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Chapter · January 2014

DOI: 10.2174/97816080549161140100004

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CHAPTER 1

Family History and Genetics of Mandibular Prognathism

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Abstract: Often referred to as mandibular prognathism, the Class III phenotype can be a result of mandibular prognathism, maxillary hypoplasia (also termed maxillary retrognathism), or a combination of the two. These terms reflect the anatomical heterogeneity of Class III, as either or both jaws may be affected in sagittal length, or in position relative to each other. Familial aggregation studies suggest that familial environmental factors and/or heredity can play a substantial role in the etiology of Class III phenotype. This is supported by the findings that prevalence and anatomical characteristics of Class III malocclusions vary largely according to ethnic background, and may represent the effects of cultural differences at least to some degree. Current genetic inheritance patterns proposed for the Class III malocclusion include autosomal-recessive, autosomal-dominant, autosomal-dominant with incomplete penetrance, and a polygenic threshold model. Studies will be presented showing that the familial distribution of mandibular prognathism could be explained by the presence of a dominant major gene with an autosomal Mendelian mode of transmission that is affected by other genes and environmental factors leading to incomplete penetrance and variable expressivity. Finally, findings from both genetic linkage and association analyses in humans will be presented implicating variation in chromosomal locations with the Class III phenotype, including 1p35, 1p36. 4p16.1, 6q25, 12q13, 14q24.3-31.2 and 19p13.2 in Asian populations; and 1p22.1, 3q26.2, 7p22, 11q22, 12q13.13, and 12q23 in families from South American; and 12q24.11 in primarily a Caucasian sample residing in the United States.

Keywords: Mandibular prognathism, Class III malocclusion, Craniofacial genetics, Genetics, Genetic linkage.

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INTRODUCTION

Although all Angle occlusion types were initially based on the sagittal relationship of the permanent first molars, including the Class III malocclusion, it has generally been recognized that this dental relationship is often observed with a corresponding skeletal relationship as well. This is exemplified in Class III malocclusion cases, which characteristically result in the appearance of a prominent mandible. In its most severe form, the Class III malocclusion can be functionally and/or socially debilitating [1]. Affected individuals with a distinctive facial profile often seek orthodontic treatment, frequently combined with orthognathic surgery, to correct this malocclusion [2]. Often referred to as mandibular prognathism (taken from the Greek *pro* =forward and *gnathos* =jaw), skeletal aspects of this disorder can be a result of pure mandibular prognathism, maxillary hypoplasia/retrognathism, or a combination of the two. These phenotypic variations create a significant heterogeneity among Class III subjects and account for some of the difficulty encountered when scientifically investigating the condition [2].

Environmental factors that have been thought to influence Class III malocclusion as reviewed by El-Gheriani *et al.* [3] include enlarged tonsils [4], endocrine "imbalances"/hormonal disturbances [5, 6], posture, trauma and disease including premature loss of the first permanent molars [7]; nasal blockage [8], "congenital" anatomic defects [9], instrument deliveries [10], and trauma, infection or inflammation in the temporomandibular joint [11]. The roles these factors in Class III, however, are largely based on only a few observations. Clearly, different anatomical features of Class III can be classified into subgroups that appear to be influenced by ethnicity and may have a common environmental and/or genetic basis. While the relative contribution and interaction of genetic and/or environmental factors in the complex etiology of Class III is unclear, familial aggregation studies suggest that heredity plays a substantial role [2, 12, 13].

Prevalence of Class III Malocclusion

It has been demonstrated that both prevalence rates and anatomical characteristics of the Class III malocclusion vary largely according to ethnic background, with the

highest prevalence observed in East Asian populations such as Korean, Chinese, and Japanese (8%-40%) [1, 4, 14-17]. By comparison, African populations exhibit a reduced Class III prevalence rate (3%-8%) compared to Asians and Class III is relatively rare in individuals of European-American descent (0.48%-4%) [4, 8, 16, 17]. Additional studies in the United States of America (US) have suggested that the prevalence of Class III malocclusion in Caucasians can be as high as (5.5%-9.5%) [18-20], while the prevalence in US Native American Indian populations is relatively low (2.6%-3.1%) [21]. North American Eskimos in Labrador, Canada have a Class III prevalence of approximately 16% [22].

