

MYOSIN 1H AND THE SOFT TISSUE PROFILE OF AFRICAN AMERICAN FEMALES WITH MANDIBULAR PROGNATHISM

John Burnheimer^{1*}, Kathleen Deeley², Alexandre R. Vieira²

¹Department of Orthodontics and Dentofacial Orthopedics, University of Pittsburgh, Pittsburgh, USA.

²Department of Oral Biology, University of Pittsburgh, Pittsburgh, USA.

Palavras-chave: Miosina 1H. Perfil de Tecido Mole. Prognatismo.

RESUMO

Introdução: O objetivo desse estudo foi determinar a influência da miosina 1H nos tecidos moles de mulheres americanas negras. **Métodos:** Foram estudadas quatorze mulheres americanas negras participantes do projeto Dental Registry and DNA Repository da Faculdade de Odontologia da Universidade de Pittsburgh com o genótipo comum GG do marcador rs10850110, localizado no locus 12q24.11. Medidas de onze parâmetros que compõem a análise de tecidos moles de Holdaway foram utilizadas. Diferenças entre etnicidade e medidas normais correspondentes, foram exploradas através do teste t de Student de amostras independentes para todas as medidas faciais. O teste t de Student para médias independentes foi usado para determinar diferenças em comparação à medidas normais. A significância foi estabelecida em $p < 0,05$. **Resultados:** Houve uma diferença estatisticamente significativa entre quatro das onze medidas de Holdaway. A convexidade média da mulher americana negra foi de 1,0 mm a menos que o valor normal de 5.7 mm ($p > 0.000$). Em contraste, o ângulo H das mulheres americanas negras foi maior que o valor normal. **Conclusões:** O nosso estudo confirma resultados anteriores que a miosina 1H contribui para o prognatismo mandibular. Nossos resultados concordam com a ideia de que a miosina 1H tem menor influência nos tecidos moles da maxila. Entender a influência genética no crescimento dos tecidos moles irá possivelmente permitir melhorar as abordagens de tratamento e prevenção atuais.

Keywords: Myosin 1H. Soft Tissue Profile. Prognathism.

ABSTRACT

Introduction: The aim of this study was to explore the influence of Myosin 1H on the soft tissue profile of African American females. **Methods:** Fourteen African American females from the University of Pittsburgh School of Dental Medicine Dental Registry and DNA Repository with the ancestral genotype GG, marker rs10850110, locus 12q24.11 were analyzed. For this investigation, measurements were taken of the eleven items that comprise the Holdaway soft tissue analysis. Profile differences between ethnicity and corresponding normative values were explored by independent-sample t tests for all facial profile measurements. Student's t test for independent means was used to determine differences with accepted norms. Significance was set a $p < 0.05$. **Results:** There were significant differences between four of the eleven Holdaway values and the reported values for African Americans. The mean convexity value of the African American female group was 1.0 mm less the normative value of 5.7 mm ($p > 0.000$). In contrast, the H angle of the African American females was larger than the normative value. **Conclusions:** Our study confirms previous research that Myosin 1H contributes to mandibular prognathism. It agrees with the idea that Myosin 1H is less influential in the maxillary soft tissue complex. Understanding the genetic influence of soft tissue growth would allow improved therapies and prevention approaches.

Submitted: May 5, 2019

Modification: September 23, 2019

Accepted: September 27, 2019

*Correspondence to:

John Burnheimer

Address: University of Pittsburgh, 3501 Terrace Street, Pittsburgh, USA.

Zip code: 15260

Telephone number: (412) 648-8689

E-mail: jmb334@pitt.edu

INTRODUCTION

In contemporary orthodontics, predicting mandibular growth continues to be one of the most difficult aspects of treating younger patients. The clinical aspects of a Class III malocclusion can be recognized in childhood and become progressively more evident with growth, contributing to disturbances in both function and esthetics.¹ It has been well documented that there is a substantial link between mandibular prognathism and genetics.² Tassopoulou-Fishell et al³ and da Fontoura et al⁴ showed evidence that a polymorphism in Myosin 1H (MYO1H) was associated with mandibular prognathism. . Additionally, in a study of Japanese people, a genome-wide association study showed 2 loci (1p32.2 and 1p22.3) susceptible to mandibular prognathism.

