Original Article

Growth hormone receptor gene is related to root length and tooth length in human teeth

Yu Hikita[a]; Tetsutaro Yamaguchi[b]; Daisuke Tomita[c]; Mohamed Adel[d]; Takatoshi Nakawaki[e]; Koshu Katayama[c]; Koutaro Maki[f]; Ryosuke Kimura[g]

ABSTRACT

Objectives: To examine the relationship between tooth length and growth hormone receptor (GHR) gene variants in a healthy Japanese population.

Materials and Methods: The subjects consisted of 193 Japanese adults (69 men, 124 women), aged 13 to 56 years. Genomic DNA was extracted from saliva and genotyped GHR rs6184 and rs6180 variants using the Taqman genotyping. Computed tomography (CT) images were acquired using a dental cone-beam CT scanner and reconstructed using open-source OsiriX medical image processing software. The maxillary (upper; U) and mandibular (lower, L) central incisors (1), lateral incisors (2), canines (3), first premolars (4), second premolars (5), first molars (6), and second premolars (7) were evaluated. Teeth were assessed for crown height (CH), root length (RL), overall tooth length (C+R), and crown to root ratio (C/R). The relationships between GHR variants and CH, RL, C+R, and C/R were statistically examined.

Results: The GHR variant rs6184 was associated with the root lengths and tooth length for the upper and lower lateral incisors and upper canines (U2 RL; U3 RL, C+R; L2 RL [$P < .05$]).

Conclusions: The results indicate that the GHR rs6184 variant is associated with tooth length and ratio dimensions in a Japanese cohort. Further studies utilizing a larger sample size are needed to confirm this finding. (*Angle Orthod.* 2018;88:575–581.)

KEY WORDS: Growth hormone receptor (GHR) gene; Tooth; Length; Crown; Root

INTRODUCTION

The crown-root ratio is an important consideration in orthodontic and prosthodontic treatments.[1] The overall tooth length (crown height and root length) determines the orthodontic force that can be transmitted during orthodontic treatment, and it is involved in the pattern of tooth movement.[2–4] Furthermore, the identification of the root length at the time of orthodontic diagnosis and treatment is essential.[5]

Both environmental and genetic factors can lead to dental variation.[6] The inheritance patterns of dental variation have been studied, and it has been suggested[7] that genetic factors are strongly involved in dental variation. However, there is limited knowledge about human genetic variants associated with common dental variations.[7] Studies[8] on human crown variation have linked the shovel-shaped incisor, a characteristic feature of Mongoloids, with EDAR variants. Others have also shown that the mesiodistal width of the human crown is associated with EDAR,[7] WNT10A,[9] and PAX9.[10] WNT10A is also associated with the distolingual cusp in the lower second premolars, the fifth cusp in the upper first molars, and the hypoconulid

[a] Graduate Student, Department of Orthodontics, School of Dentistry, Showa University, Tokyo, Japan.
[b] Associate Professor, Department of Orthodontics, School of Dentistry, Showa University, Tokyo, Japan.
[c] Research Assistant, Department of Orthodontics, School of Dentistry, Showa University, Tokyo, Japan.
[d] Research Assistant, Department of Orthodontics, Suez Canal University, Ismailia, Egypt.
[e] Assistant Professor, Department of Orthodontics, School of Dentistry, Showa University, Tokyo, Japan.
[f] Professor, Department of Orthodontics, School of Dentistry, Showa University, Tokyo, Japan.
[g] Associate Professor, Department of Human Biology and Anatomy, Graduate School of Medicine, University of the Ryukyus, Okinawa, Japan.
Corresponding author: Dr Tetsutaro Yamaguchi, Department of Orthodontics, School of Dentistry, Showa University, 2-1-1 Kitasenzoku, Ota-ku, Tokyo 145-8515, Japan
(e-mail: tyamaguchi@dent.showa-u.ac.jp)

Accepted: February 2018. Submitted: September 2017.
Published Online: April 18, 2018

in the lower second molars.[9] However, no human genetic variant has been reported to be associated with tooth length.

