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**Abu-Hussein Muhamad**  
Universitätsklinikum Würzburg,  
Klinik und Polikliniken für  
Zahn-, Mund- und  
Kieferkrankheiten der Julius-  
Maximilians-Universität  
Würzburg, Germany, University  
of Debrecen/ Hungary, Faculty  
of Dentistry of the University of  
Sevilla/Spain, Arab American  
University/Jenin, Palestine

**Nezar Watted**  
Universitätsklinikum Würzburg,  
Klinik und Polikliniken für  
Zahn-, Mund- und  
Kieferkrankheiten der Julius-  
Maximilians-Universität  
Würzburg, Germany, University  
of Debrecen/ Hungary, Faculty  
of Dentistry of the University of  
Sevilla/Spain, Arab American  
University/Jenin, Palestine

### Correspondence

**Abu-Hussein Muhamad**  
Universitätsklinikum Würzburg,  
Klinik und Polikliniken für  
Zahn-, Mund- und  
Kieferkrankheiten der Julius-  
Maximilians-Universität  
Würzburg, Germany, University  
of Debrecen/ Hungary, Faculty  
of Dentistry of the University of  
Sevilla/Spain, Arab American  
University/ Jenin, Palestine

## Genetics and Orthodontics

**Abu-Hussein Muhamad and Nezar Watted**

### Abstract

Growth is the combined result of interaction between several genetic and environmental factors over time and malocclusion is a manifestation of genetic and environmental interaction on the development of the orofacial region. It is important to consider genetic factors in orthodontic diagnosis, in order to understand the cause of existing problem, which may also have an influence on the final outcome of orthodontic treatment. Generally, malocclusions with a genetic cause are thought to be less amenable to treatment than those with an environmental cause. Greater the genetic component, worse the prognosis for a successful outcome by means of orthodontics intervention. Knowing the relative influence of genetic and environmental factors would greatly enhance the clinician's ability to treat malocclusions successfully.

Orthodontists maybe interested in genetics to help understand why a patient has a particular occlusion and consideration of genetic factors is an essential element of diagnosis that underlines virtually all the dentofacial anomalies.

**Keywords:** History, dental anomalies, genetics, orthodontics

### Introduction

Malocclusion is a manifestation of genetic and environmental interaction on the development of the orofacial region. Orthodontists may be interested in genetics to help understand why a patient has a particular occlusion. Consideration of genetic factors is an essential element of diagnosis that underlies virtually all dentofacial anomalies. This part of the diagnostic process is important to understanding the cause of the problem before attempting treatment. Knowing whether the cause of the problem is genetic has been cited as a factor in eventual outcome; that is, if the problem is genetic, then orthodontists may be limited in what they can do (or change) [1-3]. In the orthodontic literature, there are inappropriate uses of heritability estimates as a proxy for evaluating whether a malocclusion or some anatomic morphology is "genetic." As will be explained, this had no relevance to the question. How genetic factors will influence the response to environmental factors, including treatment and the long-term stability of its outcome as determined by genetic linkage or association studies, should be the greatest concern for the clinician [4,5].

Genetics is a science of potentials. It deals with the transfer of biological information from cell to cell, from parents to offspring, and thus from generation to generation. Genetics has revealed that any two individuals share 99.9% of their DNA sequences. Thus, the remarkable diversity of humans is encoded in about 0.1% of our DNA. Genetics has revealed that any two individuals share 99.9% of their DNA sequences [6].

According to Stent (1971) the first evidence of inheritance was taught and developed by Hippocrates in fifth century BC in Greece. Hippocrates ideas can be termed as 'bricks and mortar theory' which states that hereditary material consists of physical matter. He postulated that elements from all part of the body became concentrated in male semen and then formed into a human in the womb. He also believed in the inheritance of acquired characteristics. A century later Aristotle criticized Hippocrates theory and instead proposed that heredity involved the transmission of information- a blueprint model'. Aristotle discarded Hippocrates theory for several reasons. He pointed out that individuals sometimes resemble remote ancestors rather than their immediate parents [1, 4, 5].

William Bateson a British geneticist was the first person to use the term — genetics (from the Greek genno, i.e. to give birth) to describe the study of inheritance and the science of variation. He first used the term "genetics" publicly at the Third International Conference on-

Plant Hybridization in London in 1906 [6, 7].