We have demonstrated that type II muscle fiber occupancy correlates with malocclusion⁶ and MYO1H in particular was associated with mandibular prognathism in humans^{3,4,7-9} and zebrafish.¹⁰ Unlike Class II myosin heavy chains, which are responsible for muscle contraction and are the basis for classification of skeletal muscle types, Class I is an unconventional myosin group of single-headed monomers involved in cellular signaling mechanisms that regulate membrane dynamics, intracellular vesicle transport and auditory mechanotransduction. The specific molecular functions of MYO1H are yet to be discovered, but defects in the gene lead to jaw cartilage defects.^{6,10} To continue to elucidate the underlying mechanism that MYO1H is involved and that leads to mandibular prognathism, this study focused on an analysis of African American women, who have lower third facial lengths higher than their White counterparts.¹¹

Whereas many previous studies have focused on a hard tissue analysis, little is known of the influence of MYO1H on the soft tissue profile. One tool that can be utilized to assess soft tissue profiles is the Holdaway soft-tissue cephalometric analysis.

The Holdaway soft tissue analysis has been utilized in several studies to compare different ethnicities to the accepted Holdaway norms. For example, in both Anatolian Turkish and Chinese adults, the skeletal profile convexity value is smaller indicating straighter profile with a tendency to the concave, whereas the Japanese adults exhibit a larger convexity value indicating a more convex profile. The H angle also varies with the ethnicity with the Anatolian Turks closer to the established norm of Holdaway and the Japanese and Chinese exhibiting an increased angle.¹³⁻¹⁵

The Holdaway analysis consists of¹¹ measurements which are utilized to study the soft tissue profile. The purpose of this study was to compare the characteristics of the soft tissue profile Class III female African American patients (genotype GG, marker rs10850110) to population cephalometric norms.

MATERIAL AND METHODS

The subjects in this study were orthodontic patients from the Department of Orthodontics and Dentofacial Orthopedics of the School of Dental Medicine at the University of Pittsburgh, who were identified through the Dental Registry and DNA Repository project. Beginning in September 2006, people seeking treatment at the

University of Pittsburgh, School of Dental Medicine are invited to participate in this registry. After informed consent authorizing the use of data from their dental records, saliva samples were obtained from which DNA can be extracted. These samples were stored in Oragen DNA self-collection kits (DNA Genotek, Ottawa, Ontario, Canada) at room temperature until processing. No centrifugation was performed on the samples prior to the DNA extraction and the processing was completed per manufacturer's instructions. This project was approved by the University of Pittsburgh Institutional Review Board (IRB # 0606091).

The WITS appraisal was used to select the participants for this study because this value indicates the relationship of the maxillary and mandibular jaws regardless of intracranial relationship. Our sample included 160 African American females with a negative WITS value. Subjects were excluded if presenting with any abnormal anterior cranial base defects, any facial clefting, or any midfacial growth abnormalities

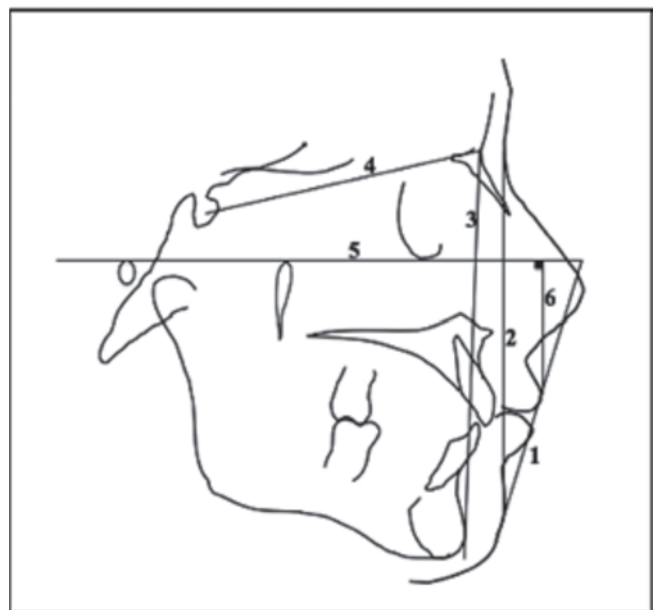


Figure 1: Reference lines used in this study 1, The H line drawn tangent to the soft tissue chin and the upper lip; 2, a soft tissue facial line from soft tissue nasion to the point of the soft tissue chin overlaying Ricketts' suprapogonion; 3, the hard tissue facial plane from nasion to pogonion; 4, the sella-nasion line; 5, Frankfort horizontal plane; 6, a line running at a right angle to the Frankfort plane down tangent to the vermilion border of the upper lip.