The human growth hormone receptor (GHR) gene, located at 5p13.1-p12, measures about 87 kb and comprises 10 exons.[11] The major function of growth hormone (GH) is in the promotion of postnatal growth[12] through the GH/GHR/insulin-like growth factor I signaling axis, as identified through the study of GHR knockout mouse phenotypes.[13] GHR also plays a role in maintaining proportional skeletal growth,[13] with GHR mutations responsible for Laron syndrome (GH insensitivity syndrome) and idiopathic short stature.[14] Treatment of Laron syndrome with insulin-like growth factor I tends to induce dental maturation, particularly in younger patients.[15] In patients with idiopathic short stature, dental age is rarely affected and is less responsive to GH,[16] yet tooth eruption patterns are identical to those of patients with normal GH secretion.[16] Other studies have shown that GH secretion is associated with both tooth eruption and maturation[17,18] and that rodent cellular cementum also relies on GH.[19]

Given the clear role of GH in skeletal growth and development, in the present study, the relationship between tooth length and two gene variants of GH (rs6184 and rs6180) were examined in Japanese subjects.

MATERIALS AND METHODS

Subjects

The subjects were patients who visited the Department of Orthodontics at Showa University Dental Hospital and who underwent cone-beam computed tomography (CBCT) imaging for orthodontic assessment. The final cohort comprised 193 Japanese adults, with 69 men (mean age 26.9 years; range, 16–50 years) and 124 women (mean age 26.7 years; range, 13–57 years). Subjects with congenital disorders, such as cleft lip and palate, or those with other general physical diseases were excluded from this study. Subjects with previous orthodontic treatment, root resorption, and loss of the original crown morphology due to caries, trauma, attrition, wear, and dental prosthesis were excluded. All CBCTs were taken for orthodontic diagnosis and treatment planning, and no patient was contacted and no CBCTs were taken for the purpose of the present study.

The study was approved by the ethics committee of the Showa University (IRB No. 108) and the University of the Ryukus (IRB No. 120), and all subjects provided written informed consent to participate.

Tooth Size Measurements

CBCT images were acquired using a dental cone-beam X-ray CT scanner (CB MercuRay, Hitachi Medico Technology, Tokyo, Japan) or a KaVo 3DeX-am (KaVo, Biberach, Germany) at the radiology department of the university hospital. The scanning conditions were 100 kVp, 10 mA, F-mode 512 slices/scan (slice width: 377 mm), and 9.6-second acquisition time. Data obtained were reconstructed using the open-source OsiriX medical image processing software (Pixmeo, Geneva, Switzerland; www.osirix.viewer.com) and exported using the DICOM format to a MacBook Pro personal computer (Mac OsX El Capitan 10.11.6 Apple, Cupertino, Calif). The difference in measurement between the two models of CBCT was evaluated using the method reported by Katayama et al.[20] The difference was small and nonproblematic.

For the measurement of tooth length, CBCT images were oriented using multiplanar reconstruction, and teeth were measured using a modification of the method described by Abeleira et al.[21] After each target tooth was positioned following the method of Abeleria et al.,[21] the crown height (CH) and root length (RL) were measured in the coronal plane. To measure CH, a perpendicular line was drawn from the line between the buccal and palatal limits of the cementoenamel junction to the incisal edge or tip of each cusp in the case of the premolars and molars. RL was measured by drawing a perpendicular line from the line between the buccal and palatal limits of the cementoenamel junction to the apex of the tooth or each root, respectively. The distance between the incisal edge or cusp and the root apex was measured in central incisors (upper [U]1, lower [L]1), lateral incisors (U2, L2), and canines (U3, L3). The distance between the buccal cusp and buccal root apex was measured in the premolars (U4, U5, L4, L5) when it had two roots. The distances between the mesiobuccal cusp tip and the mesiobuccal root apex (U6M, U7M), between the distobuccal cusp tip and distobuccal root apex (U6D, U7D), and between the mesiopalatal cusp tip and palatal root apex (U6P, U7P) were measured in the upper molars. In the lower molars, the distances between the mesiobuccal cusp tip and mesial root apex (L6M, L7M) and between the distobuccal cusp tip and distal root apex (L6D, L7D) were measured. Figure 1 describes these measurements. CHs and RLs were averaged between left and right sides for each tooth. If the tooth on only one side was measurable, the value of this tooth was used. Where teeth on both sides were unable to be measured, the value was considered missing. Overall tooth length (C+R) was calculated by