Populations in South America are often a mixture of Caucasian/European, African and Amerindian decent. While the percentage of children in Bogotá, Colombia with Class III has been reported as 3.7%, Brazilian children exhibited a frequency between (4%-10%) [23-25]. The prevalence of Class III in Europe appears to vary based largely on geography with 2.9% reported in Britain [26], 4% in Sweden [27], 5% in Finland [28], (1.4%-4.3%) in Germany [29, 30] and 8% in Scotland [31]. In areas of the Middle East, the prevalence of Class III also displays geographic tendencies with the highest prevalence in Egypt at 10.6% [32], followed by 7.8% in Iran [33] and 5.1% in Lebanon [34].

Influence of Ethnicity on Class III-Related Facial Dimensions

When comparing craniofacial features of soft and skeletal tissue between ethnicities, a number of features may appear accentuated or diminished. These ethnicity-related features are most likely determined or at least strongly influenced by genetic factors [2]. For example, Singh and colleagues demonstrated differences in both horizontal and vertical craniofacial dimensions when comparing Korean and American-Caucasian patients with Class III malocclusions. Korean subjects with Class III malocclusion had shorter anterior cranial base and more pronounced midfacial retrusion compared with European Americans [35]. Additional studies by Ngan *et al.* (1997) have reported on the ethnic differences between Chinese and Caucasians with Class III malocclusion. Chinese subjects exhibited a shorter anterior cranial base, a larger posterior cranial base, a smaller gonial angle, and an increased mandibular length compared to Caucasians [36].

Several differences have also been reported between Japanese and Caucasians. Japanese subjects with severe Class III malocclusion exhibit an increased mandibular ramus and total mandibular length when compared to Caucasians. Japanese females showed a statistically significant reduction in the anterior cranial base, a reduced midfacial component, and increased lower anterior face height associated with a more obtuse gonial angle when compared to Caucasians. In addition, more proclined upper incisors were also noted in the Japanese females [15]. Finally, differences in the cephalometric measurements between Saudi and Japanese adult females have also been reported in the literature. Saudi females had an increased anterior cranial base length, decreased posterior cranial base length, smaller cranial base angle, smaller anterior and posterior facial heights, downward tipping of the maxilla, retruded chin, less steep mandibular plane, increased joint angle, smaller ramus, body and total mandibular length, and less retroclined mandibular incisors when compared to their Japanese counterparts [37].

Gender and Class III-Related Facial Dimensions

It should not be surprising that gender differences exist during normal craniofacial growth that are influenced, at least in part, by variations in sex hormone concentrations during the pubertal growth spurt [38]. The ratio of estrogen and testosterone is responsible for skeletal sexual dimorphisms like greater bone mass in adult males [39], and characteristics of the human face [40]. A high testosterone/estrogen (T/E) ratio in puberty facilitates facial characteristics such as the lateral growth of mandible and chin, and the lengthening of the lower face [40, 41].

Although preliminary indications suggest that Class III skeletal disharmony can become apparent as early as in the deciduous dentition phase, few papers have reported on gender differences specifically related to the Class III malocclusion [42]. In one study, a greater maxillary and mandibular protrusion with reduced facial convexity has been described for Chinese girls than observed for boys [43]. In a Slovenian population sample with mixed dentition, larger than average values for anterior and posterior face height were observed in males than in females [44]. In addition, studies have shown a significant degree of sexual dimorphism in craniofacial features especially after the age of 13 in Caucasian subjects with Class III malocclusion, with female subjects presenting smaller linear dimensions

in the maxilla, mandible, and anterior facial heights than male subjects [45]. Miyajima and colleagues reported similar changes in Japanese females, with the retruded position of the maxilla maintained during growth, while the mandible became more protrusive [46].

Class III Anatomical Characteristics and Subphenotypes

Several studies have suggested the existence of multiple patterns or sub-phenotypes of the Class III malocclusion based on anatomical appearance. For example, Ellis and McNamara (1984) reported considerable variation among Class III malocclusion patients, where the most common combination of variables included a retrusive maxilla with protrusive incisors, a protrusive mandible with retrusive incisors, and a long lower facial height. Interestingly, they also found no significant gender differences [47]. Martone and colleagues have suggested the existence of three anatomical subgroupings of Class III in a study of craniofacial growth and head form including the brachycephalic, dolichocephalic and dinaric patterns [48]. In a cluster analysis of skull shapes among fifty British mandibular prognathism subjects, only 15% of them also presented with maxillary retrognathism, it was demonstrated that 58% of the subjects exhibited increased lower facial height, and five sub-grouping of Class III skull shapes could be defined [49]. Cluster analysis of 106 Korean patients with Class III malocclusion resulted in seven distinct clusters being identified [50]. Differences in the methods between these two cluster analyses make a clear comparison of the studies difficult.