caused by cysts, tumors or trauma. After this process,¹⁴ African American females with the ancestral allele GG, marker rs10850110, locus 12q24.¹¹ were analyzed. The cephalometric radiographs had been previously uploaded into Dolphin Imaging Software. The landmarks of all subjects were digitized by one examiner using Dolphin Imaging Software (version 11.8; Dolphin Imaging and Management Software, Chatsworth, California). For this investigation, measurements were taken of the eleven items that comprise the Holdaway soft tissue analysis and were compared to the software normative values. The reference lines used are shown in Figure 1.¹³ The definitions for the linear and angular measurements used are as follows:

1. Skeletal profile convexity (convexity): the distance from point A to the hard tissue line Nasion–Pogonion (Na–Pog).
2. Lower lip to H line (LL-H line): the distance from the lower lip to H line (a tangent drawn from the tip of the chin to the vermilion).
3. Soft tissue facial angle (face angle): the inner angle formed by the intersection of soft tissue nasion–soft tissue suprapogonion line with the Frankfort horizontal plane.
4. Superior sulcus depth (SS depth): the distance between the upper lip sulcus and a perpendicular line drawn from the

vermilion to Frankfort plane.

5. Soft tissue subnasale to H line (sub-H line): the distance from subnasale to H line.
 6. Basic upper lip thickness (UL-A point): the distance from a point about 3 mm below point A to the drape of the upper lip.
 7. Upper lip thickness (UL-vermilion): the distance from the labial surface of upper incisors to the vermilion border of the upper lip.
 8. H angle (H angle): the angular measurement of the H line to the soft tissue facial plane.
 9. Inferior sulcus to the H line (IS-H line): the distance at the point of maximum curvature on the lower lip and the H line.
 10. Soft tissue chin thickness (chin thick): the distance between the two vertical lines representing the hard tissue and soft tissue facial planes at the level of Ricketts' suprapogonion.¹⁶
 11. Nose prominence (nose prom): the distance from a line perpendicular to Frankfort horizontal and running tangent to the vermilion border of the upper lip to the tip of the nose.
- All cephalometric radiographs were retraced 2 weeks after the initial assessment by the same examiner and interrater intrarater reliability coefficients were calculated indicating excellent reliability. Descriptive summary of the soft tissue measurements is listed in Table 1.

Table 1: Descriptive statistics of sample measurements

	Minimum	Maximum	Mean	SD
Convexity (mm)	-7.1	9.9	1.0	3.7
LL-H line (mm)	3.3	9.4	6.0	1.7
Facial angle (°)	92.6	106.7	98.5	4.8
SS depth (mm)	4.1	9.3	6.4	1.8
Sub-H line (mm)	3.3	13.5	9.6	2.9
UL-A point (mm)	10.9	21.2	15.2	2.4
UL-vermilion (mm)	11.7	16.8	14.1	1.5
H angle (°)	4.4	20.6	15.6	3.9
IS-H line (mm)	0.2	4.5	1.9	1.2
Chin thick (mm)	11.6	21.2	14.1	2.6
Nasal prom (mm)	-1.2	8.9	4.6	2.7

Note: n=14

Table 2: Comparison of facial profile measurements to established ethnic values

A. A. Females					
	Mean	SD	Norms	SD	p values
Convexity (mm)	1.0	3.7	5.7	2	0.000 *
LL-H line (mm)	6.0	1.7	2.9	2	0.000 *
Facial angle (°)	98.5	4.9	98	7	0.715
SS depth (mm)	6.3	1.8	5.5	1	0.093
Sub-H line (mm)	9.6	2.9	10	2	0.581
UL-A point (mm)	15.2	2.4	16	3	0.263
UL-vermillion (mm)	14.1	1.5	13.6	3	0.204
H angle (°)	15.6	4.1	10	4	0.000 *
IS-H line (mm)	1.9	1.3	3.9	2	0.000 *
Chin thick (mm)	14.1	2.6	14.7	3.5	0.425
Nasal prom (mm)	4.6	2.8	5.7	3	0.154

STATISTICAL ANALYSIS

JMP Pro (SAS Institute Inc., Cary, North Carolina, USA) was used for data analysis. Descriptive statistics comprising means and standard deviations were obtained. Profile differences between ethnicity and corresponding normative values were explored by

independent-sample t tests for all facial profile measurements. Student's t test for independent means was used to determine differences with accepted norms. Significance was set a $p < 0.05$.

