Original Article

Influence of genotype and perioral musculature on maxillary and mandibular development

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ABSTRACT

Objectives: To determine whether there is an association between skeletal jaw position and perioral musculature, and if genotypes can predict skeletal growth.

Materials and Methods: A prospective study on 42 patients over 1 year was performed. The study included 22 females and 20 males with and average age of 28.5 years. Lip strength was compared to radiographic cephalometric measurements. Allelic and genotypic frequencies from polymorphisms rs678397 and rs1815739 in *ACTN3* and rs10850110 in *MYO1H* were compared to each variable. Chi–square and Fisher exact tests were used to determine if differences were statistically significant (alpha = 0.05).

Results: The data showed significant differences between rs678397 genotype and allele frequencies and SNA angle ($P = .01$; $P = .003$, respectively); between rs1815739 allele frequency and SNA angle ($P = .01$); between rs678397 allele frequency and ANB angle ($P = .049$); between rs678397 genotype and allele frequencies and lip strength in females ($P = .045$; $P = .02$); and between rs678397 allele frequency and overall lip strength ($P = .049$), after mean strength values used as cut off being customized by sex.

Conclusions: Polymorphisms in *ACTN3* are associated with weak lips and larger SNA and ANB angles. (*Angle Orthod.* 2022;92:628–634.)

KEY WORDS: Myosin; Actinin; Genetics; Muscle; Maxilla; Mandible

INTRODUCTION

Growth and development of the human craniofacial skeleton are complex processes that cannot be explained by a single determinant. The functional matrix hypothesis has been applied to the effects of masticatory muscles on hard tissue, including measuring bite force,[1] muscle cross-section sizes,[2] and electromyography activity.[3] Muscle fiber types have been associated with variation in skeletal facial morphology.[4,5] For example, patients with higher electromyography activity in the masticatory muscles tended to have a wider maxilla and a shorter lower anterior facial height than those with lower activity.[6,7] Others found a relationship between perioral force and tooth position.[8] When twins were studied, vertical facial measurements showed substantial genetic control (varying from 57% to 81% depending on the measurement), in addition to a relevant environmental contribution (18% to 42% depending on the measurement).[9] Genetic impact on malocclusion may also be indirect, through contributions to variation in tooth size discrepancies.[10]

Previous work suggested a role for *MYO1H* (myosin 1H) and *ACTN3* (α-actinin-3) in skeletal malocclusion. In *MYO1H*, the G allele of marker rs10850110 tended to be overrepresented in subjects with mandibular prognathism.[11–15] Overrepresentation of the G allele at marker rs10850110 has also been associated with more qualitative factors of the Class III phenotype,

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including Class III molar relationship and negative overjet.[12] ACTN3 in cranial muscles appears to be less responsive to activity.[16–18] The absence of α-actinin-3 resulted in smaller diameters of fast-contracting type II fibers in the masseter muscles.[19] Additionally, single nucleotide polymorphisms rs1815739 and rs678397 in *ACTN3* were found to be associated with Class II and deep bite malocclusions,[20] craniofacial asymmetry,[21] and self-reported bruxism.[22]

To further explore the value of these associations and genetic variants in the prediction of postnatal craniofacial growth, the aims of this study were: (1) to determine whether there is an association between skeletal jaw position and labial musculature function, and (2) to determine if genotype is associated with skeletal growth patterns in the maxilla or mandible.

MATERIALS AND METHODS

Forty-two patients that presented to the Orthodontic Department at the University of Pittsburgh, School of Dental Medicine in Pittsburgh, Pennsylvania, from January 2017 to January 2018, that were part of the Dental Registry and DNA Repository project were studied. Written consent was obtained from each subject before recruitment, and the study was approved by the University of Pittsburgh Institutional Review Board (IRB approval # 0606091). Subjects were required to be over 18 years of age, have had no previous orthodontic treatment, and have provided a DNA sample, a measurement of lip strength, and a lateral cephalogram.

