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Genetics of the dentofacial variation in human malocclusion

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Abstract

Malocclusions affect individuals worldwide, resulting in compromised function and esthetics. Understanding the etiological factors contributing to the variation in dentofacial morphology associated with malocclusions is the key to develop novel treatment approaches. Advances in dentofacial phenotyping, which is the comprehensive characterization of hard and soft tissue variation in the craniofacial complex, together with the acquisition of large-scale genomic data have started to unravel genetic mechanisms underlying facial variation. Knowledge on the genetics of human malocclusion is limited even though results attained thus far are encouraging, with promising opportunities for future research. This review summarizes the most common dentofacial variations associated with malocclusions and reviews the current knowledge of the roles of genes in the development of malocclusions. Lastly, this review will describe ways to advance malocclusion research, following examples from the expanding fields of phenomics and genomic medicine, which aim to better patient outcomes.

Keywords

candidate genes; cephalometry; craniofacial; genetics; genomic medicine; genotype–phenotype correlation; phenomics

Introduction

Human malocclusion is a disarrangement of teeth and jaws that may lead to distorted facial appearance, limited masticatory function, increased risk for dental trauma, and compromise quality of life (1, 2).

The interactions of genetic and environmental factors may account for the variability in expression of malocclusion. The etiological complexity lies not only in unpredictable expression, but also in the wide spectrum of dentofacial variation present in affected individuals. This complexity explains in part why most treatment approaches for

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malocclusion are directed to the symptoms rather than to etiology. However, despite this complexity, the study of malocclusion etiology is fundamental to understanding the biology underlying craniofacial growth and dental relations. Understanding the biology will aid progress toward effective treatment, prevention, thereby decreasing the burden of this condition.

Dentofacial variation in human malocclusion

Given the abundance of hard and soft tissue information contained within lateral cephalometric images, most phenotypic characterization has been in two dimensions. Different analytical methods have been employed, including shape analyses, and principal components and cluster analyses. The following is a brief review of these studies.

Class II

Longitudinal studies indicated that Class II dentoskeletal characteristics can appear during the primary dentition (3). Although catch up growth can occur in some individuals, such discrepancies in general do not self-correct due to differences in growth magnitudes and directions between individuals with Class II and Class I malocclusions (4). The most recent study of Class II variation evaluated 309 Class II Caucasian adults and resulted in seven principal components explaining 81% of the variation. About half of this variation was depicted by vertical mandibular rotation, incisor angulations and the size of the ramus and body of the mandible (Fig. 1). Moreover, five distinct clusters representing the spectrum of Class II phenotypes were identified, thereby highlighting how variation of a limited number of principal components affect the craniofacial complex (5) (Fig. 2).

Class III

Similarly to the class II malocclusion, class III malocclusion features affect multiple craniofacial structures, appear early in development, worsen with age, and are present in most Class III individuals regardless of ethnicity (6, 7). A recent study in 292 Caucasian adults identified six principal components which accounted for 81% of the phenotypic variation recorded. About 54% of the variation was explained by the anterior–posterior (AP) position of the mandible compared to the cranial base, the size of the maxillomandibular horizontal discrepancy, and the lower incisor AP position (Fig. 3). Cluster analyses identified five distinct phenotypic subgroups (8) (Fig. 4) which were remarkably similar to those found by previous studies (9).

The studies described above have demonstrated the utility of data reduction methods applied to multidimensional data to capture meaningful categorical and quantitative malocclusion phenotypes for future studies of malocclusion etiology.

Current knowledge on the genetics of human malocclusion

Multiple data sources suggest that genetic factors contribute to malocclusion susceptibility. 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. Conversely, overbite (53%) and overjet (28%) have lower heritability, which suggested a higher susceptibility to environmental factors (10, 11).

Familial aggregation studies suggested that an autosomal dominant model with incomplete penetrance has the greatest validity for Class III pedigrees, including the royal Habsburg family (12) and others from Middle Eastern (13), South American (14, 15), and Eastern European descent (16). In contrast, polygenic inheritance and autosomal dominance models, with incomplete penetrance and variable expressivity, have been suggested for Class II subdivision 1 and 2, respectively (17–19).