Gregor Johann Mendel (1822-1884) often called the-father of genetics for his study of the inheritance of traits in pea plants. Mendel was the one who showed that the inheritance of traits follows particular laws, which were later named after him.

Ray E Stewart, a medical geneticist, listed malocclusion as the most common hereditary deviation in dentistry followed by periodontal disease and dental caries.

In 1836 Friedrich Kussel reported that malocclusion both skeletal and dental can be transmitted from one generation to another. He also reported that chromosomal defects account for about 10% of all malocclusions [1-8].

The genome contains the entire genetic content of a set of chromosomes present within a cell or an organism. Within genome are genes that represent the smallest physical and functional units of inheritance that resides in specific sites called —locil or —locus for a single location. The term gene was coined by Wilhelm Johannsen in 1909. The gene was first defined as the unit of genetic information that controls a specific aspect of the phenotype. At a more fundamental level the gene has been defined as the unit of genetic information that specifies the synthesis of one polypeptide [3].

A gene can be defined as the entire DNA sequence necessary for the synthesis of a functional polypeptide molecule (production of a protein via a messenger RNA intermediate) or RNA molecule (transfer RNA and ribosomal RNA) Operationally, the gene includes the 5' and 3' non coding regions that are involved in regulating the transcription and translation of the gene and all introns within the gene. The structural gene refers to the portion that is transcribed to produce the RNA product [8].

Orthodontists maybe interested in genetics to help understand why a patient has a particular occlusion and consideration of genetic factors is an essential element of diagnosis that underlines virtually all the dentofacial anomalies.

### **Craniofacial skeletal and dentoalveolar occlusal heritability studies**

Consideration of the genetic aspect of occlusal variations and malocclusion has been a major focus of interest to orthodontists. The different studies directed toward heritability of occlusion have varied in method. In addition to environmental covariance, a limitation of many of these studies is that they were based just on twins or siblings who did not receive orthodontic treatment. Possibly, twin pairs and sibships containing one or more treated patients (with moderate to severe malocclusion) were excluded from most studies. Therefore, estimates of genetic and environmental contributions may have been affected by lack of accounting for a common environmental effect [9, 10].

The cause of most skeletal-and dentoalveolar based malocclusions is essentially multifactorial in the sense that many diverse causes converge to produce the observed outcome.40 Numerous studies have examined how genetic variation contributes to either or both occlusal and skeletal variation among family members [11]. Many reviews of the genetics of malocclusion actually focus on the cephalometric component of craniofacial form, not on the occlusal component.

In most studies (particularly those that try to account for bias from the effect of shared environmental factors, unequal means, and unequal variances in monozygotic and dizygotic twin samples) [10], variations in cephalometric skeletal dimensions are associated in general with a moderate to high degree of genetic variation, whereas in general, variation of

occlusal relationships has little or no association with genetic variation [12].

Although the heritability estimates are low, most of the studies that looked at occlusal traits found that genetic variation has more to do with phenotypic variation for arch width and arch length than for overjet, overbite, and molar relationship. Still, arch size and shape are associated more with environmental variation than with genetic variation [13]. Because many occlusal variables reflect the combined variations of tooth position and basal and alveolar bone development, these variables (e.g., overjet, overbite, and molar relationship) cannot be less variable than the supporting structures. They will vary because of their own variation in position and those of the basilar structures [14].

The example of reported heritability estimates for anterior and posterior face height and the observed effect of perennial allergic rhinitis and mouth breathing are interesting. Some (although not all) studies suggest that a greater heritability exists for total anterior face height and lower anterior face height than for upper anterior face height and posterior face height. This implies that the greater estimate of heritability for the total anterior face height is due to the greater estimate of lower anterior face height than upper face height. Possibly a lower heritability for the upper anterior face height reflects the effect of the airway, and a lower heritability for posterior face height reflects dietary effects [15, 16].

How those findings are reconcilable with an increase in total anterior face height and lower anterior face height, in particular, being associated with perennial allergic rhinitis and mouth breathing? One hypothesis is that the lower anterior face height may have a greater heritability than the upper anterior face height in some groups of individuals unless increased nasal obstruction resulting in mouth breathing becomes a predominating factor in group members. Remembering that heritability is a descriptive statistic for a particular sample under whatever environmental conditions existed is essential [17].