Genomic DNA was extracted from saliva samples according to published protocols.[23] Three single nucleotide polymorphism (SNP) probes were selected in *MYO1H* and *ACTN3* based on associations confirmed in previous studies.[11,12] TaqMan chemistry[24] and end-point analysis to determine genotypes were used.

Lip strength was measured via the Iowa Oral Performance Instrument (IOPI), Model 2.3. Patients were asked to close their teeth together, and the bulb was placed inside each patient's right cheek, posterior and lateral to the corner of the mouth. They were then asked to press the bulb against their teeth by pursing their lips as hard as they could for two seconds. The peak pressure, corresponding with the magnitude of the strength of the lips,[25] was recorded in kilopascals (kPa). The maximum pressure was recorded three times for each subject with one minute of rest between each measurement. The highest value was used for analysis.

Maxillary and mandibular positions were determined through digital tracings of lateral cephalograms (Dolphin Imaging, Chatsworth, CA). Tracings were completed by one observer (SEH), and intra-examiner agreement was assessed by a second cephalometric tracing done by the same observer at the end of data collection. The mean variation in angle measurement was 0.42° (intraclass coefficient 0.8). Tracings were evaluated with the Steiner analysis. The ANB value was used to classify the subjects as Steiner Class I, Class II, or Class III. All values were compared with their respective norms used for Whites.

Table 1. Demographics

	White	Black	Asian	Total
Male	14	3	5	20
Female	11	5	4	22
Total	25	8	9	42

The SNA norm was set at 82°. Those values equal to or greater indicated a tendency toward a protrusive maxilla, and those less, a tendency toward a retrusive maxilla. The SNB norm was set at 80.9°. Values equal to or greater were considered to have a protrusive mandible tendency and those less were considered to have a retrusive mandible tendency. The ANB norm was set at 1.6°. Values above or equal to 1.6° indicated a Class II tendency, and values that were less indicated a Class III tendency.

Lip strength was compared to continuous skeletal measurements (SNA angle, SNB angle, and ANB angle) using a simple linear regression. Chi-square or Fisher exact tests were used to determine associations between genetic markers rs678397, rs1815739, and rs10850110, and Steiner classification, SNA angle, SNB angle, ANB angle, sex, ethnicity, and lip strength. The number of copies of each allele and each genotype per marker were compared for each variable. A P value of less than .05 was considered statistically significant.

RESULTS

The distribution of sex and ethnicity is shown in Table 1. For the original 42 patients in the sample, the average age was 28.5 years (range: 18 to 65 years; standard deviation: 9.63 years); 22 were female and 20 were male; and 25 were White, eight Black, and nine Asian. No differences were found in the distribution of genotypes by sex and ethnicity.

There was a significant negative correlation between SNA angle and lip strength ($P = .03$; Figure 1). There was no significant association between SNB or ANB and lip strength. Steiner class comparisons are summarized in Table 2.

There were significant differences in genotypic and allelic frequencies for the *ACTN3* markers in patients that had a more protrusive maxilla compared to those with a more retrusive maxilla. Genotypic and allelic variations for rs678397 were significantly different