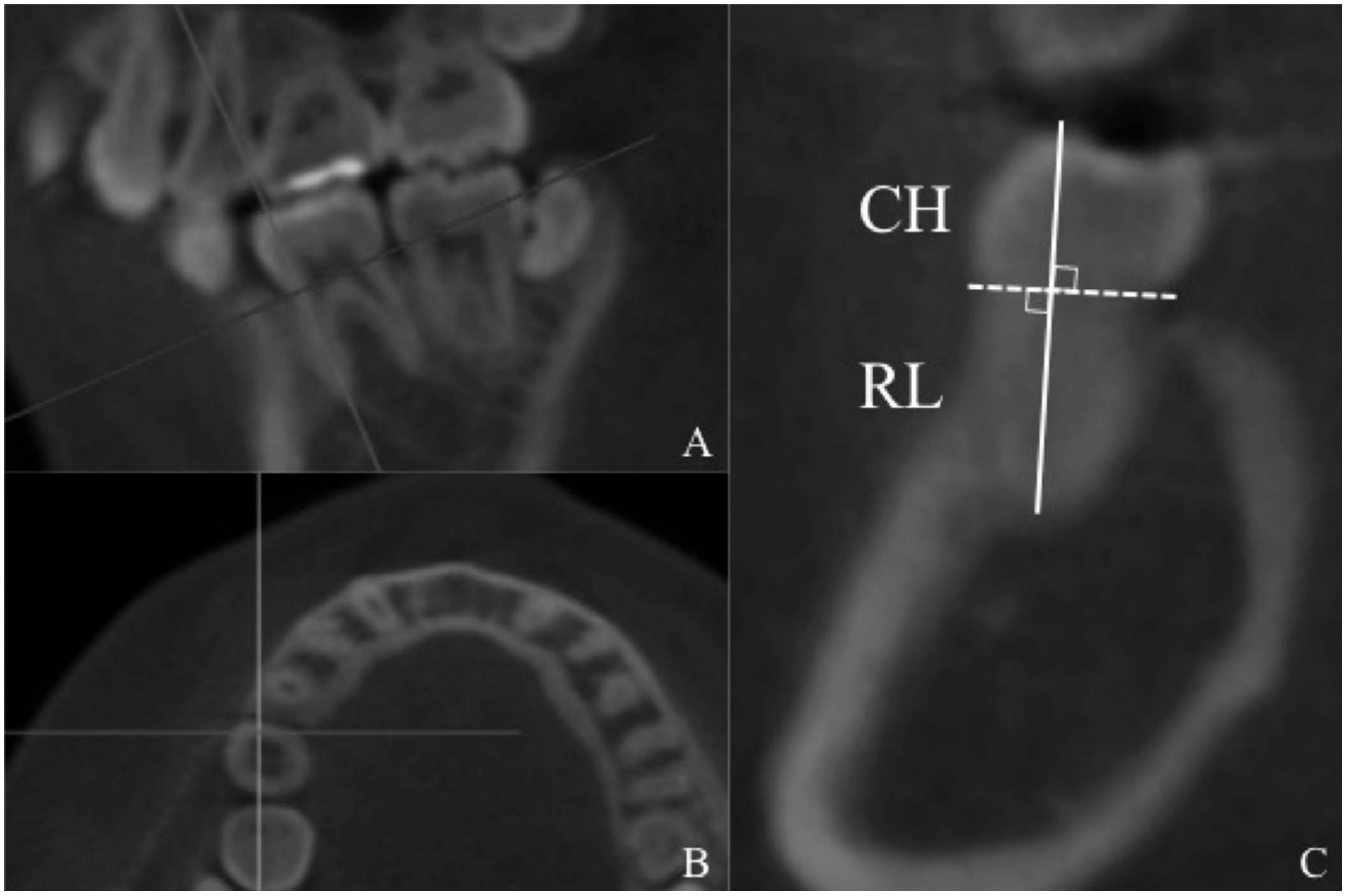

Figure 1. Tooth size measurements performed using CBCT images: (A) sagittal plane; (B) axial plane; and (C) coronal plane. Tooth size was measured in the coronal plane (CH indicates crown height; RL, root length).

adding CH and RL. The crown-to-root ratio (C/R) was calculated by dividing CH by RL.

The measurements were performed by one researcher (YH). To investigate intraoperator error, 25 subjects were chosen randomly and remeasured in separate sessions at a 2-week interval under identical conditions. Measurement error was estimated according to Dahlberg's formula ($S2 = \sum d2/2n$).[22,23]

Genotyping

Saliva was collected from the subjects using the Oragene DNA self-collection kit (DNA Genotek, Ottawa, Ontario, Canada) and stored at room temperature. Genomic DNA was extracted from the saliva samples. Two *GHR* variants (rs6184 and rs6180) were genotyped using the Taqman genotyping assay (Applied Biosystems assay No. C 2389458_20, C 2841422_10; Life Technologies, Carlsbad, Calif).

Statistical Analysis

Multiple regression analyses were performed to test the association between the focal trait and each variant with the additional covariate of sex (male, 0; female, 1). In the regression analysis for rs6180, an additive model was used (AA = 0, AC = 1, CC = 2), whereas a dominant model was used (CC = 0 and CA or AA = 1) for rs6184 since only one homozygote was observed for the derived allele in rs6184. Statistical analyses were performed using Statcel3 software (OMS Publishing, Saitama, Japan), with significance set to 5%.

RESULTS

The mean values and standard deviations for each tooth measurement are shown in Table 1. The measurement error estimated by Dahlberg's formula was 3% or lower for each measure, indicating sufficient reproducibility. The allele frequencies of the *GHR* variants were 46.6% and 8.1% for rs6180 and rs6184, respectively (Table 2). The multiple regression analysis revealed that the GHR rs6184 variant was associated with the tooth size of U2 RL, U3 RL, C+R, and L2 RL ($P < .05$) (Table 3).

Table 1. Means and Standard Deviations (SDs) of the Measurements from Cone-Beam Computed Tomography (CBCT)[a]

