



Review Article

Unraveling the genetic threads: Exploring orthodontics through a genetic lens- A review

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ABSTRACT

Malocclusion is a manifestation of the interplay between genetic and environmental variables on the development of the orofacial region, whereas growth is the cumulative effect of numerous environmental and genetic variables over time. When diagnosing orthodontic problems hereditary variables should be taken into account in order to identify the root of the problem, as this may also impact how orthodontic therapy turns out in the end. Treatment options for malocclusions resulting from genetic causes are generally considered to be less effective than those resulting from environmental factors. The likelihood of a good orthodontic intervention outcome decreases with increasing hereditary component. A clinician's capacity to treat malocclusions effectively would be substantially improved by understanding the different effects of inherited and environmental variables.

When diagnosing almost all dentofacial anomalies, orthodontists may be concerned with genetics to learn more about the reasons behind a patient's specific occlusion. Genetic variables are a crucial component of treatment.

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1. Introduction

The word "genetics" originates from the Ancient Greek word "genetikos." It is the study of genetic diversity, heredity, and genes in living things. The fields of genetics include gene distribution, variation, population change, the structure of molecules and purpose of genes, gene behaviour within a cell or organism (such as dominance and epigenetics), and variations in inheritance from parent to child. Genetics provides information on the characteristics that define humanity and set each person apart.¹

The study of how traits are inherited—that is, how they are transferred from parents to children—led to the foundation of genetics. Compared to the 100,000 genes previously estimated, humans only contain 30,000 genes.

Alternative splicing, on the other hand, is known to produce over 100,000 proteins from 30,000 genes. Genetics has shown that 99.9% of the DNA sequences in any two people are identical.²

2. History

The term "genetics," which comes from the Greek word "genno," which means "to give birth," was originally used by British geneticist William Bateson to refer to the study of inherited and the study of variation. At the third global meeting on —Plant hybridization held in London in 1906, he coined the term "genetics" for the first time in public.³

Gregor Johann Mendel (1822–1884), known for his research on the inheritance of features in pea plants, is frequently referred to as the "father of genetics." Mendel is credited with demonstrating that certain principles govern

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how traits are inherited; these laws carry his name. Medical geneticist Ray E. Stewart stated that tooth caries and periodontal disease are the 2 most common inherited deviations in dentistry, with malocclusion coming in third.

Frederick Kussel noted in 1836 that skeletal and dental malocclusions can be passed down through generations. Additionally, he stated that roughly 10% of the total malocclusions are caused by chromosomal abnormalities.

3. Malocclusion

A significant deviation from what is considered an ideal or typical occlusion might be referred to as a malocclusion. Malocclusion is a result of genetic and environmental factors interacting during the craniofacial complex's development.³ A number of environmental factors have been linked to malocclusion, including trauma, hormonal disorders, muscle disorder, poor nutrition, medical conditions, pituitary gland diseases, caries experience, mandibular posture habits, early primary tooth loss, prolonged tongue resting or sucking history, oral breathing, larger tonsils, atypical swallowing, and low economic status.⁴

4. Genetics in Malocclusion

Population research, particularly family and twin studies, support the idea that genetic factors play an important part in the onset of malocclusion. According to Lauweryns' 1993 analysis of the literature, hereditary factors account for 40% of the abnormalities in the skeleton and teeth that cause malocclusion.⁵ The degree of variation in various occlusal traits, including interdental spacing, overbite, overjet, and arch dimensions, was measured by Hughes and Townsend in 2001 in Australian twins. Their findings revealed a moderate to somewhat high hereditary changes that leads to variation.⁶

By detecting five SNPs which were significantly distinct in the genotype or alleles distribution of frequencies in a Hong Kong Chinese case-control population, Ting Wong et al. (2011) proposed a connection between the genes EDA and XEDAR and dental crowding that is present in Class I patients.⁷ Some research has reached the opposite conclusion, even though these studies support the heredity of dental occlusal traits that contribute to malocclusion. Corruccini, Sharma, et al., for example, were unable to show any discernible heritability for occlusal features in Indian twins, indicating that dental characteristics are influenced by the environment.⁸