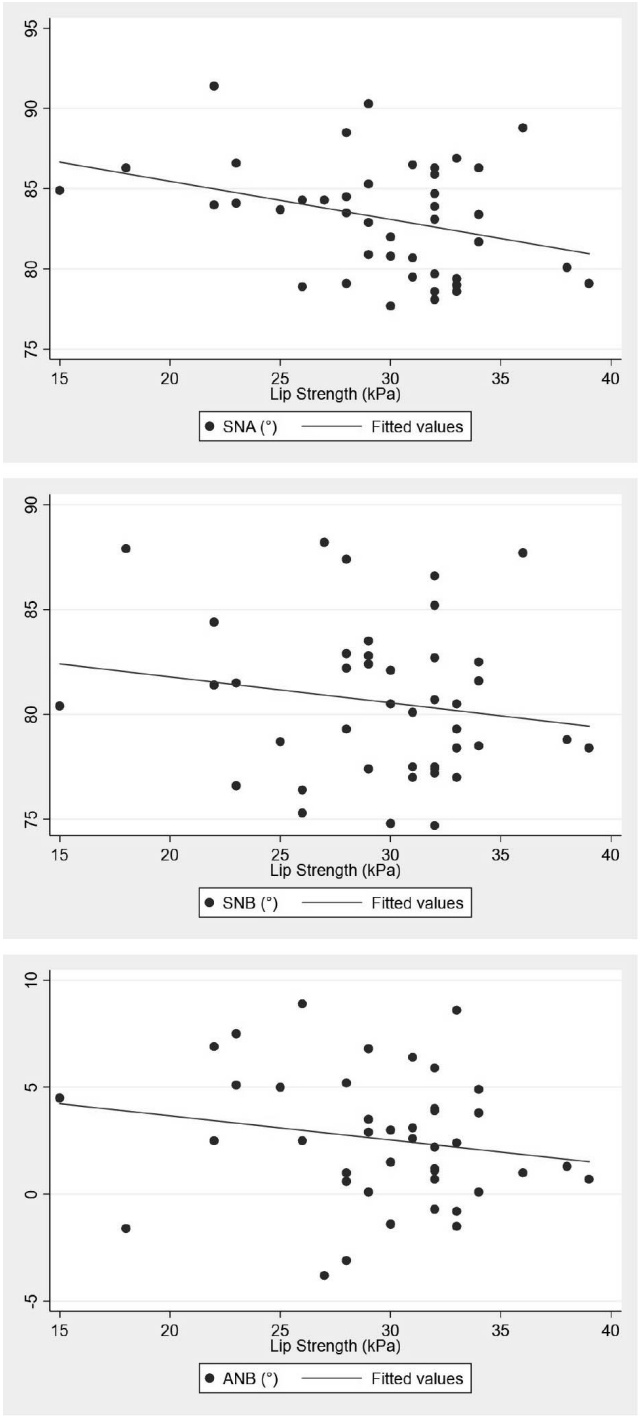

Figure 1. Summary results of regression analysis. SNA vs lip strength ($r^2 = 0.69$; $P = .03$), SNB vs lip strength ($P = .3$), and ANB vs lip strength ($P = .25$).

between the groups ($P = .01$; $P = .003$, respectively). More subjects with a high SNA angle had a homozygous CC genotype, while subjects with a low SNA angle tended to have heterozygous or homozygous TT genotypes. The presence of a C allele at rs678397 increased the patient's risk of having a high SNA by a factor of 4.5. Allelic variation of *ACTN3* rs1815739 between the two groups was found to be significantly different ($P = .01$), and the presence of a T allele lowered the risk of having a high SNA angle by 0.31 times (Table 3).

Table 2. Relationship Between genotype and Steiner's Classifications Based on ANB Values

Gene	Genotype	Class I, n	Class II, n	Class III, n
ACTN3	rs678397 (C/T)			
	CC	3	8	1
	CT	10	4	2
	TT	2	2	3
	P value	reference	.09	.19
	C allele	16	20	4
	T allele	14	8	8
	P value	reference	.16	.24
	rs1815739 (T/C)	2	2	3
	TT			
	TC	9	4	2
	CC	7	9	2
	P value	reference	.38	.2
	T allele	13	8	8
	C allele	23	22	6
	P value	reference	.41	.18
MYO1H	rs10850110 (A/G)	0	1	1
	AA			
	AG	4	3	0
	GG	13	11	4
	P value	reference	.55	.1
	A allele	4	5	2
	G allele	30	25	8
	P value	reference	.57	.5

There was a significant overrepresentation of the C allele in *ACTN3* rs678397 ($P = .049$) in patients with a higher ANB angle (Table 3).