The frequent presentation of malocclusion in patients with craniofacial birth defects also supports a strong genetic etiology. About 150 genes/loci are associated with craniofacial conditions presenting malocclusion (OMIM http://www.ncbi.nlm.nih.gov/omim). These genes represent molecular pathways to explore in malocclusion etiology.

Similarly, about 275 mouse models of malocclusion have been cataloged, with 235 genes/loci identified in the MGI database (http://www.informatics.jax.org/), contributing important information for the etiology of human malocclusions. Recently, mouse studies showed that long-range transcriptional enhancers regulate the expression of genes near and far during craniofacial development, resulting in subtle differences in craniofacial shape (20). Thus, these enhancers could be a mechanism to explain dentofacial variations underlying malocclusion.

Human genetic mapping approaches for identification of risk loci include linkage and association methods. Linkage analysis is applied to large families or affected sibling pairs and aims at detecting rare variants with large effects. Association analyses applied to case–control or case–parent triad samples are more powerful at detecting common variants with smaller effects (21). Currently, large-scale genomic data generation in the form of genomewide association scans (GWAS) and next-generation sequencing of full exomes and full genomes coupled with meta-analysis tools to identify common and rare genetic variants have significantly increased the scale and scope of complex trait mapping projects (22). However, despite this technological expansion, the identification of susceptibility genes for human malocclusion is just beginning.

Most malocclusion studies to date have focused in Class III malocclusion (Table 1). Although linkage and association findings thus far seem to cluster around chromosome 1 (loci 1p22-p36) and 12 (loci 12q13-q24), a study in 10 large Brazilian pedigrees failed to replicate linkage to chromosome 1 (23) underscoring the genetic heterogeneity of Class III malocclusions in different ethnicities.

Association studies have found positive correlations for mandibular prognathism and genes *EPB41*, *MATN1*, *SSX2IP*, and *PLXNA*, located within the 1p22-p36 locus. Also positive associations have been found for genes *COL2A1*, *MYO1H*, *TGFB3*, and *LTBP2* within the 12q13-q24 locus. Interestingly, variants in *Matn1* (1p35) were associated with mandibular prognathism and anterior cross bites in donkeys (24).

Recently, full exome sequencing of five siblings with maxillary hypoplasia identified a heterozygous missense mutation c.545C>T (p.Ser182Phe) in the gene *DUSP6* (12q21) (16). In a mouse model, *Dusp6* expression correlates with *Fgfrs* domains in the branchial arches and it is stimulated by *Fgf* signaling, a key morphogenetic pathway in the outgrowth of maxillary prominences. Mice null for *Dusp6* exhibit skeletal dwarfism and craniosynostosis (25). It is possible that variants within *DUSP6* could account for Class III malocclusion due to maxillary hypoplasia subsequent to premature fusion of maxillary sutures.

Genetic studies for Class II and Class I malocclusion are more rare. In four Colombian families, individuals with mandibular hypoplasia were homozygous for the rare allele on SNP rs1348322, within the *Noggin* gene (26). This gene is essential for mandibular formation in mice (27). For Class I malocclusion, a reported SNP rs6504340 within the *HOXB* cluster was associated with delayed tooth eruption and occlusion irregularities that required orthodontic therapy (28). Also, significant associations between more than 5 mm of crowding and genes *EDA* (rs3764746 and rs3795170), *XEDAR* (rs372024), and *BMP2* (rs1005464) were reported in Class I Chinese subjects (29).

While informative, the studies above are limited by modest sample sizes, unknown generalizability of results to populations of other ancestries, and restrictive traits that ignore the complex phenotypic spectrum of malocclusion. Nonetheless, these studies have converged to highlight that genes implicated in bone (*TGFB3*, *LTBP*, *IGF1*, *ENPP1*, *EVC*, and *EVC2*), cartilage development (*Matrilin-1* and *COL2A1*), muscle function (*MYO1H* and *DUSP6*) and tooth morphogenesis (*EDA*, *XEDAR*, and *BMP2*), may be putative candidates for jaw and tooth size discrepancies.