Additionally, Harris and Johnson observed that virtually all of the dental variability in the group of untreated individuals was acquired as opposed to inherited.⁹ These contradictory findings imply that environmental variables have a greater influence on dental variety. In a study by Yamaguchi et al., the Pro561Thr (P56IT) variant in

the growth hormone receptor (GHR) gene was linked to measurements of the mandibular ramus length (condylion-gonion) on lateral cephalometric radiographs. The study included 50 men and 50 women in a normal Japanese sample, and the individuals without the GHR P56IT allele had a significantly longer mandibular ramus length. Individuals with the GHR P56IT allele had an average mandibular ramus height that was 4.65 mm lower than that of individuals lacking the GHR P56IT allele.

The GHR P56IT genotype and shorter mandible ramus height were shown to be significantly correlated. This association was additionally verified in 80 women.¹⁰ Predisposing or causal elements for formal occlusion may theoretically result from two broad types of heritable features. In one scenario, a disproportion in the location, size, or shape of the maxilla and mandible would be inherited, whereas in the other, a disproportion in the size of teeth and the jaws would result in crowding or spacing. Malocclusion would have to result from the straightforward inheritance of distinct skeletal and dental characteristics, which is uncommon given the genetic impact on each of these aspects. Rather, they are frequently polygenic and susceptible to environmental influences. According to Lundstrom's twin investigations, the following traits were significantly influenced by heredity: tooth size, dental arch breadth and length, palate height, tooth crowding and spacing, and the degree of overbite.¹¹

In a study on triplets using cephalometrics, Kraus, Wise, and Frei demonstrated that while there is strong genetic control over the shape of individual bones, the environment greatly influences how different bony parts are integrated to form a harmonious or disharmonious craniofacial skeleton.¹²

5. Malocclusions Associated with Genetic Syndromes

Malocclusions involving significant skeletal abnormalities may occasionally be associated with a hereditary condition. It is known that a few hereditary diseases can affect how the craniofacial complex develops.¹³ The first branchial arch develops abnormally most of the time due to chromosomal abnormalities, deficits, transpositions, failures, deletions, or enlargements.¹⁴ Due to this genetic predisposition, other forms of malformations and deficiencies in other body parts coexist with dentofacial problems such as oligodontia, malocclusions, facial asymmetry, clefts in the face, oral clefts and micrognathia.^{15,16}

A syndrome is characterized as a group of symptoms or a sequence of occurrences that frequently indicate the presence of a specific illness or condition.¹⁷ The following syndromes are categorized as frequently occurring with malocclusions:¹⁸

1. Malformation disorders along with deficient mandible.

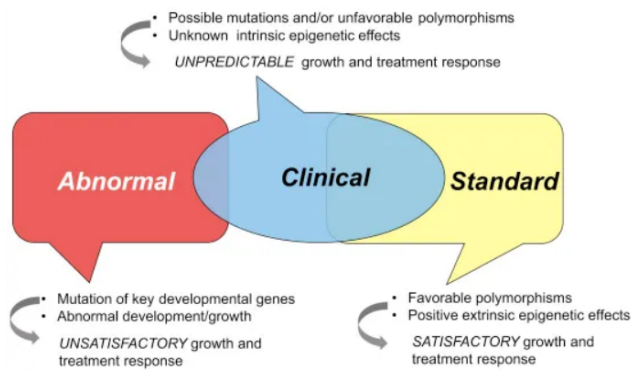


Figure 1: Heuristic model demonstrating the logic and foundation for using genetics in the management of dentofacial malformations and malocclusions

2. Malformation disorders having Class III tendency with prognathism of maxilla.
3. Malformation syndrome associated with increased or decreased facial height.
4. Syndrome associated with the facial asymmetry.