The mean lip strength of all subjects in this study was 30 kPa. Subjects with a lip strength greater than or equal to 30 kPa were considered "strong" and subjects with a lip strength less than 30 kPa were considered "weak." The average lip strength for females was 28 kPa versus an average lip strength of 31 kPa for males. For *ACTN3* rs678397, a significant difference was found between genotype and lip strength in females ($P = .04$), as well as between allelic frequency and lip strength in females ($P = .02$). Females with a C allele were 0.14 times more likely to have strong lips than weak lips. Half of females with strong lips had T alleles, while only 12.5% of those with weak lips had T alleles at *ACTN3* rs678397 (Table 4).

DISCUSSION

The results of this study supported findings from previous research regarding select polymorphisms and their associations with jaw development.[11,12,20] In the current study, *ACTN3* polymorphisms rs678397 and rs1815739 were associated with larger SNA and ANB

Table 3. Relationship Between Genotype and Cephalometric Measurements

Gene	Genotype	SNA≥82, N	SNA<82, N	SNB≥80.9, N	SNB<80.9, N	ANB≥1.6, N	ANB<1.6, N
ACTN3	rs678397 (C/T)						
	CC	11	1	6	6	10	2
	CT	8	8	6	10	8	8
	TT	2	5	3	4	3	4
	P value	.01		.16		.12	
	C allele	30	10	18	22	28	12
	T allele	12	18	12	18	14	16
	P value	.003		.67		.05	
	rs1815739 (T/C)						
	TT	2	5	3	4	3	4
	TC	9	6	6	9	7	8
	CC	14	4	9	9	13	5
	P value	.07		.84		.22	
	T allele	13	16	12	17	13	16
	C allele	37	14	24	27	33	18
	P value	.01		.62		.08	
MYO1H	rs10850110 (A/G)						
	AA	1	1	0	2	1	1
	AG	4	3	3	4	4	3
	GG	18	10	13	15	18	10
	P value	.88		.44		.88	
	A allele	6	5	3	8	6	5
	G allele	40	23	29	34	40	23
	P value	.57		.25		.57	

angles, and rs678397 was almost significantly associated with a Class II skeletal phenotype. *MYO1H* SNP at rs10850110 was associated with a Class III skeletal phenotype, although it was not associated with a protrusive mandible. The hypothesis that jaw position would be associated with lip strength was supported by the present findings for the maxilla. Weak lips were significantly associated with a higher SNA angle, or a more protrusive maxilla. Additionally, in females, weak lips were associated with an overrepresentation of the