Phenotypic resources for malocclusion studies

To understand causal mechanisms of human disease, a large emphasis has been placed in the field of phenomics, the comprehensive study of the full set of possible phenotypes on an individual (39). Comprehensive phenotypes in combination with large-scale genomic data maximize the efficiency at detecting genotype–phenotype correlations of clinical importance. Consequently, phenomic initiatives and specimen repositories have been developed for various human conditions. The website dbGAP (http://www.ncbi.nlm.nih.gov/gap), for example, is a repository of phenotype–genotype correlation studies, which includes data on dental caries, oral clefts, and limited dental malocclusion variables. Also, the FaseBase consortium (https://www.facebase.org/) offers access to a central repository of 3D facial surface images and DNA resources for normative data. Also, dental phenomic initiatives for caries, periodontal disease, and dental morphology are underway (40). With respect to orthodontics, there is limited information available through orthodontic growth studies (e.g., http://www.aaoflegacycollection.org/aaof_home.html) since no biological specimens were collected during the periods over which serial lateral cephalometric radiographs were produced. To date, none of the existing databases contains comprehensive dentofacial data for malocclusions. Therefore, phenotype–genotype correlation studies of malocclusion are greatly needed as the knowledge gained from them will aid in our understanding of the mechanisms responsible for human malocclusions and craniofacial anomalies.

The orthodontic community constitutes a great resource for phenomic data and biological specimens because of access to large patient pools with wide ranges of malocclusions and the routine use of diagnostic records. Of these, lateral cephalometric radiographs and clinical photographs are the most abundant and thus are likely to be the primary data source for large-scale genotype–phenotype correlation projects. Although 2D photographs have dimensional errors due to variations in projection and patient positioning, 2D photographs can still be utilized for facial phenotyping through estimates of facial proportions, angles, and shape analyses.

3D facial surface imaging offers more accurate data, without errors due to projection distortion or patient positioning. This imaging method increases the scope of facial variation studies (41). It can be used to detect soft tissue features specific to craniofacial conditions such as cleft lip and palate (42). However, 3D facial surface images do not include dentoalveolar data, limiting its use in characterizing malocclusion phenotypes unless accompanied by cone-beam computed tomographic imaging (CBCT), or dentoalveolar data generated from scanned dental casts or intraoral scanners.

Despite the challenges of cost, storage, and analyses of deep phenotypic approaches, the advantages of generating malocclusion phenomic data will be numerous. For instance, comprehensive phenotyping may help predict individuals with adverse or favorable treatment responses, thus making practice more rewarding for clinicians. Also, comprehensive phenotyping could reduce problems with missing heritability in genetic studies, as will be discussed below.

Clinical relevance of phenotype–genotype studies of malocclusion

Candidate gene (42–44) and GWAS studies (45–47) of 3D facial soft tissue variation resulted in significant associations between genes *PRDM16*, *PAX3*, *TP63*, *C5orf50*, *Col17A1*, *HMGA2*, *AJUBA*, and *ADK*, and facial width and height. Also, genes and loci associated with oral clefts (*IRF6*, *8q24*, *SNAI1*, *MSX1*, *ABCA4-ARHGAP29*, and *MAFB*) were found to be associated with normal facial variation and facial features within the cleft phenotypic spectrum. Although studies above did not evaluate malocclusion directly, their results help prioritize genes for future projects given these gene's roles in craniofacial and dental development.

Unfortunately, similar to other complex traits such as human height (48, 49) and dental tooth eruption (47), the variants identified above have small size effects in facial variation (<10% of trait variability) and explain only a small proportion of the trait's heritability. This missing heritability has been attributed to poor genotyping coverage of low frequency (0.5–5%) and rare variants (<0.5%) and small effect sizes of common variants. Moreover, the presence of gene–gene and/or gene–environment interaction as mechanisms in the trait's etiology, partial or incomplete phenotypic approaches and the combined effect of genetic variants in non-coding regulatory regions (50, 51) could also result in missing heritability.