Following along this same idea, with a view more towards genetic analysis, was a detailed phenotypic characterization of Class III malocclusions that resulted in five clusters representing distinct sub-phenotypes in a sample of 309 North Carolina subjects. Several ethnic groups were represented in the study, although 73% of the sample was Caucasian. The groupings of variables reflected anteroposterior and vertical dimensions rather than specific craniofacial structures, suggesting that different genes are involved in controlling dimension *vs.* structure. The five subgroupings or "*Prototype Clusters*" were described as follows: (1) prognathic mandible with long face, (2) maxillary deficiency with decreased vertical dimension (low angle), (3) maxillary deficiency with increased vertical dimension (high angle), (4) mild prognathic mandible with normal

vertical dimension, and (5) a combination of prognathic mandible and maxillary deficiency with normal vertical dimension [51].

Inheritance Models of the Class III Malocclusion

Although the relative contribution and interaction of genetic and environmental factors in the etiology of the Class III malocclusion is unclear, familial aggregation studies suggests that heredity plays a substantial role. The familial nature of mandibular prognathism was first reported by Strohmayer in 1937 as noted by Wolff *et al.* (1993) in their analysis of the pedigree of the Hapsburg family [52]. Chudley presented examples of the Habsburg jaw printed on postage stamps of Spain and wrote that autosomal recessive and multifactorial inheritance were considered as possibilities by some geneticists, because of the incomplete penetrance in association with extensive consanguinity in the "Royal" Family [53]. It is also possible that portraits of the Hapsburg Family may have enhanced the prominence of the lower jaw as a feature of royalty, thereby making unbiased ascertainment of the affected in the family potentially problematic. Investigations of less inbred groups have resulted in a variety of modes of inheritance being proposed, with monogenic influences in some families (usually autosomal dominant with incomplete penetrance and variable expressivity) and multifactorial (polygenic complex) influences in others [3, 5, 12, 13, 52, 54-58]. Although the X chromosome does play a role in some syndromes with mandibular prognathism, the Class III phenotype is not X-linked since the numbers of affected males and females are similar [59].

Genetic Analyses of the Class III Phenotype

With the broad range of phenotypic heterogeneity observed among Class III cases, it is not surprising that genetic linkage studies have implicated multiple genetic loci, located on a number of different chromosomes in this malocclusion [60-68]. In this complex disorder, it has been hypothesized that the effects of one or more genes are modified (diminished, masked, enhanced, *etc*…) by another gene and/or its gene product, thereby leading to variable gene expressivity, incomplete gene penetrance, and ultimately large phenotypic variations. Statistically, this phenomenon is termed "*genetic epistasis"* and it describes a departure from the theoretical concept that a single genetic locus will act "independent" of another genetic allele. In addition to epistasis, variations in the

incidence of Class III malocclusion by ethnicity may reflect a variation in the genes or gene sets contributing to the overall phenotype within a specific genetic background.

Genetics of Class III in Asians

Up until recently, the vast majority of Class III genetic research had been completed with Asian populations and has implicated genetic linkage to on multiple chromosomal regions including 1p35, 1p36, 4p16.1, 6q25, 12q13, 14q24.3 and 19p13.2 [60-64, 68] (Table **1A**). One of the most promising genetic regions connected to Class III malocclusion within this population appears to be on human chromosome 1. In a case-control genetic Linkage Disequilibrium (LD) association analysis of Korean individuals with mandibular prognathism, a haplotype of three single nucleotide polymorphisms (SNPs) within the Matrilin 1 (*MATN1) gene* (1p35) was identified as conferring an increased risk for mandibular prognathism (rs1149054 T>C, rs20566 G>A and rs1065755 C>T; $p<0.01$ and OR= 5.16) [61] In addition, the *MATN1* rs20566-AA genotype was shown to be protective against mandibular prognathism formation (OR = 0.16) while the rs1065755-TT genotype conferred an increased risk of mandibular prognathism (OR = 9.28) [61]. The *MATN1* gene encodes a cartilage matrix protein that belongs to the von Willebrand Factor type A (VWA) family of proteins and it appears to play a role in skeletal formation (reviewed in [69-71]). Since mandibular shape originates both from bone growth and/or surrounding muscle growth and function (reviewed in [72-74]), the *MATN1* gene is a reasonable gene candidate for Class III formation. At this time, however, there is no direct evidence that these particular SNPs are themselves causal, and may just be predictors of susceptibility to the phenotype. Thus, sequencing analysis of the *MATN1* gene in Asian Class III cases could be highly informative. It is also noteworthy that genetic variations in *MATN1* have been associated with osteochondrodysplasias (disorders of bone and cartilage development) and idiopathic scoliosis (which affects the musculosketal system) [75, 76]. Moreover, evidence for the role of *MATN1* in Class III malocclusion exists in a dental occlusion model in *Equus asinus*, the Zamorano-Leonés donkey [77]. In this model, Rodrigues *et al.,* identified a genetic variation within intron 7 (g503G > A) of the donkey *MATN1* gene that was significantly associated with donkeys exhibiting a prognatic lower jaw compared to the donkeys