Table 4. Relationship Between Genotype and Lip Strength

Gene	Genotype	Strength ≥ 30 kPa, n (%)	Strength < 30 kPa, n (%)	Female ≥ 28 kPa, n (%)	Female < 28 kPa, n (%)	Male ≥ 31 kPa, n (%)	Male < 31 kPa, n (%)	Strong Lips, n (%)	Weak Lips, n (%)
ACTN3	rs678397 (C/T)								
	CC	5 (25)	7 (46.7)	2 (22.2)	6 (75)	3 (25)	1 (16.7)	5 (23.8)	7 (50)
	CT	9 (45)	7 (46.7)	5 (55.6)	2 (25)	5 (41.7)	4 (66.7)	10 (47.6)	6 (42.9)
	TT	6 (30)	1 (6.7)	2 (22.2)	0 (0)	4 (33.3)	1 (16.7)	6 (28.6)	1 (7.1)
	P value	.17		.04		.6		.049	
	C allele	19 (47.5)	21 (70)	9 (50)	14 (87.5)	11 (45.8)	6 (50)	20 (47.6)	20 (71.4)
	T allele	21 (52.5)	9 (30)	9 (50)	2 (12.5)	13 (54.2)	6 (50)	22 (52.4)	8 (28.6)
	P value	.06		.02		.81		.49	
	rs1815739 (T/C)								
	TT	6 (26.1)	1 (5.9)	3 (27.3)	0 (0)	3 (23.1)	1 (12.5)	6 (25)	1 (6.3)
	TC	7 (30.4)	8 (47.1)	3 (23.0)	2 (25)	5 (38.5)	5 (62.5)	8 (33.3)	7 (43.8)
	CC	10 (43.5)	8 (47.1)	5 (45.5)	6 (75)	5 (38.5)	2 (25)	10 (41.7)	8 (50)
	P value	.22		.13		.56		.31	
	T allele	19 (41.3)	10 (29.4)	9 (40.9)	2 (12.5)	11 (42.3)	7 (43.8)	20 (41.7)	9 (28.1)
	C allele	27 (58.7)	24 (70.6)	13 (59.1)	14 (87.5)	15 (57.7)	9 (56.3)	28 (58.3)	23 (71.9)
	P value	.27		.06		1.0		.21	
MYO1H	rs10850110(A/G)								
	AA	2 (9.5)	0 (0)	2 (20)	0 (0)	0 (0)	0 (0)	2 (9.5)	0 (0)
	AG	4 (19)	3 (18.8)	1 (10)	2 (25)	3 (27.3)	1 (12.5)	4 (19)	3 (18.8)
	GG	15 (71.4)	13 (81.3)	7 (70)	6 (75)	8 (72.7)	7 (87.5)	15 (71.4)	13 (81.3)
	P value	.44		.33		.44		.44	
	A allele	8 (19)	3 (9.4)	5 (25)	2 (12.5)	3 (13.6)	1 (6.3)	8 (19)	3 (9.4)
	G allele	34 (81)	29 (90.6)	15 (75)	14 (87.5)	19 (86.4)	15 (93.8)	34 (81)	29 (90.6)
	P value	.25		.34		.46		.25	

C allele in rs678397 ($P = .02$) and rs1815739 ($P = .06$) (Table 4). Although lip strength was not significantly associated with SNB angle, there was a trend toward a negative association.

The results suggested that an overrepresentation of C alleles for markers in gene *ACTN3* may be related to weaker lips, as well as more protrusive maxillae, larger jaw discrepancies, and a Class II skeletal relationship. It was found that a marker in gene *MYO1H* may be related to a Class III skeletal relationship. Therefore, it is possible that genotype and soft tissue have an effect on skeletal development of the jaws.

An underrepresentation of T alleles for rs1815739 in deep bite patients, and an overrepresentation in Class II patients, have been established by prior research.[20] In the current study, parameters of the vertical dimension of the occlusion were not examined and an association between a Class II phenotype due to a protrusive maxilla and an overrepresentation of C alleles was found. Although Zebrick et al.[20] found that skeletal Class II malocclusion was associated with the homozygous TT genotype, and the results seem contradictory, there were notable differences between the populations in that study and the present one.

In the study by Zebrick et al.,[20] subjects were organized into three groups of skeletal malocclusion. In the current study, skeletal malocclusion was considered, and patients were grouped into high and low measurements for SNA, SNB, and ANB. The patients in the study by Zebrick et al. were Class II and Class III orthognathic cases from the University of Lille in France but the control group was from Pittsburgh, Pennsylvania.[20] All of the patients were of European descent. In the present study, the necessity for orthognathic surgery was not examined, so there was most likely a mixture of orthognathic and nonorthognathic cases, and patient ethnicity was not uniform. Also, the entire sample consisted of patients presenting for treatment at the University of Pittsburgh. Allele frequencies between the populations in Pittsburgh, Pennsylvania, may be different than the population in France.

It is also possible that the discrepancy was due to the type of Class II malocclusion present. A Class II skeletal discrepancy can be due to a protrusive maxilla, a retrusive mandible, or a combination of the two. There are also two divisions of Class II patients. Class II division 1 patients often present with flared incisors and significant overjet, while Class II division 2 patients tend to have retroclined upper incisors and mild overjet. The specific type of Class II malocclusion that was present was not recorded, and vertical measurements were not measured. The number of patients with a protrusive maxilla or the number of Class II division 1 patients in this study may have been greater than the number of patients with a retrusive mandible or Class II division 2 patients. It is possible that only Class II relationships with a protrusive maxilla, a division 1 malocclusion, or an open bite may have been associated with the C allele, while those with a retrusive mandible, division 2 malocclusion, or deep bite were not.