	Males (n = 69)		Female (n = 124)	
	Mean ± SD	Range	Mean ± SD	Range
U1				
CH	10.87 ± 0.86	8.55–12.75	10.50 ± 0.84	8.01–12.55
RL	13.22 ± 1.44	9.81–16.37	12.45 ± 1.30	8.29–15.32
U2				
CH	10.13 ± 0.96	8.05–12.11	9.74 ± 0.97	7.23–12.52
RL	12.82 ± 1.47	8.92–17.31	12.01 ± 1.24	9.18–16.12
U3				
CH	11.38 ± 0.90	9.46–13.55	10.69 ± 0.93	8.43–13.26
RL	15.79 ± 1.52	11.74–18.73	15.07 ± 1.61	11.50–21.27
U4				
CH	9.43 ± 0.86	7.83–12.04	9.14 ± 0.77	7.35–10.87
RL	12.11 ± 1.27	9.16–15.00	11.65 ± 1.19	7.64–14.84
U5				
CH	8.71 ± 0.89	6.92–10.63	8.33 ± 0.77	6.64–10.31
RL	11.49 ± 1.22	9.18–14.30	11.07 ± 1.41	8.00–14.50
U6P				
CH	8.54 ± 0.80	6.11–10.02	8.28 ± 0.71	6.27–9.84
RL	12.20 ± 1.26	9.75–15.05	11.59 ± 1.27	9.19–15.14
U6M				
CH	8.37 ± 0.77	6.68–10.35	7.95 ± 0.75	6.03–9.99
RL	10.24 ± 1.08	8.30–13.28	9.98 ± 1.14	7.66–13.97
U6D				
CH	8.04 ± 0.58	6.49–9.32	7.80 ± 0.71	6.47–10.46
RL	10.01 ± 1.07	7.75–12.65	9.81 ± 1.15	7.40–12.80
U7P				
CH	8.49 ± 0.78	6.73–9.91	8.27 ± 0.77	6.52–10.09
RL	11.24 ± 1.14	8.65–13.98	10.75 ± 1.20	7.67–13.95
U7M				
CH	8.41 ± 0.71	6.31–10.15	8.12 ± 0.74	6.56–10.12
RL	9.92 ± 1.24	7.87–13.56	9.55 ± 1.12	7.12–12.59
U7D				
CH	8.07 ± 0.67	6.68–9.53	7.70 ± 0.66	6.03–9.65
RL	10.04 ± 1.11	8.09–12.66	9.71 ± 1.13	7.52–12.99
L1				
CH	8.55 ± 0.68	6.88–10.20	8.40 ± 0.70	6.65–10.23
RL	12.07 ± 1.03	9.35–14.33	11.55 ± 0.95	9.20–13.91
L2				
CH	9.07 ± 0.69	7.66–10.79	8.77 ± 0.76	6.60–10.60
RL	12.83 ± 1.14	10.31–15.82	12.14 ± 1.05	9.29–15.23
L3				
CH	10.78 ± 0.95	9.30–12.87	9.92 ± 0.74	7.98–11.42
RL	15.44 ± 1.51	12.46–18.48	14.30 ± 1.38	11.06–17.44
L4				
CH	9.21 ± 0.69	7.44–11.07	8.71 ± 0.69	7.31–10.43
RL	13.42 ± 1.13	11.48–16.24	12.89 ± 1.13	10.23–17.11
L5				
CH	8.42 ± 0.75	5.93–10.26	7.97 ± 0.65	6.14–9.25
RL	13.07 ± 1.53	10.30–18.24	12.50 ± 1.25	9.21–15.26
L6M				
CH	8.08 ± 0.61	6.82–9.39	7.84 ± 0.63	6.00–9.44
RL	12.16 ± 1.12	10.16–14.87	11.75 ± 1.01	8.36–14.44
L6D				
CH	7.53 ± 0.65	6.41–10.29	7.28 ± 0.61	5.89–9.33
RL	11.86 ± 1.20	9.37–14.05	11.52 ± 1.12	8.65–14.72
L7M				
CH	7.85 ± 0.65	6.55–9.30	7.58 ± 0.66	5.91–9.56
RL	11.62 ± 1.26	8.69–14.22	11.21 ± 1.05	7.90–14.30
L7D				
CH	7.57 ± 0.66	6.33–9.38	7.33 ± 0.55	5.59–8.53
RL	11.38 ± 1.26	8.73–14.46	10.88 ± 1.03	8.21–14.93

[a] CH indicates crown height; RL, root length; U, upper; L, lower; U1, L1, central incisors; 2, lateral incisors; 3, canines; 4, 5, premolars; M, distance between the mesiobuccal cusp tip and root apex; D, distance between the distobuccal cusp and root apex; and P, distance between the mesiopalatal cusp tip and root apex. All measurements are in millimeters.

DISCUSSION

In the present study, the relationship between GHR variants (rs6180 and rs6184) and tooth length was examined using CBCT imaging in Japanese healthy subjects. The GHR gene variant rs6184 was associated with the root lengths of U2, U3, and L2. This is the first study reporting a genetic variant associated with human tooth lengths.