Given the etiological complexity of malocclusion, future studies could anticipate missing heritability problems. These could be minimized utilizing multivariate phenotypes which include both quantitative and dichotomous phenotypes simultaneously to capture more

variation information and thus increase analytical power (52). Also, malocclusion studies could benefit from a ‘comparison of extremes’ approach. This powerful method requires fewer individuals and can reduce genetic heterogeneity as at the extremes of the trait’s distribution, the expectation is to find fewer loci with greater effect sizes (49). To date, the comparison of extremes approach has been applied to individuals with long or short mandibular ramus, resulting in significant correlations for the growth hormone receptor (*GHR*) gene in Asian populations (53).

The benefits of identifying genotype–phenotype correlations rest on the potential to develop approaches to improve treatment outcomes. Carriers of risk alleles can be screened for prevention, and risk alleles can be targeted for pharmaceutical interventions that may increase the efficiency of orthopedic appliances in patients with maxillomandibular discrepancies. For example, 3D imaging to date has provided direct visualization of size and volume changes in the condyle produced by orthopedic effects (54). This knowledge coupled with the identification of molecular regulators of cell proliferation in the condylar cartilage following mandibular propulsion experiments (55) suggest exciting translational approaches to carry this research into the clinical setting. This includes the possibility of identifying detrimental genetic variation in patients with mandibular size deficiencies, particularly if these are found in molecular mediators of condylar cartilage proliferation. Moreover, studies may confirm that such variants lead to poor orthopedic force responses, and lastly, localized pharmaceutical interventions can be developed to target or compensate for the functional deficiencies caused by such variants.

Conclusions and future directions

Understanding the genetics underlying the dentofacial variation in patients with malocclusion is fundamental to develop preventive strategies and innovative treatment modalities that will benefit individual patients. The technology to acquire comprehensive phenotypic and genetic data to accomplish these discoveries is within our reach, and therefore, it is important for the orthodontic academic centers to establish large consortiums of images and data to speed up such discoveries.

Advances in this field will require researchers to move beyond the discovery of genetic variants conferring susceptibility to malocclusion into translational research to identify those with clinical utility. Moreover, methods to provide access to this information need to be developed almost simultaneously so that actionable genetic information gets rapidly implemented in the clinical setting (56), one of the constant challenges in genomic medicine to date (57).

Clinical relevance

As progress in comprehensive phenotyping and genomic data generation continue, clinically relevant phenotype–genotype correlations will be discovered, providing orthodontists with opportunities to use this information for clinical action. This article summarizes the current knowledge on these topics with the goal of making orthodontists aware of their future potential for making significant impacts in clinical practice.

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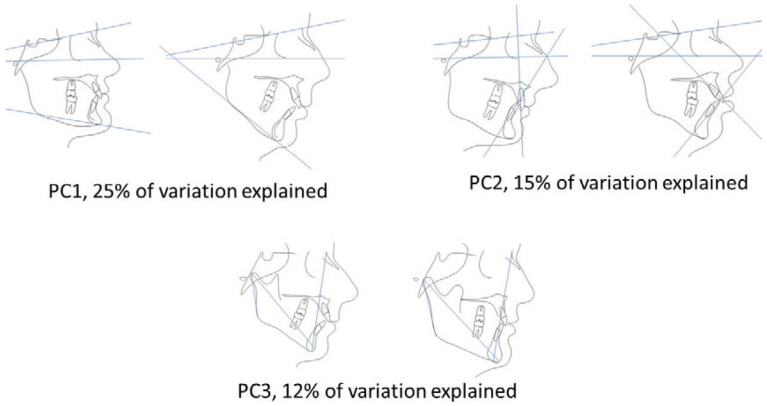
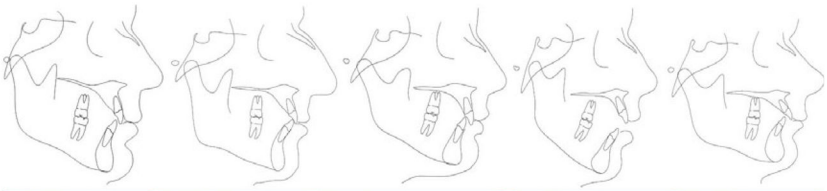


Fig. 1.