Although the CC genotype has been associated with faster and more powerful muscle contractions, in this study, the C allele was associated with weaker lip strength. Masseter muscles are used for mastication and need to provide, quick, strong movements to operate effectively. The orbicularis oris, however, does not provide the same function. The orbicularis oris is a muscle of facial expression, primarily used in speech. Regulation of lip movement involves a coordinated, sustained muscle contraction[26] that may not necessarily be influenced by an absence of α–actinin–3. In this case, greater amounts of α–actinin–2 may be preferred for endurance. It is also possible that, although fast twitch fiber diameter may be decreased, the number of fibers may be increased.[20]

The relationship between lip strength and position of the maxilla was more significant in females. Previously, the effect of *ACTN3* on muscle performance appeared to be influenced by the sex of the subject. No female sprint athletes had a homozygous TT genotype that would cause α–actinin–3 deficiency, and 57% were heterozygous. Conversely, 29% of female endurance athletes had a homozygous CC genotype. In males, this difference was not found. It was suggested that the influence of α–actinin–3 on muscle power may be lower in males because the androgen hormone response to strength training may contribute to performance.[27]

The relationship between the GG genotype at rs10850110 and a Class III skeletal phenotype has also been suggested by previous studies,[11,12] although this association was not detected in the current study. Myosin 1 is a motor protein that produces mechanical force,[12] and the G allele marker at rs10850110 is associated with mandibular prognathism[10–12] as well as the Class III phenotype.[12] Because myosins are involved in cell motility, phagocytosis, and vesicle transport,[4] it is possible that jaw development may not be strictly dependent on skeletal growth but that muscular force may be involved.

Lip strength was not significantly associated with rs10850110. Because of the association previously discovered between Myosin 1 and mandibular prognathism,[11] it is possible that sample size may not have been large enough to detect differences, or that a muscle other than orbicularis oris may have had more of an effect on the mandible. A method for testing the strength of muscles closer to the lower lip and chin,

such as the mentalis muscle, may provide a different result.

The associations discovered in this study between genotype, lip strength, and skeletal development supported the ideas expressed by Moss in the functional matrix hypothesis of 1962. Moss understood that genetic factors played a role in skeletal growth, but proposed that growth was also linked to the underlying muscular matrix.[28] The sustained forces of facial expression and speech from the orbicularis oris may contribute to the position of the maxilla. A stronger orbicularis oris may place pressure on the maxilla, limiting the amount of forward growth possible, and weaker perioral musculature may allow the maxilla to continue to grow forward with less resistance. It could also be suggested that the maxilla influences the strength of the lip, and a more protrusive maxilla results in weaker labial musculature.

If growth of the maxilla is associated with strength of the orbicularis oris, there may be an opportunity to alter its position before patients have completed growth. Normally, altering anteroposterior growth of the jaws is difficult, depending on the age of the patient and how much skeletal growth remains. If genotypic information from a saliva sample allows prediction of skeletal growth tendencies, intervention to modify skeletal growth would be possible.

In the future, knowing if a patient is genetically predisposed to skeletal discrepancies in jaw position may result in improved diagnosis and treatment planning. Patients whose genotypes are associated with a retrusive maxilla may benefit from the use of myofunctional appliances to resist lip pressure. Patients susceptible to a protrusive maxilla might be able to reduce their risk through lip strength exercises. The IOPI device used to measure lip strength in this study can be used for exercise therapy and has been used to improve orofacial muscle strength in dysphagia patients.[29] If jaw position can be predicted, risk of unfavorable growth may be reduced, thus decreasing the number of patients requiring retreatment.