Growth hormone is involved in the maturation and formation of teeth. In pituitary dwarfism, tooth size or arch dimensions are smaller than normal,[16] whereas in pituitary gigantism, patients demonstrate premature tooth eruption and hypercementosis.[19] Smid et al.[19] previously reported that in the mouse, cellular cementum relies on the presence of GH, confirming the results of Becks and colleagues,[24] who found that daily injections of GH in rats for several months likely resulted in hypercementosis in the molar teeth. Indeed, the GHR mutation causes delayed tooth maturation and eruption in patients with Laron syndrome and idiopathic short stature, which can be improved with GH supplementation.[15,25] Previous studies have found associations for GHR with the mandibular ramus height,[14,26,27] mandibular growth during early childhood,[28] and the distance between the left and right coronoid processes.[29] Several groups[30–32] have hypothesized, but not tested for, an association between tooth length and mandibular morphology. More comprehensive and larger-scaled studies will be needed to validate the complete associations of GHR variants with various aspects of the jaw.

The cell sensitivity to GH and the site of GH action are closely coordinated to affect the formation and eruption of teeth.[33] At sites of new matrix formation, cementoblasts and odontoblasts displayed expression specifically against GHR, although cementocytes and mature odontoblasts at later stages of tooth development did not.[33] The functional mechanism by which the GHR gene variant identified may be responsible for tooth length is still unclear.

Table 2. Single Nucleotide Polymorphisms Examined in this Study

rs No.	Chr: Position (GRCh38.p2)	mRNA Position (Forward to chr)	Function	Alleles: Ancestral/Derived (Forward to chr)	Individuals Tested	No Call	Genotype Frequency AA	AD	DD	Derived Allele Frequency, %
rs6180	chr5: 42719137	A1822C	I544L(I526L[a])	A/C	179	3	45	74	27	46.6
rs6184	chr5: 42719242	C1927A	P579T(P561T[a])	C/A	179	0	151	27	1	8.1

[a] Previous amino acid number.

In this study, the association of the root lengths and tooth length with GHR variants was investigated in CBCT images in a large number of subjects and compared with the results of a number of previous reports.[21,34–40] A maximum 8.4-mm difference in U3-R was found between the current cohort and Finnish males,[34,35] suggesting that the crown and root lengths in Japanese may be smaller than those in Europeans, excluding those of U1, U2, L1, and L2. Interpopulational and regional differences in the crown width are well known.[41–45] With larger crown widths in Africans, intermediate widths in Asians, and much smaller widths in Europeans, these variations in the crown width are different from those in the crown and root lengths. [44] In addition, a recent report[45] comparing crown width in Japanese from the 1940s, the 1980s, and the 1990s suggests that changes in nutritional condition and dietary habits may have affected crown width. As described above, changes over time and regional differences in crown length and root length may be observed. Moreover, the current results were not significant when a multiple testing correction was implemented. Further studies with a larger sample size are needed to validate the result and to better understand the relationship between the human genome and dental variation.

Table 3. Association Tests Using Multiple Regression Analyses[a]

Traits	Single-Nucleotide Polymorphism	B	Standard Error	β	*P*
U2					
CH	rs6184	−0.148	0.202	−0.730	.465
RL	rs6184	−0.578	0.280	−2.060	.041*
C+R	rs6184	−0.727	0.386	−1.880	.062
C/R	rs6184	0.030	0.021	1.410	.160
U3					
CH	rs6184	−0.107	0.196	−0.540	.587
RL	rs6184	−0.756	0.332	−2.280	.024*
C+R	rs6184	−0.863	0.427	−2.020	.045*
C/R	rs6184	0.032	0.018	1.840	.067
L2					
CH	rs6184	−0.055	0.152	−0.360	.719
RL	rs6184	−0.490	0.220	−2.230	.027*
C+R	rs6184	−0.545	0.288	−1.900	.060
C/R	rs6184	0.025	0.016	1.560	.122

[a] CH indicates crown height; RL, root length; C+R, overall tooth length; and C/R, crown-to-root ratio.