with normal occlusion. Both the GA and AA genotypes are associated with a decreased risk of prognathism formation , supporting the possible role of *MATN1* variation with mandibular prognathism [77]. No equivalent variation to the donkey g503G>A variation has yet been identified in human.

In addition to these findings with the *MATN1* gene loci, studies in Asians have implicated several additional loci which may influence the Class III phenotype. For example, a case-control genetic linkage disequilibrium association analysis of chromosome 1p36 in a presumably Hong Kong Chinese population said to have "mandibular prognathism" found four SNPs located within the *Erythrocyte Membrane Protein Band 4.1 (EPB4.1)* gene to be significant [62]. The implication(s) of this finding remains to be determined given the known roles/functions of *EPB4.1,* which appear to be restricted largely to red blood cells. In a genome wide linkage analysis of mandibular prognathism in 40 Korean sibling pairs and 50 Japanese sibling pairs encompassing a total of 42 families, researchers identified linkage at three chromosomal locations: 1p36 (D1S234; maximum Z(lr) = 2.51, p=0.0012), 6q25 (D6S305; maximum Z(lr) = 2.23, p=0.025) and 19p13.2 (D19S884; maximum Z(lr) = 1.93, p=0.0089) [60]. Microsatellite marker D1S234 resides within an intron of the *Chloride intracellular channel 4, (CLIC4)* gene and near the *Runt-related transcription factor 3 (RUNX3)* gene on human chromosome 1. D6S305 resides witin an intron of the *Parkin RBR E3 Ubiquitin Protein Ligase (PARK2)* gene, and D19S884 resides within an intron of the *fibrillin 3 (FBN3)* gene. The potential significance of these gene loci in Class III remains to be determined. Multipoint linkage analysis of a genome wide scan with 6,090 single nucleotide polymorphisms (SNP) in two Chinese families found significant (highest LOD 3.308) linkage to chromosome 4p16.1 for mandibular prognathism [63]. Suggestive linkage (LOD 2.03) of mandibular prognathism to chromosomal region 14q24.3-31.2 has also been found in one Han Chinese family [64]. Finally, an association has been identified between mandibular prognathism and rs1793953, which is associated with the *Collagen, type II, alpha 1 (COL2A1)* gene [68]. This is particularly noteworthy since the *COL2A1* gene is located at 12q13, which is a chromosomal region that has also been found to be significiant for Class III maloclussion in a South American sample [65].

Table 1A: Studies Examining the Genetics of Class III Malocclusions within Asian Populations

Chromosomal Location	Type of Study	Number of Subjects Studies	Phenotype	Markers	Findings / Significance Level	Refs.
1p35	Case Control	164 Korean subjects with Mandibular Prognathism 132 Controls	MP= Mandibular Prognathism	rs1149054 (-158T/C); rs20566 (+7987G/A); rs1065755 (+8572C/T)	rs1149054 rs20566 rs1065755 alleles together had a pronounced risk effect for MP	[61]
1p36	Case Control	Hong Kong Chinese	MP	rs2249138 rs2254241 rs2788890 rs2788888	p=0.018 p=0.015 p=0.028 p=0.023	[62]
1p36	GWAS	40 Korean Sibling Pairs (SPs) 50 Japanese SPs 42 Families Total	MP	D1S234	Maximum Z(Ir)=2.51 P=0.0012	[60]
4p16.1	Genome Wide Linkage Scan (GWLS); 6,090 SNP markers; Illumina Linkage-12 DNA Analysis Kit (average spacing 0.58 cM)	Two Unrelated Chinese Han Families (from different provinces) each comprised of 4 generations; 42 total individuals 18 affected individuals	MP	rs726111 rs875864 rs7658616 rs875579	NPL=2.71 LOD=3.308; NPL=3.65 LOD=3.166; NPL=3.63 LOD=3.156; NPL=3.54 LOD=3.106	[63]
6q25	GWAS	40 Korean SPs 50 Japanese SPs 42 Families Total	MP	D6S305	Maximum Z(Ir)=2.23 P=0.025	[60]
12q13	Association	211 cases and 224 controls of Hong Kong Chinese Han ethnicity However, MP was not associated with haplotypes that included rs1793953	MP	rs1793953	p=0.025	[68]