5.1. *Syndromes associated with deficient mandible are as follows*

1. Pierre Robin Syndrome.
2. Franceschetti Syndrome (Treacher Collins Syndrome, Mandibulofacial dysostosis).
3. Goldenhar syndrome (Hemifacial Microsomia).
4. Hallerman Streiff syndrome.
5. Wilder Vanck Smith Syndrome.

5.2. *Syndromes associated with Class III tendency in patient having mandibular prognathism*

1. Marfan’s syndrome
2. Klinefelter syndrome

5.3. *Syndromes associated with facial asymmetry*

1. Goldenhar syndrome
2. Hemifacial hypertrophy
3. Hemifacial microsomia

5.4. *Syndromes associated with deformity in facial height*

1. Beckwith Weidmann Syndrome
2. Von Recklinghausen’s disease:
3. Down’s syndrome
4. Apert syndrome
5. Crouzon Syndrome
6. Cleidocranial dysostosis

The Pierre Robin sequence exhibits autosomal recessive inheritance and is a disease with a diverse etiology. There’s

an X-linked version as well.¹⁸

The treacle gene (TCOF1), which is located on the long arm of the chromosome, is mutated in Treacher Collins syndrome, an autosomal dominant monogenic condition.

It has an impact on the development of the craniofacial region and manifests as hypoplastic zygomatic bones, micrognathia, and usually cleft palate.¹⁹

Anomalous growth of the first and second branchial arches is linked to Goldenhar syndrome. Although there might be a hereditary component, which would explain some familial patterns, it is believed to be multifactorial. On typically the one side of the body, it is defined by inadequate development of the nose, ears, lips, soft palate, and mandible.²⁰

Another name for the Hallermann-Streiff Syndrome is the Hallermann-Streiff and François Dyscephalic Syndrome, Oculomandibulodyscephaly with hypotrichosis, Oculomandibulofacial syndrome, and François syndrome. It is a congenital condition linked to the GJA1 gene. It has an impact on dental, hair, cranial, and growth development. Individuals suffering from this disease tend to be shorter than average and may not grow hair on their faces, legs, or pubic regions, among other locations.²¹

Fibrous connective tissue is inherited in Marfan syndrome. Frequent skeletal and dental features of this syndrome include increased height, disproportionately long limbs and fingers, mild to moderate laxity of the joints, increased overjet, retrognathia, micrognathia, a narrow and highly arched palate with dental crowding, and tooth conditions resembling dentinogenesis imperfecta.²²

The fibroblast growth factor receptor-2 (FGFR-2) genes, which are known to influence suture development, are the source of discrete point mutations that cause human craniofacial malformations like Crouzon, Apert, and Pfeiffer syndromes. These syndromes are characterized by a common combination of craniosynostosis, maxillary hypoplasia, relative mandibular prognathism, and associated dental issues and malocclusions.

One of the most prevalent conditions that causes mandibular deficiency, hypoplasia of the face muscle, and facial asymmetry is hemifacial microsomia. A common birth abnormality affecting both the first and second branchial arches derivative is hemifacial microsomia. Its form is rather changeable. There are family cases displaying autosomal dominant, autosomal recessive, or X-linked inheritance, despite the fact that the majority of cases are random.²³

5.5. *Crouzon’s syndrome*

A group of disorders known as craniosynostosis syndromes are defined by early cranial synostosis, or the closing of cranial sutures, which can occur alone or in combination with a range of other anomalies.²⁴

The premaxillary region exhibits significant underdevelopment of the maxilla, which results in tooth crowding and a V-shaped arch. A bifid uvula, partial anodontia, a cross bite or an open bite, and either a high arched palate or a complete cleft palate is also common.

6. Clinical Implications

Every malocclusion in clinical orthodontics has a unique place on the genetic/environmental spectrum. The likelihood of a successful orthodontic intervention depends on the degree of genetic contribution to the malocclusion. Of course, the challenge lies in the fact that it is rarely easy to determine the exact role that environment and heredity play in a given situation.