Malocclusion is less frequent and less severe in populations not industrialized (urbanized) and that tend to be isolated. Typically an increase in malocclusion occurs as these populations are “civilized” or become more urbanized. This has been attributed to the interbreeding of populations with, to some degree, different physical characteristics, presumably resulting in a synergistic disharmony of tooth and jaw relationships. This idea was supported by the crossbreeding experiments of Stockard and Anderson [18] in inbred strains of dogs, increasing the incidence of malocclusion, typically caused by a mismatch of the jaws. However, the anomalies they produced have been attributed to the influence of a major gene or genes that have been bred to be part of specific breeds. Considering the polygenic nature of most craniofacial traits, it seems improbable that racial crossbreeding in human beings could resemble the condition of these experiments and thereby result in a synergistic increase of oral-facial malrelations [19].

A study of disparate ethnic groups that have interbred in Hawaii found that children of racial crosses are at no increased risk of malocclusion beyond what would have been expected from the usual parental influence.

In addition, the increase in malocclusion in populations that have moved recently into an industrialized lifestyle is too quick to be the result of genetic change caused by evolutionary fitness pressure [19]. The most likely explanation for the increased malocclusion seen in “civilization” is changed environment, such as food and airway effects [20].

There is dental anthropological evidence that population groups are genetically homogeneous tend to have normal occlusion. Malocclusion is almost nonexistent in pure racial stocks/ethnic groups, such as the Melanesians of the Philippine Islands. However in heterogeneous population, the incidence of malocclusion is significantly high. Although increased occurrence of malocclusion in urbanized populations has been attributed to racial interbreeding the most likely explanation may be the changed environment, such as food and airway effects <sup>[21]</sup>.

### Methods of studying heritability of malocclusion

The bulk in the evidence for the heritability of various types of malocclusion comes from familial and twin studies. The methods to estimate heritability are based on correlation and measurements of the traits between various kinds of pairs of individuals in families, including <sup>[22]</sup>:

- Monozygotic Twins
- Dizygotic Twins
- Parent-Child
- Sib-Sib (Sibling Pairs).

### Familial studies/pedigree studies

The nature of inheritability of traits can be studied by constructing family trees called pedigrees in which males are denoted by squares and females by circles and by noting who in the family has the trait and who does not <sup>[3]</sup>.

A particular trait is observed in successive generation to assess its mode of inheritance. Autosomal recessive traits are best studied in consanguineous marriages where interbreeding (Marriage into a family) is permitted <sup>[23]</sup>.

### Twin studies

Twin studies offer the best evidence in establishing the relative contribution of genes and environment in the development of malocclusion <sup>[24]</sup>. Twins are of two kinds:

- i. Monozygotic twins
- ii. Dizygotic twins

**Monozygotic twins:** The identical twins develop from single fertilized egg that later divides into two zygotes at an early stage of development. They are identical in genetic makeup and sex, i.e. genotype is identical <sup>[23]</sup>.

**Dizygotic twins:** Dizygotic twins develop from two separately fertilized eggs at the same time. Dizygotic twins share only 50% of their total gene complement.

The underlying principle of twin studies is that <sup>[6]</sup>:

- The observed difference within a pair of monozygotic twins (whose genotype is identical) is due to environmental factors.
- Differences observed within a pair of dizygotic twins, (who share 50% of their total gene complement) are due to both environment and genetic makeup.

### Craniofacial disorders and genetic etiology with malocclusion

Some of the craniofacial abnormalities, which have genetic cause and have.

### Genetic influence on skeletal and dental malocclusion

In general, heritability estimates of craniofacial skeletal structures are greater than those for dentoalveolar traits, such as tooth position, number and size. In other words, studies have shown that skeletal malocclusions are more influenced

by genetics whereas dental malocclusions are more often due to environmental factors.

Studies of Lundstrom (1948) concluded that although genetic factors appear to govern the base skeletal forms and size, environmental factors in their multitudinous facets have much influence on the bony elements, and both the genetic and environmental factors combine to achieve the harmonious/disharmonious head and face <sup>[25]</sup>.