Table 1A: contd…

Chromosomal Location	Type of Study	Number of subjects studies	Phenotype	Markers	Findings / Significance Level	Refs.
14q24.3	GWLS; 6,090 SNP markers; Illumina Linkage-12 DNA Analysis Kit (average spacing 0.58 cM)	1 Han Chinese Family; 11 Affected 10 unaffected	MP	between rs1468507 and rs7141857	NPL=11.341 (empirical p = 0.020); LOD= 2.032 (empirical p = 0.008)	[64]
19p13.2	GWAS	40 Korean SPs 50 Japanese SPs 42 Families Total	MP	D19S884	Maximum Z(Ir)=1.93 P=0.0089	[60]

SPs = Sibling Pairs; GWAS=Genome wide association study; GWLS=Genome wide linkage scan; *NPL = Nonparametric Linkage; **PL = parametric Linkage; ***LOD= logarithm (base 10) of the odds score for parametric analysis; ****Zlr for nonparametric analysis.

Genetics of Class III in South Americans

These findings for the Asian subjects are in contrast to a recent study of four Hispanic families primarily with maxillary hypoplasia that were recruited at the Universidad de Antiouqia in Medellin, Colombia, South America [65] (Table **1B**). For this study, researchers performed a genome wide scan followed by a statistical linkage analysis. In this analysis, 10 of 500 microsatellite markers found on 5 different chromosomal locations segregated in an autosomal-dominant manner with the Class III phenotype [65]. These 5 locations included 1p22.1-22.2 (D1S2865 and D1S435), 3q26.2 (D3S3041), 11q22.2-q22.3 (D11S1886 and D11S4206), 12q13.13 (D12S1613, D12S1583, D12S354 and D12S369), and 12q23 (D12S368) [65].

In a separate genome wide linkage scan of one large Hispanic family from Bogotá, Colombia, South America, researchers have identified genetic linkage on chromosome 7 [78]. Further analysis of additional Hispanic families from Bogotá along with 10 families from Brasilia, Brazil, all primarily with mandibular prognathism in the presence or absence of maxillary hypoplasia, has confirmed this linkage to the Class III phenotype on chromosome 7 [78]. In studies of South

American families, Turner *et al.* (2011) was unable to confirm genetic linkage on chromosome 11 in the regions of D11S1886 and D11S4206 when examining cases of Class III with mandibular prognathism in the presence and absence of maxillary hypoplasia [79]. Recently Cruz *et al.* (2011) studied the genetic linkage with 6 microsatellite markers (D1S234, D4S3038, D6S1689, D7S503, D10S1483, and D19S56) for Class III malocclusion. They showed that there was no evidence

Table 1B: Studies Examining the Genetics of Class III Malocclusions within South American Populations

Chromosomal Location	Type of Study	Number of Subjects Studies	Phenotype	Markers	Findings / Significance Level	Refs.
1p22.1-22.2	4 cM Genome wide microsatellite scan (GWMS); 546 markers	4 Families from Medellín, Colombia; (Dichotomous classification) 28 affected 29 unaffected	primarily maxillary deficiency	D1S2865 D1S435	ZLR=2.92 (PL) LOD=1.8554 ZLR=2.54 (NPL) LOD=1.6382	[65]
1p36.11	Microsatellite Study	42 individuals from 10 Families in Brazil		D1S234	No Linkage Identified	[66]
3q26.2	4 cM GWMS; 546 markers	4 Families from Medellin, Colombia; (Dichotomous classification) 28 affected 29 unaffected	primarily maxillary deficiency	D3S3041	ZLR=2.97 (NPL) LOD=1.9136	[65]
4p16.3	Microsatellite Study	42 individuals from 10 Families in Brazil		D4S3038	No Linkage Identified	[66]
4p16 region		32 Colombian families	MP and maxilla retrognathia		No association to Class III identified for *MSX1* located on chromosome 4p16.3-p16.1	[67]
6p21	Microsatellite Study	42 individuals from 10 Families in Brazil		D6S1689	No Linkage Identified	[66]
7p22	*Illumina*® *Infinium Human Linkage*-y; 6,090 SNPs;	40 Individuals in 1 Family from Bogotá, Colombia; 25 Affected	MP +/- maxillary hypoplasia	rs1044701 rs1299548 rs1882600	LOD =2.3 LOD = 1.52 LOD = 1.9	[78]