For instance, in the case of mouth breathing, where the morphology that is genetically defined on the basis of habits and posture are strongly influenced, and where the morphology may have had a role in the initial development of habit.²⁵

Furthermore, there is currently insufficient data to support the theory that orthopedic appliances can considerably affect skeletal base growth in addition to the innate genetic potential. There is currently little data to suggest that utilizing orthopedic appliances can have any major long-term effects on the mandibular and maxillary dental bases, which is consistent with human research that tend to support the hereditary determination of craniofacial form.

7. Personalized Orthodontics, The Future of Genetics in Practice

The term "personalized medicine," which was first popularized by pharmaco-genetics, is currently gaining immense popularity due to the completion of genome-wide association studies.²⁶

It is yet unclear, though, if this will actually impact day-to-day operations. One may predict the same for orthodontics in the future. What would be the foundation for individualized orthodontics, and how would the research be carried out and then verified in real-world settings? How is this going to be paid for?.

Fundamental to the evidence-based practice of orthodontics is the comprehension of the combined effect and interaction of hereditary and environment (including treatment) factors that influence our patients' response to treatment (nature and nurture together).

It's the first patient you see of the day, for a first assessment. This crowding example, classified as Class I borderline, with well-aligned incisors. Based on an analysis of the primary polymorphism changes and altering susceptibility to external apical root resorption genes, it can be concluded that the patient is comparatively at risk for developing external apical root resorption. You utilize this

diagnostic data to construct a treatment plan, taking into account the projected movement of teeth based on whether you recommended excision of the remaining teeth, as well as other criteria including root form and expected duration of treatment.

The 7-year-old patient you see next has a negative anterior overjet. The maxilla appears to be retruded compared to other anatomical components, according to cephalometric research. A diagnosis of Class III malocclusion is indicated by the analysis of the polymorphic variants of the major and modified Class III malocclusion genes, your examination, and the radiographic evaluation. This allows you to determine the type of treatment that will have the most chance of success at what point in the patient's development.

When we can assert that an amalgamation of distinct variants in a number of genes, in addition to specific environmental (including treatment) factors, is linked to a significantly higher degree of variance in the pathology or other trait, genetic research will become much more valuable and impactful.

8. Studies of Genome-Wide Associations (GWAS)

Finding out if a specific polymorphism variance (marker allele) is more common in a group of patients with the pathology or another kind of trait that is important compared to a control group is known as association analysis.²⁷ In the beginning, this was frequently accomplished by examining polymorphism variants in or near a candidate gene, which was typically chosen based on prior understanding of the gene's function and potential influence on the emergence of a trait of interest. Naturally, this restricts the identification of potentially significant genes—after all, you can't expect to find anything if you don't know where to look for it—especially those that might have a more cumulative or moderating effect.

Since there is variation in response within a population, further research examining the response to different treatments are predicted. However, almost these types of genome-wide association studies are more concerned with etiology than with treatment response. Future research may therefore concentrate on factors related to etiology (diagnostic), response to treatment, or both.

9. Conclusion

Given that malocclusion is essentially a manifestation of the interaction between hereditary and environmental factors on the growth of the orofacial complex, orthodontic professionals must have a thorough understanding of the role that genetics plays in explaining why an individual has a specific occlusion.

A crucial component of evaluation that underlies almost all dentofacial abnormalities is taking hereditary factors

into account. Therefore, it's critical to identify genetic abnormalities early on before they completely appear.

Understanding how the dentofacial underdevelopment is expressed genetically can be a valuable tool for orthodontists in treating malocclusions. This is because it can distinguish between malocclusions that are inherited and those that are the result of environmental factors, which can help with diagnosis, treatment, and possibly preventing malocclusions in future generations.

Genetics may be of interest to orthodontists in order to better understand a patient's specific occlusion, as genetic variables are a crucial component of diagnosis for almost all dentofacial malformations.

The interaction of protein from expressed (or not) genetic variables and other environmental factors at that time, in the context of the individual's developmental maturity, will determine the treatment's outcome of an individual patient.

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11. Conflict of Interest

There is no conflict of interest.

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