According to Hughes mandible and maxilla are under separate genetic controls and certain positions of individual bones, such as ramus, body and symphysis of the mandible are under different genetic and environmental influences. Various familial and twin studies indicate that class II division 1 and class II division 2 malocclusions are multifactorial (interaction of both environmental factors) while class III malocclusion is heavily influenced by genetics. Class II division 2 malocclusion is often considered as a genetic trait and class III malocclusion resulting from mandibular prognathism often runs in families as an autosomal dominant trait <sup>[26]</sup>.

### Class II division 1 malocclusion

Class II division I malocclusion appears to have a polygenic/multifactorial inheritance as explained below <sup>[2]</sup>.

- Extensive cephalometric studies have showed that in class II division 1, the mandible is significantly extended than in class I patients with the body of the mandible smaller and overall mandibular length reduced.
- Higher correlation between the parts and their immediate family than in unrelated siblings is noted. \_ However, environmental factors, such as tongue pressure, digit sucking habit can also contribute to class II division 1 malocclusion <sup>[6]</sup>.

### Class II division 2 malocclusion

Class II division 2 malocclusion exhibits high genetic influence and is often considered as a genetic trait <sup>[3, 6]</sup>.

Familial occurrence of Class II division 2 malocclusion has been documented in several published reports, including twin and triplet studies and in family pedigrees [Ckloepfel (1953), Markovic (1992) Korkhaus (1930), Peck (1998)]. Markovic (1992) carried out a clinical and cephalometric study of 114 Class II division 2 malocclusion (48 twin pairs and six sets of triplets). The results of his study showed that there was 100% concordance for class II division 2 malocclusion in monozygotic twin pairs. This gives a strong evidence for genetics as main ethological factor in development of class II division 2 malocclusion.

Results of various family pedigree studies suggest the possibility of autosomal dominant inheritance with incomplete penetrance. High lip line, lip morphology and behavior are also considered to be causing class II division 2 malocclusion.

In general, simultaneous and synergistic influence of genetics and environment (multifactorial inheritance) is attributed to the development of class II division 2 malocclusion, also it has a strong genetic influence <sup>[27]</sup>.

### Class III malocclusion

The most famous example of a genetic trait in humans passing through several generations is probably the pedigree of the so-called "Hapsburg Jaw." This was the famous mandibular prognathism demonstrated by several generations of the Hungarian/Austrian dual monarchy.

Strohmayr (1937) from his detailed pedigree analysis of

Hapsburg family concluded that mandibular prognathism was an autosomal dominant trait [28]. Other studies, such as Suzuki's (1961) study on 243 Japanese families and twin studies have also suggested strong genetic basis for mandibular prognathism. Although various environmental factors, such as enlarged tonsils, nasal blockage, posture, premature loss of permanent molars due to trauma can also cause class III malocclusion, the overall inheritance pattern best fits an autosomal dominant model [29].

Tooth size, hypodontia, and dental root development additive genetic variation for mesial-distal and buccolingual crown dimensions of the permanent 28 teeth (excluding third molars) ranged from 56% to 92% of phenotypic variation, with most over 80%. [30] 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 or overall crown size was associated more with genetic variation than was the morphology of the occlusal surfaces [31].

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 (isolated). Note that "isolated" in this use means not a part of a syndrome, although it still may be familial. 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 [30, 32]. 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, 80-82 although there are other chromosomal locations that nonsyndromic hypodontia has been mapped to and candidate genes, including 10q11.2 and KROX-26 [33, 34, 35].

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). Mesial-distal size of the permanent maxillary incisor and canine crowns tends to be large in cases with supernumerary teeth [30, 35]. 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 [36].

The presence of a single primary and permanent maxillary incisor at first may appear to be a product of fusion. However, if the single tooth is in the midline and symmetric with normal crown and root shape and size, then it can be an isolated finding or can be part of the solitary median maxillary central incisor syndrome. This heterogeneous condition may include other midline developmental abnormalities of the brain and other structures that can be due to mutation in the sonic hedgehog (SHH) gene, SIX3 gene, or genetic abnormality. Although rare, the development of only one maxillary central incisor is an indication for review of the family medical history and evaluation for other anomalies [37].

Analysis of the variation in dental age as determined by root development was explained best by additive genetic influences (43%) and by environmental factors common to both twins (50%). Environmental factors unique or specific to only one twin accounted for the remainder. The importance of the common environmental factor was thought to be due to twins sharing the same prenatal, natal, and immediate

postnatal conditions that are important for tooth formation [38]. Incisor mesial distal crown dimensions were found to be small as a part of the extreme form of the Class II, Division 2 malocclusion in which the mandibular incisors are concealed in habitual occlusion, along with strong vertical development of the posterior mandible, forward rotation, and skeletofacial hypodivergence.