Table 1B: contd…

Chromosomal Location	Type of Study	Number of Subjects Studies	Phenotype	Markers	Findings / Significance Level	Refs.
7p22	SNP Study	156 individuals in 21 families from Bogotá, Colombia and 77 individuals in 14 Families from Brasilia, Brazil	Mandibular Prognathism +/-maxillary hypoplasia	rs1044701 rs1299548 rs1882600 rs1294611 rs9640034 rs9640038 rs11526212 rs7800782	evidence of linkage(PL) at rs1882600 (LOD=2.36); Exclusion of linkage (PL) in the marker rs1044701	[78]
7p21.2	Microsatellite Study	42 individuals from 10 Families in Brazil		D7S503	No Linkage Identified	[66]
10q26	Microsatellite Study	42 individuals from 10 Families in Brazil		D10S1483	No Linkage Identified	[66]
11q22.2-q22.3	4 cM GWMS; 546 markers	4 Families from Medellín, Colombia; (Dichotomous classification) 28 affected 29 unaffected	primarily maxillary deficiency	D11S1886 D11S4206	ZLR=3.03 (PL) LOD=1.9960; ZLR=2.90 (PL) LOD=1.8377	[65]
11q22.2-q22.3	4 SNP markers in regions of D11S1886 and D11S4206	21 families from Bogotá, Colombia and 10 Families from Brasilia, Brazil	MP +/- maxillary hypoplasia	rs666723 rs578169 rs12416856 rs1386719	No Linkage Identified	[79]
12q13.13	4 cM GWMS; 546 markers	4 Families from Medellin, Colombia; (Dichotomous classification) 28 affected 29 unaffected	primarily maxillary deficiency	D12S1613 D12S1583 D12S354 D12S369	ZLR=2.79 (PL) LOD=1.6971; ZLR=2.93 (PL) LOD= 1.8730; ZLR=2.91 (PL) LOD=1.8412; ZLR=2.91 (PL) LOD=1.8355	[65]
12q23	4 cM GWMS; 546 markers	4 Families from Medellin, Colombia; (Dichotomous classification) 28 affected 29 unaffected	primarily maxillary deficiency	D12S368	ZLR=2.70 (NPL) LOD=1.7820	[65]
19p13.1	Microsatellite Study	42 individuals from 10 Families in Brazil		D19S56	No Linkage Identified	[66]

for linkage of any of the 6 microsatellite markers and excluded 5 of the 6 markers evaluated [66]. These findings emphasize the importance to ultimately study genetic factors of each sub-phenotype of Class III independently, since the genetic factors that influence maxillary hypoplasia may differ dramatically from those leading only to true mandibular prognathism.

Genetics of Class III in Other Ethnic Groups

Most of the Class III studies cited have been genetic linkage studies in families or linkage disequilibrium association studies in unrelated individuals. Another study of the later type was recently performed at the University of Pittsburgh [80, 81]. In this study, 40-44 mandibular prognathic cases were matched based on race, age and gender to 36-40 Class I/orthognathic control subjects in an association analysis examining 33-36 single nucleotide polymorphisms (SNPs) within 8 to10 previously reported candidate gene loci, including 1p22.1, 1p22.2, 1p36, 3q26.2, 5p13-p12, 6q25, 11q22.2-q22.3, 12q23, 12q13.13, and 19p13.2 (Table **1C**). They identified a significant (p=0.02) association of the Class III malocclusion with the marker rs10850110 located upstream of the Myosin 1H gene (*MYO1H*) on chromosome 12q24.11 [80, 81]. Four additional candidate genes within this region of human chromosome 12q24.11 were also noted that may play a role in the Class III phenotype including *ACACB* (acetyl-CoA carboxylase beta), *FOXN4* (forkhead box N4), *KCTD10* (potassium channel tetramerisation domain containing 10), and *UBE3B* (ubiquitin protein ligase E3B) [81].