RESULTS

Descriptive statistics of the sample measurements of the fourteen African American females are shown in Table 1.

Regarding the soft tissue profile measurements, there were significant differences between four of the eleven Holdaway values and the reported values for African Americans (Table 2).

In this study, the mean convexity value of the African American female group was 1.0 mm, a significantly smaller value, when compared to the normative value of 5.7 mm ($p > 0.001$). In contrast, the H angle of the African American females was significantly larger than the normative value.

Two other soft tissue characteristics were significant in this sample and both are located in the lower facial third. The inferior sulcus to the H line was less deep, and the lower lip to the H line significantly more protrusive than normative values.

Of the seven Holdaway values that are not significant, the mean facial angle is nearly identical (98.5° v. 98°) to the normative value and many of the linear measurements are within 1.0 mm of the established values.

DISCUSSION

The present research aimed to investigate the variation in soft profile tissue of fourteen African American females with the ancestral allele of a marker near MYO1H (rs10850110).

The contribution of MYO1H on mandibular prognathism as assessed by hard tissue metrics has been previously documented.^{3,8,17}

MYO1H is a class 1 myosin, but in a different protein grouping than those heavy chain isoforms found in skeletal muscle.³ However, the influence of muscles on facial growth is well recognized.

Previous studies have indicated that MYO1H has a role in mandibular prognathism when using bony skeletal landmarks,^{3,8} however its role in soft tissue profile has not been established.

According to the values presented in Table 1 (min, max and SD) there was great variation for some measures.

The selected sample was not homogeneous in relation to the cephalometric characteristics evaluated. Even though Class III patients were selected, the phenotypic variation of this condition is large. The risk of bias is high, since different conditions could be considered as equal: Class III by mandibular prognathism; Class III by maxillary retrognathism; or Class III by the two conditions.

In this study, when the mean value for each of the eleven Holdaway variables were compared, statistically significant differences were associated with four variables. The skeletal profile convexity, the H angle, the lower lip to H line and inferior sulcus to H line were all statistically different from the established values.

The skeletal profile convexity mean was 4.7 mm less than the norm, indicating a more concave soft tissue profile. This is in contrast to the study of Sushner¹⁸, who in a photographic study of the African American population, found both Class I males and females to be more convex. Similarly, Fonseca and Klein¹⁹, in a cephalometric study of African America women, and Bacon et al.²⁰, in a study of African Bantu males, found a more convex soft tissue profile. In these studies, patients were selected who had Class I occlusions and either considered attractive or with no obvious facial abnormalities. This difference could be explained by the fact that our subjects exhibited Class III profile characteristics.

Whereas convexity was less than the norm in our sample, the H angle mean was greater than the established African American norms. This compares favorably with the norms reported for Chinese, Saudi and Anatolian Turkish populations.^{13, 14, 21} The H angle can be influenced by the position of either the mandible or chin, individually, or in combination.

Ideally, the skeletal profile convexity moves in tandem with the H angle for a harmonious soft tissue profile.⁷ Typically, a higher angle correlates with greater convexity. However, our sample showed a higher value for the H angle in relation to the norms, which would indicate more convexity, that is, a more Class II profile. Nonetheless, in mandibular prognathic patients, the influence of MYO1H may have a different effect on the soft tissue development, primarily an increased upper lip thickness as opposed to its effects on the hard tissue.⁶ Extreme values of the H angle are shown in Figure 2.



Figure 2: Example of extreme values of H angle

Two other soft tissue profile areas, both in the lower facial third, had values significantly different than accepted norms for African Americans.

Significant protrusion of the lower lip to H line (LL-H line) was found in our sample of African American females. This is in agreement with Fonseca and Klein¹⁹ who found that the projection of the lower lip to be significantly greater in American Black women, but in contrast to other research which found the lower lip in better proportion to the soft

tissue profile.^{18,21} Farrow et al.²² surveyed 465 people and found that all groups preferred an African American soft tissue profile that was slightly convex with lips anteriorly placed. Perhaps, the most likely explanation for what appears to clinically be an increase in lip thickness is actually an increased eversion of the lower lip tissue between the upper and lower vermilion borders. While there is no significant difference in chin thickness from the normative values, the influence of MYO1H on this area of the soft tissue profile cannot be excluded.