Following a review of published family pedigrees involving Class II, Division 2 malocclusion, Peck and colleagues noted the probability of autosomal dominant inheritance with incomplete penetrance, although polygenic inheritance was also a possibility [39].

One of the most common, if not the most common, pattern of hypodontia (excluding the third molars) involves the maxillary lateral incisors. This can be an autosomal dominant trait with incomplete penetrance and variable expressivity as evidenced by the phenotype sometimes "skipping" generations and sometimes being a peg-shaped lateral instead of agenesis and sometimes involving one or the other or both sides [40]. A polygenic mode of inheritance also has been proposed [41]. Unidentified currently, the gene mutation that primarily influences this phenotype has been suggested, in the homozygous state, to influence agenesis of the succedaneous teeth or all or almost all of the permanent dentition [42, 43]. In addition, an associated increased agenesis of premolars occurs, [44] as well as with palatally displaced canines [45].

Maxillary canine impaction or displacement is labial/ buccal to the arch in 15% of the cases of maxillary canine impaction and often is associated with dental crowding. The canine impacted or displaced palatally occurs in 85% of the cases and typically is not associated with dental crowding [46]. Palatally displaced canines frequently, but not always, are found in dentitions with various anomalies. These include small, peg-shaped or missing maxillary lateral incisors, hypodontia involving other teeth, dentition spacing, and dentitions with delayed development [47]. Because of varying degrees of genetic influence on these anomalies, there has been some discussion about palatally displaced canines themselves also being influenced by genetic factors to some degree. In addition, the occurrence of palatally displaced canines does occur in a higher percentage within families than in the general population [48].

A greater likelihood exists of a palatally displaced canine on the same side of a missing or small maxillary lateral incisor, emphasizing a local environmental effect [49].

Also, in some cases, a canine is displaced palatally without an apparent anomaly of the maxillary lateral incisors, and in some cases, lateral incisors are missing without palatal displacement of a canine. Adding to the complexity is the heterogeneity found in studies of cases of buccally displaced canines and palatally displaced canines [30, 35]. Although the canine eruption theory of guidance by the lateral incisor root cannot explain all instances of palatally displaced canines, it does seem to play some role in some cases [50].

With apparent genetic and environmental factors playing some variable role in these cases, the cause appears to be multifactorial [21]. The phenotype is the result of some genetic influences (directly or indirectly or both, for example, although a primary effect on development of some or all of the rest of the dentition) interacting with environmental factors. Some of these cases may be examples of how primary genetic influences (which still interact with other genes and environmental factors) affect a phenotypic expression that is a variation in a local environment, such as the physical structure

of the lateral incisor in relation to the developing canine. [30]Candidate genes that are proposed possibly to influence the occurrence of palatally displaced canines and hypodontia in developmental fields include MSX1 and PAX9. Investigations so far indicate that a number of heterogeneous genetic factors may be involved in hypodontia [30-36]. Increased understanding of the various morphogenetic signaling pathways regulating tooth development should allow for induction of tooth development in areas of tooth agenesis [30]. In addition to hypodontia and its primary or secondary relationship to maxillary canine eruption, there are emerging data regarding the influence of genetics on dental eruption. Presently this is most clear in cases of primary failure of eruption (PFE), in which all teeth distal to the most mesial involved tooth do not erupt or respond to orthodontic force. The familial occurrence of this phenomenon in approximately onequarter of cases facilitated the investigation and discovery of the PTHR1 gene being involved [30-36]. Advancements in this area could not only help to define patients who are likely to develop or have PFE, but also potentially result in the molecular manipulation of selective tooth eruption rates to enhance treatment protocols on an individual basis [21, 30, 32, 50].

#### Other studies [51]

##### Class I Malocclusion with crowding

EDA (Ectodysplasin) gene associated with crowding EDA was shown to act in a morphogenetic role in teeth and other ectodermal organs. eg, teeth, hair, and sweat glands. Mutations in the EDA gene: defects in ectodermal organs [52]. Mutations results in differential gene expression which causes large tooth phenotype. This ultimately results in crowding [32].