Individuals in the extreme opposite ends for the first three principal components explaining about 50% of the total variation in Class II malocclusion. PC1 refers to variation in the inclination of the mandibular plane angle. PC2 depicts maxillary incisor angulation. PC3 refers to the mandibular AP and vertical length and posterior facial height.



Cluster 1 features:	
Pro:	Mildly convex
CB:	Normal
Mx:	Slightly retrusive
Mn:	Retropositioned
Vert:	Normal
U1:	Uprighted
L1:	Normal
St:	Protrusive soft tissue chin

Cluster 2 features:	
Pro:	Moderately convex
CB:	Normal
Mx:	Normal
Mn:	Moderately retrusive flat Mn plane angle
Vert:	Normal
U1:	Uprighted
L1:	Protrusive
St:	Retrusive soft tssue chin

Cluster 3 features:	
Pro:	Moderately convex
CB:	Normal
Mx:	Slightly protrusive
Mn:	Retropositioned, smaller, shorter posterior facial height
Vert:	Shorter anterior face height
U1:	Uprighted
L1:	Normal
St:	Slightly redundant lips

Cluster 4 features:	
Pro:	Severely convex
CB:	Shorter with decreased saddle angle
Mx:	Slightly protrusive
Mn:	Retrusive, smaller decreased ramus height
Vert:	Increased anterior face height
U1:	Normal
L1:	Protrusive
St:	Interlabial gap

Cluster 5 features:	
Pro:	Mildly convex
CB:	Normal
Mx:	Slightly protrusive
Mn:	Mildly retrusive flat mandibular plane
Vert:	Shortene d anterior facial height
U1:	Proclined
L1:	Normal
St:	Redundant lips

Fig. 2.

Cluster analyses for Class II malocclusion showing dentofacial features of cluster centroids and their main features. Pro, profile; Cb, cranial base; Mx, maxilla; Md, mandible; Vert, vertical; U1, upper incisor; L1, lower incisor; St, soft tissue.

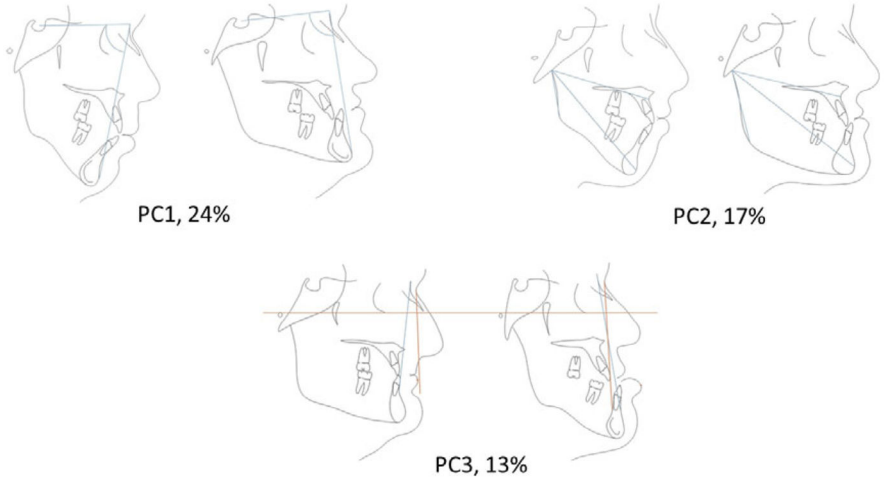


Fig. 3.

