary and mandibular arches, and the region of pharyngeal pouches, thereby confirming the significance of PAX9 in craniofacial, tooth, and skeletal development[28].

Future endeavours of Genetic Research in Orthodontics:

Finding the genetic, epigenetic, and molecular elements that affect craniofacial development, growth, and treatment response should be the main goal of future orthodontic research. To find genes connected to developmental differences, tissue reactivity, tooth mobility, stability, and dentofacial abnormalities, this involves carrying out extensive genome-wide association studies. To improve individualised treatment outcomes, progress will also need to be made in discovering potential genes and creating well-structured randomised controlled trials that categorize individuals according to certain genetic variations.

CONCLUSION

Although most malocclusions are polygenic and complex, advances in genetically supported orthodontics particularly following the Human Genome Project have made it increasingly possible to identify and map inherited conditions related to dentofacial development. To identify every single gene responsible for a certain skeletal variation, more genetic research is necessary. Genome-wide association studies are required to conduct more evaluations and create a database for evidence-based practice.

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