Surprisingly, the inferior sulcus to the H line (IS-H line) was found to be significantly shallower when compared to the African American norms. Other research has found that the inferior sulcus depth is deeper.²¹ Typically, as the protrusion of the lower lip rolls out beyond the H line, the inferior sulcus becomes deeper, not shallower.⁷ Once again, this may be under the influence of MYO1H.⁸

Other researchers have shown that in Saudi and Anatolian Turkish adults, both the superior sulcus depth and the UL-vermillion border values were less than our sample.²¹ Additionally, Sushner¹⁸ found in his sample of attractive looking North American blacks that the soft tissue of the upper lip was tending to either straight or convex.

In this study, the deeper sulcus depth could partially be attributed to retrusive A- point and a thinner than normal upper lip thickness in conjunction with a slightly thicker lip at the vermilion border. If the vermilion border area were thinner in comparison to the UL-A point area, this would be indicative of lip strain.⁷ This was not apparent in our sample.

The facial angle was nearly identical (98.5° v. 98.0°) indicating chin prominence of this sample is nearly identical when compared to the African American norms. The facial angle for both the Saudi and Anatolian Turkish norms compare favorably to the original norms of Holdaway.^{13,21} This is somewhat surprising as the mandible exhibits the greatest variation in size and form of all the bones that make up the face.¹²

Nasal prominence was 1mm less than the African American norm. This is in agreement with Fonseca¹⁹ and Isiekwe²³ who also found the nasal tip projection to be shorter in their evaluation of a population of African descent. Similarly,

in studies involving Saudi and Anatolian Turks, the Saudi nasal prominence is reduced when compared to the Anatolian Turkish norms.²¹ However, both are larger than the African American nasal prominence in this study.

Our study would advance the idea MYO1H may influence variations in the soft tissue profile characteristics in Class III female African American patients (genotype GG, marker rs10850110). Once again, supporting the work of Subtelny²⁴ that not all areas of the face follow the underlying structures. Certainly, a better understanding the genetic influence of soft tissue growth would allow improved therapies and preventive strategies, especially in younger patients with developing mandibular prognathism.

Since our sample size was modest, one cannot discount the possibility that other genes play a role in the variation of the soft tissue profile. Given that a post hoc power analysis would suggest the study was under powered, the main objective of this research was to compare these findings to normative values. Even though these variations in the soft tissue could be found in any other sample of Class III patients, we hypothesize that the differences are influenced by MYO1H, but more conclusive evidence would arise from a comparison with individuals without the genetic variant. Future research would need to consider all genes in the family as candidates for a role in the soft tissue profile variation in mandibular prognathism of African American females.

CONCLUSIONS

In this study of African American females with the ancestral allele of MYO1H who exhibit mandibular prognathism, four of the eleven Holdaway soft tissue values were significantly different from the established norms for African Americans. The suggestion that muscle function, as related to MYO1H, may have a role in the development of the soft tissue profile in mandibular prognathism is intriguing. Certainly, with this modest sample size, replication of these findings and expansion to other populations is indicated.

REFERENCES

1. Stenvik A, Espeland L, Berg RE. A 57-year follow-up of occlusal changes, oral health, and attitudes toward teeth. *Am J Orthod Dentofacial Orthop* 2011;139:102-8
2. Watanabe M, Suda N, Ohyama K. Mandibular prognathism in Japanese families ascertained through orthognathically treated patients. *Am J Orthod Dentofacial Orthop* 2005;128:466-70. doi.org/10.1016/j.ajodo.2004.09.018
3. Tassopoulou-Fishell M, Deeley K, Harvey EM, Sciote J, Vieira AR. Genetic variation in myosin 1 H contributes to mandibular prognathism. *Am J Orthod Dentofacial Orthop* 2012;141:51-9. doi.org/10.1016/j.ajodo.2011.06.033

