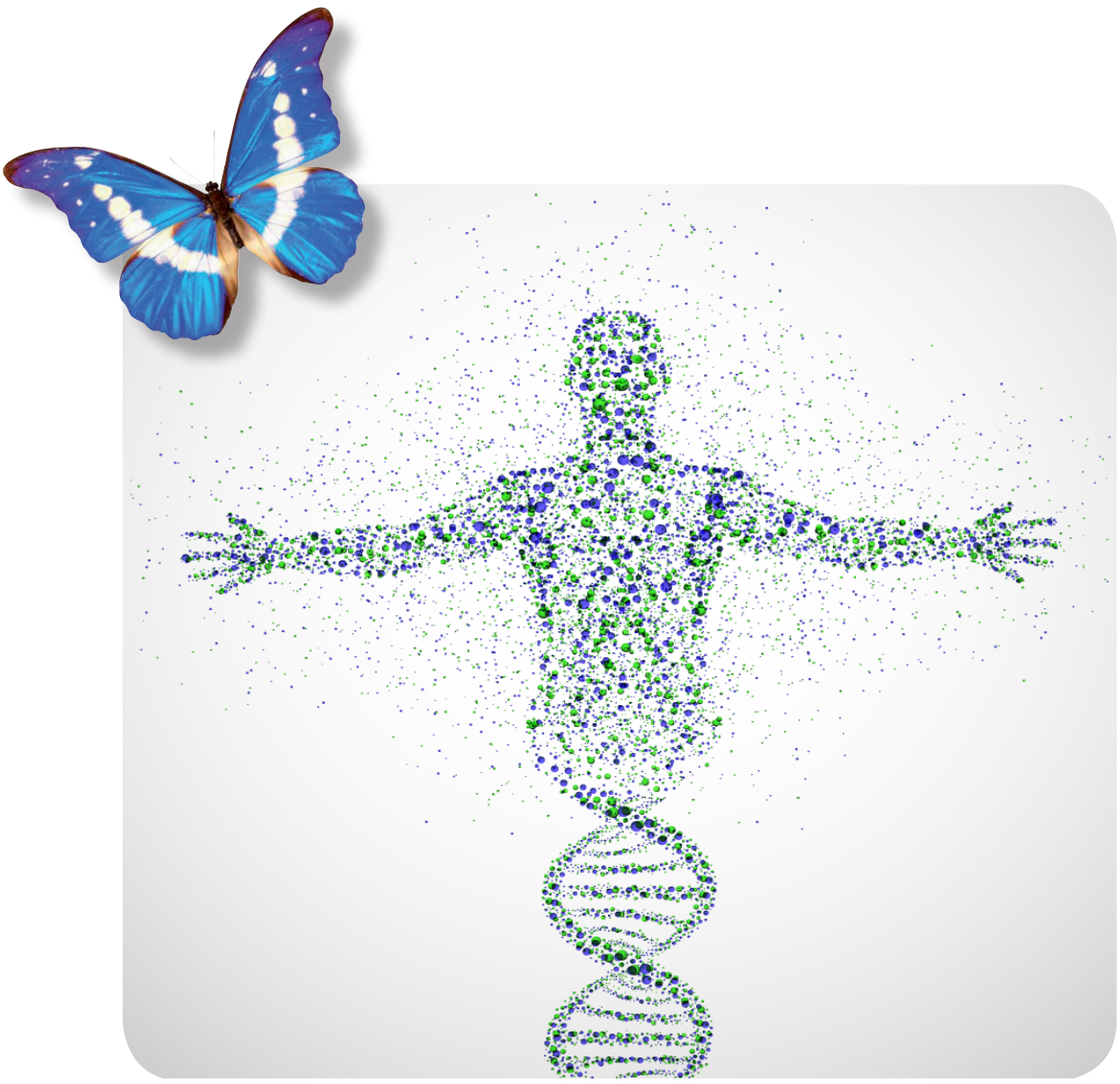
Australian Society of Orthodontists

University of Sydney



Genetics in Orthodontics

Creating Brighter Futures

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Introduction

Malocclusions occur due to an adverse interplay between genetic [1,2] and environmental factors. Growth pattern and dentofacial morphology is genetically determined [3] but it can be influenced to some extent by environmental factors. Orthodontic therapy serves as an environmental factor that can influence craniofacial growth to correct a malocclusion and achieve an aesthetic and harmonious occlusion with good facial balance.

This article will review the genetic factors contributing to malocclusion. The influence of environmental factors should however always be kept in mind.

Malocclusion associated with genetic syndromes

The genetic component of most malocclusions is difficult to understand as craniofacial traits are polygenic in nature. The Human Genome project has opened new avenues to a better understanding of this. Severe jaw discrepancies and malocclusions can be due to syndromes caused by aberrations, transpositions, deficiencies, deletions and breakage at the chromosomal level in the first branchial arch. Some key syndromes are listed in Table 1.