Individuals in the extreme opposite ends for the first three principal components explaining about 54% of the total variation in Class III malocclusion. PC1 shows the anteroposterior position of the mandible in relationship to the cranial base. PC2 depicts the maxillomandibular horizontal and vertical size discrepancies. PC3 refers to the lower incisor and lower lip variation.

Cluster 1 features		Cluster 2 features		Cluster 3 features		Cluster 4 features		Cluster 5 features	
Pro:	Concave	Pro:	Straight	Pro:	Slightly convex	Pro:	Concave	Pro:	Straight
CB:	Acute short ant. CB	CB:	Acute short ant. & post. CB	CB:	Normal angle long ant. & post. CB	CB:	Acute short ant. & post. CB	CB:	Normal angle slightly short ant. & post. CB
Mx:	Slightly retrusive	Mx:	Moderately retrusive	Mx:	Normal	Mx:	Normal	Mx:	Severly retrusive
Mn:	Slightly protrusive	Mn:	Slightly protrusive	Mn:	Protrusive, expressed vertically	Mn:	Severely protrusive	Mn:	Normal
Vert:	Slightly flat MP increased ant. facial height normal ramus	Vert:	Normal MP increased ant. facial height short ramus	Vert:	Increased ant. facial height long ramus	Vert:	Normal MP slightly short ramus	Vert:	Increased lower anterior face height short ramus
U1:	Normal	U1:	Protrusive	U1:	Normal	U1:	Protrusive	U1:	Normal
L1:	Retrusive	L1:	Normal	L1:	Protrusive	L1:	Retrusive	L1:	Slightly protrusive
St:	Retrusive lips and protrusive chin	St:	Retrusive lips	St:	Protrusive lower lip	St:	Retrusive upper lip protrusive lower lip	St:	Retrusive upper lip normal lower lip

Fig. 4.

Cluster analyses for Class III malocclusion showing dentofacial features of cluster centroids and their main features. Pro, profile; Cb, cranial base; Mx, maxilla; Md, mandible; Vert, vertical; U1, upper incisor; L1, lower incisor; St, soft tissue.

Table 1

Summary of mapping studies for Class III malocclusion

Region	Gene/loci	Method	Phenotype	Population	References
1p36		Linkage	Mand. prog.	40 Korean & 50 Japanese sibling pairs	(30)
1p35.3	EPB41	Association	Mand. prog.	211 cases vs. 224 controls Chinese	(31)
1p35.2	MATN1	Association	Mand. prog.	164 cases vs. 132 controls Koreans	(32)
1p22.3	SSX2IP	Association	Mand. prog.	240 cases vs. 360 controls	(33)
1p22.1		Linkage	Max def.	4 Hispanic families, Colombia	(34)
1q32.2	PLXNA2	Association	Mand. prog.	240 cases vs. 360 controls	(33)
3q26.2		Linkage	Max def.	4 Hispanic families, Colombia	(34)
4p16	EVC, EVC2	Linkage	Mand. Prog.	2 Large Chinese pedigrees	(35)
6q25		Linkage	Mand. Prog.	40 Korean & 50 Japanese sibling pairs	(30)
11q22		Linkage	Max def.	4 Hispanic families, Colombia	(34)
12q13.13	COL2A1	Linkage, Association	Max def., Mand. Prog.	4 Hispanic families, Colombia, 211 cases vs. 224 controls Chinese	(34, 36)
12q21.33	DUSP6	Causal/ etiologic	Max def.	1 Estonian family (5 siblings)	(16)
12q23	IGF1	Linkage	Max def.	4 Hispanic families, Colombia	(34)
12q24.11	MYO1H	Association	Mand. Prog.	44 cases vs. 36 controls Pittsburgh, USA, mostly Caucasian	(37)
14q24.3	TGFB3, LTBP2	Linkage	Mand. Prog.	1 Han Chinese large family	(38)
19p13.2		Linkage	Mand. Prog.	40 Korean & 50 Japanese sibling pairs	(30)