* $P < .05$. For rs6184, the dominant model was used (CC = 0, CA or AA = 1). Sex was also included as a covariate in the analysis.

CONCLUSIONS

- GHR rs6184 variant is associated with root length (U2 RL, U3 RL, L2 RL) and overall tooth length (U3 C+R).
- GHR rs6180 variant is not associated with crown height, root length, overall tooth length, or crown-to-root ratio.

ACKNOWLEDGMENTS

We are deeply grateful to the subjects who participated in the present study. This work was supported by KAKENHI grant 17K11947.

REFERENCES

1. Marques LS, Generoso R, Armond MC, Pazzini CA. Short-root anomaly in an orthodontic patient. *Am J Orthod Dentofacial Orthop*. 2010;138:346–348.
2. Kamble RH, Lohkare S, Hararey PV, Mundada RD. Stress distribution pattern in a root of maxillary central incisor having various root morphologies: a finite element study. *Angle Orthod*. 2012;82:799–805.
3. Lombardo L, Scuzzo G, Arreghini A, Gorgun O, Ortan YO, Siciliani G. 3D FEM comparison of lingual and labial orthodontics in en masse retraction. *Prog Orthod*. 2014;15:38.
4. Heravi F, Salari S, Tanbakuchi B, Loh S, Amiri M. Effects of crown-root angle on stress distribution in the maxillary central incisors' PDL during application of intrusive and retraction forces: a three-dimensional finite element analysis. *Prog Orthod*. 2013;14:26.
5. Oyama K, Motoyoshi M, Hirabayashi M, Hosoi K, Shimizu N. Effects of root morphology on stress distribution at the root apex. *Eur J Orthod*. 2007;29:113–117.
6. Townsend G, Hughes T, Luciano M, Bockmann M, Brook A. Genetic and environmental influences on human dental variation: a critical evaluation of studies involving twins. *Arch Oral Biol*. 2009;54(suppl 1):S45–S51.
7. Park JH, Yamaguchi T, Watanabe C, et al. Effects of an Asian-specific nonsynonymous EDAR variant on multiple dental traits. *J Hum Genet*. 2012;57:508–514.
8. Kimura R, Yamaguchi T, Takeda M, et al. A common variation in EDAR is a genetic determinant of shovel-shaped incisors. *Am J Hum Genet*. 2009;85:528–535.
9. Kimura R, Watanabe C, Kawaguchi A, et al. Common polymorphisms in WNT10A affect tooth morphology as well as hair shape. *Hum Mol Genet*. 2015;24:2673–2680.