Myosins, in general, are actin-based, ATPase driven motor molecules. MYO1H, however, is an unconventional myosin (Class I type), which has a role in intracellular movements in contrast with the conventional Class II myosins. Myosin-1H interacts with membranous compartments to move them relative to actin fibers and is involved in such processes as cell motility, phagocytosis and vesicle transport.

MYO1H is expressed in the musculoskeletal-craniofacial tissues [80], and in a preliminary examination, Class II Orthognathic surgery patients (n=4) expressed higher levels of MYO1H mRNA in their Masseter muscle than Class III orthognathic patients (n=2). Among Class III surgical patients examined, the trend

of MYO1H mRNA expression was lowest in the single deep bite case examined and highest in the two Class III cases with normal bite. Overall, mRNA expression of MYO1H in Masseter muscle was ~0.4X of the levels observed in skeletal muscle of the limb [82]. Gene expression evaluation in masseter muscle from dentofacial deformity subjects undergoing orthoganathic surgery for skeleton-based malocclusions found a trend for increased MYO1H and MYO1C expression in class III malocclusion compared to class II malocclusion. There were significant correlations ($p < 0.05$) between MYO1C expression and fiber type percent occupancy in masseter muscle from subjects with normal and deep bite malocclusions. Significant correlations were also identified between MYO1C and MHC (myosin heavy chain) gene expression.The mechanism of how the *MYO1H* and *MYO1C* genes and their protein products influence the Class III phenotype, however, remains unknown. It has been postulated that altered glucose transport during condylar cartilage growth may be one of the cellular mechanisms that promotes mandibular prognathism, as well as development of open and deep bite skeletal malocclusions through masseter muscle fiber type differences [83].

It should be noted that the Pittsburgh group examined a small cohort size of 80 individuals including subjects with a variety of different ethnic backgrounds (26 Class I and 24 Class III cases of European descent, 6 Class I and 15 Class III cases of African descent and 3 Class I and 5 Class III cases were a combination of individuals of Hispanic, Asian and other descent) [81]. Since (1) the phenotypic expression of Class III can vary greatly between different ethnicities and may be influenced by a combination of genetics plus environmental factors, and (2) the Minor Allele Frequencies (MAFs) of the rs10850110 marker vary greatly between ethnicities (MAFs according to HapMap: 27% Caucasian, 1% African, 9% Chinese and 15% Japanese), it will remain to be determined how these findings will compare to future association studies.

Using whole exome sequencing techniques on the DNA from an Estonian family, scientists have recently uncovered a rare heterozygous missense mutation associated with Class III skeletal malocclusion in the Dual-Specificity Phosphatase 6 (*DUSP6*) gene (c.545C>T ; p.Ser182Phe; rs139318648). Affected individuals in this family were largely characterized as having a straight profile

with maxillary deficiency. This rare variant co-segregated with the disease and followed an autosomal-dominant pattern of inheritance with incomplete penetrance. The *DUSP6* gene encodes is a cytoplasmic dual-specificity phosphatase that acts as a negative regulator of the MAP kinases, ERK1/2. This protein is involved in the some fundamental signaling processes that occur at the early stages of skeletal development, and can be transcriptionally upregulated *via* the fibroblast growth factor (FGF)/FGF receptor signaling pathway [84].

Table 1C: Studies Examining the Genetics of Class III Malocclusions within North American and European Populations

Chromosomal Location	Type of Study	Number of Subjects Studies	Phenotype	Markers	Findings / Significance Level	Refs.
12q24.11	Case Control	44 Class III cases of mixed ethnicity 36 Class I controls Pittsburgh, Pennsylvania USA		33 SNPs spanning all candidate regions; (1p22.1, 1p22.2, 1p36, 3q26.2, 5p13-p12, 6q25, 11q22.2-q22.3, 12q23, 12q13.13, and 19p13.2)	*MYO1H* (rs10850110) p=-0.03	[80, 81]
12q23-24	whole-exome sequencing	five siblings from an Estonian family affected by Class III malocclusion	Straight profile with maxillary hypoplasia	rs139318648	*DUSP6 (c.545C>T ; p.Ser182Phe;*	[84]

In summary, there remains a great deal of work to be done to understand the genetic components of the Class III malocclusion. Studying the individual subgroupings of the Class III phenotype will be essential to define the genes with influence Class III heterogeneity. While linkage analysis within families will be valuable in defining ethnic contributions to the phenotype, large association analyses may help to better define genes, which influence the Class III phenotype independent of ethnicity. Clinically this reinforces the importance of a family history, including in regard to presence of, or treatment for, a “strong” lower jaw, “underbite” in lay term, or Class III malocclusion.