Genetic Predisposition to Eruption Problems and Tooth Agenesis

Any deviation from normal eruption of the dentition will affect proper occlusion as well as the vertical dimension of the supporting alveolar bone.

Adverse effects may include crowding, impaction and localised open bite from, for example, primary molar ankylosis.

Primary Failure of Eruption (PFE)

Primary Failure of Eruption (PFE), on the other hand, describes a condition where non-ankylosed teeth fail to erupt even though there is no physical impediment to its eruption. It usually affects the posterior teeth so that, over time, a posterior open bite develops [4]. It may be

Table 1. Key syndromes and their genetic basis

Syndrome	Dental Characteristics relevant to Orthodontics	Genetic involvement
Marfan	Mandibular deficiency, mild to moderate joint laxity, increased overjet, retrognathia, micrognathia, narrow and highly arched palate with dental crowding and dentinogenesis imperfecta- like tooth conditions Mandibular deficiency micrognathia, hypoplastic	Mutations in the Fibrillin (FBN) 1 gene
Treacher Collins	zygomatic bones and frequently cleft palate Mandibular deficiency	Mutation in the treacle gene (TCOF1)
Pierre Robin Sequence	Facial asymmetry, hypoplasia of facial muscles and mandibular deficiency	Point mutations in the fibroblast growth Factor receptor-2 (FGFR-2)
Hemifacial microsomia	Unilateral or bilateral cleft lip with or without palate involvement	Duplication of the orthodentile homeobox 2 (OTX2) gene
Cleft lip and palate		TGF-alpha, TGFB3, MSX1

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associated with syndromes such as cleidocranial dysplasia, ectodermal dysplasia, Down syndrome and Apert syndrome. PFE is believed to be a genetic disturbance with 'high penetrance' which means the trait it produces will almost always be apparent in the person carrying the gene [5]. Mutations in parathyroid hormone receptor 1 (PTH1R) is associated with PFE [6] which makes this a high-priority candidate gene for confirming diagnosis of PFE [7]. A comprehensive family history can benefit early diagnosis of this condition thus facilitating better treatment planning. Often, however, there is no effective orthodontic treatment for PFE as the teeth fail to respond to orthodontic forces [4].

Tooth agenesis: Hypodontia, Oligodontia, Anodontia

Congenital absence of five or fewer teeth is defined as hypodontia and is more common in the permanent than primary dentition. The cause for selective tooth agenesis in humans was found to be a missense mutation which occurred in the MSX-1 homeodomain [8]. The upper lateral incisors and lower premolars are the most frequently missing teeth, excluding third molars, and have been associated with defects in MSX-1and MSX-2 genes.

A mutation in MSX-1 gene in chromosome 4 has been identified as the causative factor for oligodontia (6 or more teeth missing) involving the absence of all second premolars and third molars [9]. Mutation of PAX-9 transcription factors has been observed in familial tooth agenesis and also in missing mandibular second premolars and central incisors [10] Also, missing teeth and reduction in tooth size were closely associated and are directed by the same gene loci [11].

While studying the family records of a Finnish family with severe familial oligodontia due to mutation in AXIN2 (axis inhibition protein 2), a history of familial adenomatous polyposis was discovered [12]. Such studies about genetic regulation of tooth agenesis helps identify dental clinical markers for cancer.

Anodontia is the complete absence of teeth which occurs in hypohidrotic ectodermal dysplasia, a hereditary disease where the ectodermal tissues or derivatives are absent. It is a sex-linked recessive trait although autosomal recessive pedigrees have also been reported [13]. Individuals with partial congenital anodontia usually have smaller teeth [14].

Ectopic and Transposed Canines

Palatally impacted and ectopic canines may also represent an inherited trait that can be explained genetically [15]. Genetics also supports the association between palatally impacted canines and other dental anomalies, such as agenesis of mandibular premolars, maxillary lateral incisors, peg laterals, infraocclusion of the deciduous molars, enamel hypoplasia and distally displaced unerupted mandibular second premolars [16]. Maxillary canine/first premolar transposition has been associated with maxillary lateral incisor agenesis [17]. Similiarly, an association between impacted canines, mandibular lateral incisor/canine transposition and congenitally missing third molars has been reported [18]. Conditions such as tooth agenesis, tooth size and positional anomalies which are often seen occurring together usually indicates that there is a complex genetically programmed dental condition [19].