One potential limitation of the study was the relatively small sample size and the inclusion of individuals with distinct geographic origins (Asian, Black, and White), which raises the possibility of population stratification. Future studies with larger samples should be designed to account for population substructure. This study was novel, however, for including an assessment of muscle strength, which was associated with *ACTN3*. Individuals were grouped according to cephalometric measurements using the same norm values. The sample size did not permit further comparisons by sex or ethnicity between groups divided using cephalometric measurements, and larger samples may allow the detection of differences based on those characteristics. When patients were divided into two groups based on the cephalometric norm, patients who were within the normal range were included in both groups. Nevertheless, the two groups showed significant differences in genotypic and allelic frequencies for SNA and ANB angles, which suggested that using these definitions as phenotypes may be useful in future genetic analyses. However, when the patients were divided into three groups (Class I, II, and III), there was no statistically significant difference among the groups in genotypic and allelic frequencies, which may have been an indication that larger samples are needed to allow for a demonstration of possible existing differences.

Further studies should be conducted to confirm the association between maxillary position and lip strength. In addition, future work should be focused on determining the effect of other muscles on the position of the mandible. Future research will require larger sample sizes including more Class III phenotypes with protrusive mandibles. Other analyses besides the Steiner analysis should be used to classify jaw position and jaw discrepancy. Finally, CBCT analysis would allow a comparison of muscle volume in addition to other skeletal measurements.

CONCLUSIONS

- Phenotypic definition including soft tissue assessment may provide new opportunities for identifying genetic associations.
- *ACTN3* polymorphisms rs678397 and rs1815739 were associated with larger SNA and ANB angles.
- The relationship between lip strength and position of the maxilla was more significant in females.

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Author Contributions

SAH: data curation and original draft, JFAP: conceptualization, supervision, and review of manuscript ARV: conceptualization, data curation, data analysis, statistics, review, overall supervision, and review of the manuscript, JMB: data, curation, review and editing of the manuscript.

REFERENCES

1. Oyen OJ, Tsay TP, Riachi R. In vivo testing of bite force and bone strain in the African green monkey. In: Dixon AD, Sarnat BG, Hoyte DAN, eds. *Fundamentals of Bone Growth:*