The patient who has a first degree relative (parent or full sibling) with a Class III malocclusion has up to a 50% likelihood of also developing a Class III malocclusion, although even in families with a clear multi-generation inheritance of Class III malocclusion, there can be unaffected "transmitting" member in which it "skipped a generation," termed non-penetrance in clinical genetics. The principle of variable expressivity is also illustrated in these families with their variation in the severity of the Class III malocclusion of affected members. These observations within families reinforce the understanding that even in autosomal dominant traits, other genetic and environmental factors may contribute to the variation in the phenotype (Fig. **1**) [85, 86].

DNA analysis in the future will likely determine the presence of genetic marker(s) present in the patient associated with the development of a Class III malocclusion. As the possible genetic factors that might be involved at this time appear likely to be several, the particular one(s) that are prognostic in a particular patient may depend on ethnic and family background. In addition, anatomical variation may contribute to Class III malocclusion. The most valuable contribution to clinical practice will be the next step. The study of how different patients respond based upon their genotypes to different treatments and the time of their utilization. These may or may not be the same genetic factors that influenced the development of the malocclusion [87, 88].

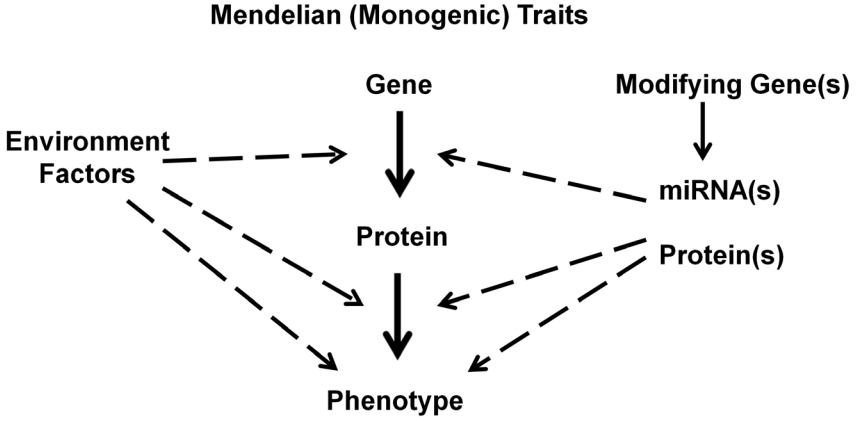

Figure 1: Genetic and environmental factors that contribute to the variation in the phenotype.

SUMMARY POINTS

- Mandibular prognathism (Class III malocclusion) can be a result of pure mandibular prognathism, maxillary hypoplasia/retrognathism, or a combination of the two.

- The prevalence of mandibular prognathism varies among different ethnic groups.

- Different anatomical features of Class III can be classified into subgroups that appear to be influenced by ethnicity and may have a common environmental and/or genetic basis.

- These phenotypic and ethnic variations indicate significant heterogeneity among Class III subjects and account for some of the difficulty encountered when scientifically investigating the condition.

- Familial aggregation and genetic linkage or association studies suggest that heredity plays a substantial role.

- It is probable that the mandibular prognathism in the Royal (Habsburg) Families of Europe was heavily influenced by inbreeding, autosomal recessive patterns, and other multifactorial inheritance possibilities. Analysis of less inbred groups usually indicate an autosomal dominant mode of inheritance with incomplete penetrance and variable expressivity) in some families and multifactorial (polygenic complex) influences in others.

- Genome wide scans indicate a number of genetic factors may be involved in different families, even within the same ethnic group.

ACKNOWLEDGEMENTS

Support for LAM and JKH from the NIH P20GM103538 Center for Biomedical Research Excellence II (COBRE II) Project, and for JKH by the E. Preston Hicks Endowed Chair at the University of Kentucky .

CONFLICT OF INTEREST

The authors confirm that this chapter contents have no conflict of interest.

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