**Ectopic maxillary canines:** Various studies by (Zilberman *et al.* 1990 and Peck *et al.* 1994) concluded that palatally ectopic canines were an inherited trait, being one of the anomalies in a complex of genetically related dental disturbances often occurring in combination with missing teeth, teeth size reduction, supernumerary teeth and other ectopically positioned teeth [51].

**Deep bite, Open bite:** The study showed that deep bite in males and open bite in females had concordance only in Mz twin-pairs [35].

**Arch dimensions:** Arch size, cross bite-arch breadth discrepancy showed high heritability Heritability: 27 % genetic and 73 % environmental. They also attributed genetic control to first molar mesiodistal relationship, overjet, overbite, tooth rotations. Study concluded that heredity played a significant role in determining the factors such as – width and length of dental arch, crowding, spacing of teeth and degree of overbite [53].

##### Genetic predisposition to external apical root resorption

Analysis of the genetic basis has been applied to EARR, Degree and severity of EARR associated orthodontic treatment is multifactorial, Genetic variation: 50%- 64% of the variation in EARR of the maxillary incisors [54]. Evidence of linkage of EARR affecting the maxillary central incisors indicates that the TNFRSF 11 A locus or another tightly linked gene is associated with EARR. Variation in interleukin 1 beta gene in orthodontically treated individuals: 15% of the variation in EARR. Persons in the orthodontically treated samples who were homozygous for IL-1B allele 1

were estimated to be 5.6 times more likely to experience EARR of 2mm or more than those who were heterozygous or homozygous [55, 56].

#### D. Oro-facial clefts [55-60]

Orofacial clefts: prevalence of 1 to 2 per 1000 live births. Two different phenotypes are: (1) cleft lip with or without cleft palate (CL/P) (2) cleft palate only (CPO) [57].

**I) Syndromic forms of CL/P:** Simple Mendelian inheritance patterns. More suitable for conventional genetic mapping strategies [53].

**Van der woude syndrome:** Autosomal dominant form of orofacial clefting. Prevalence of 1 per 34,000 live births, Gene localized by mapping to long arm of chromosome 1, 1q32-q41, Mutation in the interferon regulatory factor 6 (IRF6) gene, IRF6: medial edge epithelia of palatal shelves [54].

**CL/P ectodermal dysplasia syndrome 16:** A rare autosomal recessive trait, Gene mapped on chromosome 11, Mutations identified in the poliovirus receptor-like 1 (PVRL1) gene, PVRL1: expressed in the epithelia of the palatal shelves, nose and skin, as well as the dental ectoderm [57].

**X-linked cleft palate and ankyloglossia:** An X-linked recessive pattern on the long arm of chromosome X. Gene was identified as TBX22 which is expressed in the palatal shelves and tongue during development [57]. If a male inherits a mutated TBX22 it is highly likely that he will have the disease since this is the only copy of the TBX22 gene [58].

**II) genetics of nonsyndromic CL/P:** Genetically complex trait: Majority have no family history. Evaluation of inheritance patterns: not revealed a simple Mendelian mode of inheritance [59]. CL/P is a genetic trait; 40-fold risk for CL/P among 1st degree relatives of an affected individual, Greater concordance in MZ compared with DZ twins, Concordance rate in MZ is only 40% to 60%, suggesting the influence of environmental factors is also important [57, 60].

High association [16] between IRF6 variants, MSX1 and CL/P

- Genetic variation in IRF6 contributes to 12% of CL/P and triples the recurrence risk in some families.
- MSX1 is involved in both primary and secondary palatogenesis.
- MSX1 inactivation results in cleft palate and tooth agenesis.
- Mutations in MSX1 in 2% of patients with nonsyndromic clefting.

#### Conclusion

- Malocclusion with a “genetic cause” is generally thought to be less amenable to treatment than those with an “environmental cause”. The greater the genetic component, the worse the prognosis for a successful outcome by means of orthodontic intervention.
- In recent times, malocclusions of genetic origin (skeletal discrepancies) when detected in growing period, are being successfully treated using orthopedic and functional appliances, except in extreme cases where surgical intervention is required.
- When malocclusion is primarily of genetic origin, for example, severe mandibular prognathism then treatment will be palliative or surgical.
- Examination of parents and older siblings can give

information regarding the treatment need for a child and treatment can be begun at an early age.

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