Methodology and Applications. Boca Raton, FL, USA: CRC Press; 1991:523–535.
2. Weijs WA, Hillen B. Relationship between masticatory muscle cross-section and skull shape. *J Dent Res*. 1984; 63:1154–1157.
3. Miller A, Vargervik K. Assessment of facial masticatory muscles in hemifacial microsomia. In: Cargervik HEPK, Chierici G, eds. *Treatment of hemifacial microsomia*. New York, NY, USA: Alan R. Liss; 1983:113–132.
4. Rowlerson A, Raoul G, Daniel Y, et al. Fiber-type differences in masseter muscle associated with different facial morphologies. *Am J Orthod Dentofac Orthoped*. 2005;127:37–46.
5. Sciote JJ, Raoul G, Ferri J, Close J, Horton MJ, Rowlerson A. Masseter function and skeletal malocclusion. *Rev Stomatol Chir Maxillofac Chir Oral*. 2013;114:79–85.
6. Ingervall B, Thilander B. Relation between facial morphology and activity of the masticatory muscles. *J Oral Rehab*. 1974; 1:131–147.
7. Miralles R, Manns A, Pavic J, Palomino H. EMG, bite force and its relation to craniofacial characteristics. *IRCS J Med Sci*. 1981;9:836–837.
8. Posen AL. The influence of maximum perioral and tongue force on the incisor teeth. *Angle Orthod*. 1972;42:285–309.
9. Hersberger-Zurfluh MA, Papageorgiou SN, Motro M, Kantarci A, Will LA, Eliades T. Genetic and environmental components of vertical growth in mono- and dizygotic twins up to 15-18 years of age. *Angle Orthod*. 2021;91:384–390.
10. Marañon-Vásquez GA, Vieira AR, Santos LV, et al. FGF10 and FGF13 genetic variation and tooth-size discrepancies. *Angle Orthod*. 2021;91:356–362.
11. Tassopoulou-Fishell M, Deeley K, Harvey EM, Sciote J, Vieira AR. Genetic variation in Myosin 1H contributes to mandibular prognathism. *Am J Orthod Dentofac Orthoped*. 2012;141:51–59.
12. Cruz CV, Mattos CT, Maia JC, et al. Genetic polymorphisms underlying the skeletal Class III phenotype. *Am J Orthod Dentofac Orthop*. 2017;151:700–707.
13. Cunha A, Nelson-Filho P, Marañón-Vásquez GA, et al. Genetic variants in ACTN3 and MYO1H are associated with sagittal and vertical craniofacial skeletal Patterns. *Arch Oral Biol*. 2019;97:85–90.
14. Dalaie K, Yassaee VR, Behnaz M, Yazdanian M, Jafari F, Farimani RM. Relationship of the rs10850110 and rs11611277 polymorphisms of the MYO1H gene with nonsyndromic mandibular prognathism in the Iranian population. *Dent Med Probl*. 2020;57:433–440.
15. Atteeri A, Neela PK, Mamillapalli PK, et al. Analysis of MYO1H gene polymorphism in skeletal class-III malocclusion due to mandibular prognathism. *Glob Med Genet*. 2021; 8:156–161.
16. Miyamoto K, Ishizuka Y, Tanne K. Changes in masseter muscle activity during orthodontic treatment evaluated by a 24-hour EMG system. *Angle Orthod*. 1996;66:223–228.
17. Mew JRC. The postural basis of malocclusion: a philosophical overview. *Am J Orthod Dentofac Orthop*. 2004;126:729–738.
18. Ahmetov IL, Vinogradova OL, Williams AG. Gene polymorphisms and fiber-type composition of human skeletal muscle. *Int J Sport Nutrition Exercise Metabol*. 2012;22: 292–303.
19. North KN, Yang N, Wattanasirichaigoon D, Mills M, Easteal S, Beggs AH. A common nonsense mutation results in alpha-actinin-3 deficiency in the general population. *Nat Genet*. 1992;21:353–354.
20. Zebrick B, Teeramongkolgul T, Nicot R, et al. *ACTN3* R577X genotypes associate with Class II and deepbite malocclusions. *Am J Orthod Dentofac Orthop*. 2014;146:603–611.
21. Nicot R, Chung K, Vieira AR, Raoul G, Ferri J, Sciote JJ. Condyle modeling stability, craniofacial asymmetry and ACTN3 genotypes: contribution to TMD prevalence in a cohort of craniofacial deformities. *PLoS One*. 2020;15: e0236425.
22. Nicot R, Raoul G, Vieira AR, Ferri J, Sciote JJ. ACTN3 genotype influences masseter muscle characteristics and self-reported bruxism. *Oral Dis.* 2021. Doi: 10.111/odi.14075
23. Trevilatto PC, Line SR. Use of buccal epithelial cells for PCR amplification of large DNA fragments. *J Forensic Odontostomatol*. 2000;18:6–9.
24. Ranade K, Chang MS, Ting CT, et al. High-throughput genotyping with single nucleotide polymorphisms. *Genome Res*. 2001;11:1262–1268.
25. IOPI Medical. *Iowa Oral Performance Instrument User Manual*. Model 2.3. Redmond, WA, USA: IOPI Medical, LLC; 2013.
26. Burrows AM, Parr LA, Durham EL, Matthews LC, Smith TD. Human faces are slower than chimpanzee faces. *PLoS One*. 2014;9:e110523.
27. Yang N, MacArthur DG, Gulbin JP, et al. *ACTN3* genotype is associated with human elite athletic performance. *Am J Hum Genet*. 2003;73:627–631.
28. Moss ML, Young RW. A functional approach to craniology. *Am J Phys Anthropol*. 1960;18:281–292.
29. Byeon H. Effect of orofacial myofunctional exercise on the improvement of dysphagia patients' orofacial muscle strength and diadochokinetic rate. *J Phys Ther Sci*. 2016; 28:2611–2614.