4. da Fontoura CSG, Miller SF, Wehby GL, Amendt BA, Holton NE, Southard TE, et al. Candidate gene analyses of skeletal variation in malocclusion. *J Dent Res* 2015;94:913-20
5. Ikuno K, Kajii TS, Oka A, Inoko H, Ishikawa H, Iida J. Microsatellite genome-wide association study for mandibular prognathism. *Am J Orthod Dentofacial Orthop* 2014;145:757-62.
6. Desh H, Gray SL, Horton MJ, Raoul G, Rowlerson AM, Ferri J, Vieira AR, Sciote JJ. Molecular motor MYO1C, acetyltransferase KAT6B and osteogenetic transcription factor RUNX2 expression in human masseter muscle contributes to development of malocclusion. *Arch Oral Biol.* 2014 Jun;59(6):601-7.
7. Arun RM, Lakkakula BV, Chitharanjan AB. Role of myosin 1H gene polymorphisms in mandibular retrognathism. *Am J Orthod Dentofacial Orthop.* 2016 May;149(5):699-704.
8. Cruz CV, Mattos CT, Maia JM, Granjeiro JM, Reis MF, Mucha JN, Vilella B, Ruellas AC, Luiz RR, Costa MC, Vieira AR. Genetic polymorphisms underlying the skeletal Class III phenotype. *Am J Orthod Dentofacial Orthop* 2017;151:700-7. doi.org/10.1016/j.ajodo.2016.09.013
9. Cunha A, Nelson-Filho P, Maraño-Vásquez GA, Ramos AGC, Dantas B, Sebastiani AM, Silvério F, Omori MA, Rodrigues AS, Teixeira EC, Levy SC, Araújo MC, Matsumoto MAN, Romano FL, Antunes LAA, Costa DJD, Scariot R, Antunes LS, Vieira AR, Küchler EC. Genetic variants in ACTN3 and MYO1H are associated with sagittal and vertical craniofacial skeletal patterns. *Arch Oral Biol.* 2019 Jan;97:85-90.
10. Sun R, Wang Y, Jin M, Chen L, Cao Y, Chen F. Identification and Functional Studies of MYO1H for Mandibular Prognathism. *J Dent Res.* 2018 Dec;97(13):1501-1509
11. Porter JP, Olson KL. Anthropometric facial analysis of the African American woman. *Arch Facial Plast Surg.* 2001;3(3):191-197.
12. Holdaway RA. A soft-tissue cephalometric analysis and its use in orthodontic treatment planning. Part 1. *Am J Orthod* 1983;84:1-28. doi.org/10.1016/0002-9416(83)90144-6
13. Basciftci FA, Uysal T, Buyukerkmen A. Determination of Holdaway soft tissue norms in Anatolian Turkish adults. *Am J Orthod Dentofacial Orthop* 2003;123:395-400. doi.org/10.1067/mod.2003.139
14. Lew KK, Ho KK, Keng SB, Ho KH. Soft-tissue cephalometric norms in Chinese adults with esthetic facial profiles. *J Oral Maxillofac Surg* 1992;50:1184-9. doi.org/10.1016/0278-2391(92)90151-O
15. Alcalde RE, Jinno T, Orsini MG, Sasaki A, Sugiyama RM, Matsumura T. Soft tissue cephalometric norms in Japanese adults. *Am J Orthod Dentofacial Orthop* 2000;118:84-9. doi.org/10.1067/mod.2000.104411
16. Ricketts RM. Planning treatment on the basis of the facial pattern and an estimate of its growth. *Angle Orthod* 1957;27:14-37.
17. Moreno Uribe LM, Vela KC, Kummert C, Dawson DV, Southard TE. Phenotypic diversity in white adults with moderate to severe Class III malocclusion. *Am J Orthod Dentofacial Orthop* 2013;144:32-42. doi.org/10.1016/j.ajodo.2013.02.019
18. Sushner NI. A photographic study of the soft-tissue profile of the Negro population. *Am J Orthod* 1977;72:373-85. doi.org/10.1016/0002-9416(77)90350-5
19. Fonseca RJ, Klein WD. A cephalometric evaluation of American Negro women. *Am J Orthod* 1978;73:152-60. doi.org/10.1016/0002-9416(78)90185-9
20. Bacon W, Girardin P, Turlot JC. A comparison of cephalometric norms for the African Bantu and caucasoid population. *Eur J Orthod* 1983;5:233-240. doi.org/10.1093/ejo/5.3.233
21. AlBarakati SF, Bindayel NA. Holdaway soft tissue cephalometric standards for Saudi Adults. *King Saud Univ J Dent Sci* 2012;3:27-32.
22. Farrow AL, Zarrinnia K, Azizi K. Bimaxillary protrusion in black Americans-an esthetic evaluation and the treatment consideration. *Am J Orthod Dentofacial Orthop* 1993;104:240-50. doi.org/10.1016/S0889-5406(05)81725-1
23. Isiekwe GI, daCosta OO, Utomi IL, Sanu OO. Holdaway's analysis of the nose prominence of an adult Nigerian population. *Niger J Clin Pract* 2015;18:548-552.
24. Subtelny JD. A longitudinal study of soft tissue facial structures and their profile characteristics, defined in relation to underlying skeletal structures. *Am J Orthod* 1959;45:481-507. doi.org/10.1016/0002-9416(59)90014-4