Supernumerary Teeth

Individual supernumerary teeth are more common in the permanent dentition and occur more frequently in the anterior maxilla followed by the posterior regions of the maxilla [20]. Multiple supernumerary teeth occur more commonly in the mandibular premolar region. Their presence may lead to complications such as crowding, spacing, impaction, displacement or rotation, cystic formation and resorption of adjacent teeth. Supernumeraries run in families, demonstrate racial variation and display sexual dimorphism [21]. The fact that supernumerary teeth can be a prominent feature of many developmental disorders is the most compelling evidence for a genetic basis [22]. Some of the syndromes that are associated with the occurrence of supernumerary teeth and the genes implicated in those syndromes are shown in the Table 2.

Table 2. Syndromes associated with supernumerary teeth and the genes implicated

Syndrome	Genes
Cleidocranial Dysplasia	RUNX2
Ehlers-Danlos Type IV	PLOD
Gardner	APC
Incontinentia pigmenti	NEMO
Fabry disease	GLA

Adopted and modified from Fleming PS, 2010 (22)

Genetic predisposition to skeletal malocclusions

Class II and III skeletal patterns have long been thought to have a genetic basis. The inheritance of the "Hapsburg jaw" (mandibular prognathism demonstrated by several generations of the Austro-Hungarian monarchy) is a classic example [23]. However, a Class III malocclusion may result from deficiency in maxillary growth, excessive mandibular growth, or a combination of both.

Cephalometric prediction of craniofacial growth assumes that the facial type in a growing child is sufficient to predict future growth [24-26]. However, this ignores the possible genetic basis of growth. The prediction is valid only if the parents' craniofacial morphology is taken into consideration. A patient who has a moderate Class II malocclusion is most likely to develop a severe skeletal Class II malocclusion if his family members have a Class II malocclusion [27]. Markovic (1992), in analysing clinical cephalometric studies of 48-pair of twins suggested that Class II div 1 and 2 malocclusions have a genetic correlation which is polygenic in nature [2].

Parents of Class II patients have a greater tendency to have a convex profile with a distocclusion while the parents of Class III patients have a greater tendency to have a concave profile with a mesiocclusion. This suggests that both Class II and Class III malocclusions have a genetic basis [28].

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Along with a genetic influence there is also an environmental influence on the anteroposterior position of the maxilla and maxillary alveolar bone. Habits such as mouth breathing and digit sucking can cause an advancement of the maxillary alveolar process, whereas an anterior cross-bite relationship in Class III patients can hinder normal forward maxillary growth. The vertical position of the maxilla and maxillary alveolar process can also be influenced by environmental factors. Therefore these environmental factors may increase or decrease the inherited size and position of the maxilla in Class II and Class III patients. Mandibular growth is much less likely to be affected by environmental factors in the antero-posterior plane; however mouth breathing, tongue position and function can to some extent influence the mandible's vertical orientation.

Generally, according to the longitudinal Bolton-Brush growth study, skeletal characteristics of the facial skeleton are heritable whereas there is only low heritability of occlusal characteristics [29]. For example, palatal height, width and length dimensions showed a significant component of hereditary variability and genetics was an important etiological factor of malocclusion involving palatal dimension [30]. On the other hand, dental variations resulting in malocclusion are largely influenced by environmental factors [31].

Obstructive Sleep Apnoea

Obstructive sleep apnoea syndrome (OSAS), a potentially disabling condition which may affect the cognitive ability of an individual, is characterized by excessive daytime sleepiness, snoring, recurrent episodes of apnoea (no airflow) or hypopnoea (partially obstructed airflow), and nocturnal hypoxemia. Inherited abnormalities of craniofacial structure, such as a small mandible, appear to explain at least a portion of the familial clustering of OSAS, and some genetic involvement is identified by twin and family studies [32].

Genetics and root resorption

While orthodontic treatment can cause root resorption, an underlying genetic basis is reported. Several genes such as Interleukin-Ib gene (IL-1B), Receptor activator of nuclear factor-Kappa ligand (RANKL) and TNF- receptor superfamily [33] have been implicated. However, due to the multifactorial nature of root resorption, it has been difficult to predict root resorption in specific orthodontic patients. Research is underway to identify biomarkers of orthodontic root resorption and these will enable clinicians to predict a patient's susceptibility and therefore possibly alter the treatment undertaken.

Conclusion

Malocclusion is caused by a combination of genetic and environmental influences. Orthodontics has evolved by identifying such environmental influences and successfully manipulating them to work to the patient's benefit. The genetic influence on malocclusion is being extensively studied, with new information rapidly unfolding. As the human genome project progresses the possibility to localise the defective gene for each orthodontic problem seems promising, although it is complicated by the polygenic nature of each craniofacial trait.

An improved knowledge of genetics in orthodontics will pave the way for genetic correction of certain dentofacial abnormalities. The clinician will be more aware of the unique genetic signatures of orthodontic patients enabling the clinician to devise better treatment modalities customised according to the individual's current and future growth and development, needs, responses and goals.

References upon request