10. Lee WC, Yamaguchi T, Watanabe C, et al. Association of common PAX9 variants with permanent tooth size variation in non-syndromic East Asian populations. *J Hum Genet*. 2012;57:654–659.
11. Leung DW, Spencer SA, Cachianes G, et al. Growth hormone receptor and serum binding protein: purification, cloning and expression. *Nature*. 1987;330:537–543.
12. Ramirez-Yañez GO, Smid JR, Young WG, Waters MJ. Influence of growth hormone on the craniofacial complex of transgenic mice. *Eur J Orthod*. 2005;27:494–500.
13. Sjögren K, Bohlooly-YM, Olsson B, et al. Disproportional skeletal growth and markedly decreased bone mineral content in growth hormone receptor –/– mice. *Biochem Biophys Res Commun*. 2000;267:603–608.
14. Yamaguchi T, Maki K, Shibasaki Y. Growth hormone receptor gene variant and mandibular height in the normal Japanese population. *Am J Orthod Dentofacial Orthop*. 2001;119:650–653.
15. Campbell R, Weinshel R, Backeljauw P, Wilson S, Bean J, Shao M. Dental development in children with growth hormone insensitivity syndrome: Demirjian analysis of serial panoramic radiographs. *Cleft Palate Craniofac J*. 2009;46:409–414.
16. Tsuboi Y, Yamashiro T, Ando R, Takano-Yamamoto T. Evaluation of catch-up growth from orthodontic treatment and supplemental growth hormone therapy by using Z-scores. *Am J Orthod Dentofacial Orthop*. 2008;133:450–458.
17. Davidopoulou S, Chatzigianni A. Craniofacial morphology and dental maturity in children with reduced somatic growth of different aetiology and the effect of growth hormone treatment. *Prog Orthod*. 2017;18:10.
18. Van Erum R, Mulier G, Carels C, de Zegher F. Craniofacial growth and dental maturation in short children born small for gestational age: effect of growth hormone treatment. Own observations and review of the literature. *Horm Res*. 1998;50:141–146.
19. Smid JR, Rowland JE, Young WG, et al. Mouse cellular cementum is highly dependent on growth hormone status. *J Dent Res*. 2004;83:35–39.
20. Katayama K, Yamaguchi T, Sugiura M, Haga S, Maki K. Evaluation of mandibular volume using cone-beam computed tomography and correlation with cephalometric values. *Angle Orthod*. 2014;84:337–342.
21. Abeleira MT, Outumuro M, Ramos I, Limeres J, Diniz M, Diz P. Dimensions of central incisors, canines, and first molars in subjects with Down syndrome measured on cone-beam computed tomographs. *Am J Orthod Dentofacial Orthop*. 2014;146:765–775.
22. Springate SD. The effect of sample size and bias on the reliability of estimates of error: a comparative study of Dahlberg's formula. *Eur J Orthod*. 2012;34:158–163.
23. Harris EF, Smith RN. Accounting for measurement error: a critical but often overlooked process. *Arch Oral Biol*. 2009;54(suppl 1):S107–S117.
24. Becks H, Collins DA, Asling CW, Simpson ME, Li CH, Evans HM. The gigantism produced in normal rats by injection of the pituitary growth hormone; skeletal changes; skull and dentition. *Growth*. 1948;12:55–67.
25. Borges AH, Siqueira CR, Pedro FL, Palma VC, Sakai VT, Volpato LE. Growth hormone insensitivity syndrome: unusual oral manifestations. *J Dent Child (Chic)*. 2013;80:150–153.
26. Tomoyasu Y, Yamaguchi T, Tajima A, Nakajima T, Inoue I, Maki K. Further evidence for an association between mandibular height and the growth hormone receptor gene in a Japanese population. *Am J Orthod Dentofacial Orthop*. 2009;136:536–541.
27. Kang EH, Yamaguchi T, Tajima A, et al. Association of the growth hormone receptor gene polymorphisms with mandibular height in a Korean population. *Arch Oral Biol*. 2009;54:556–562.
28. Sasaki Y, Satoh K, Hayasaki H, Fukumoto S, Fujiwara T, Nonaka K. The P561T polymorphism of the growth hormone receptor gene has an inhibitory effect on mandibular growth in young children. *Eur J Orthod*. 2009;31:536–541.
29. Nakawaki T, Yamaguchi T, Isa M, et al. Growth hormone receptor gene variant and three-dimensional mandibular morphology. *Angle Orthod*. 2017;87:68–73.
30. Le Cabec A, Kupczik K, Gunz P, Braga J, Hublin JJ. Long anterior mandibular tooth roots in Neanderthals are not the result of their large jaws. *J Hum Evol*. 2012;63:667–681.
31. Fukase H, Suwa G. Influence of size and placement of developing teeth in determining anterior corpus height in prehistoric Jomon and modern Japanese mandibles. *Anthropol Sci*. 2010;118:75–86.
32. Smith P, Wax Y, Adler F. Population variation in tooth, jaw, and root size: a radiographic study of two populations in a high-attrition environment. *Am J Phys Anthropol*. 1989;79:197–206.
33. Zhang CZ, Young WG, Li H, Clayden AM, Garcia-Aragon J, Waters MJ. Expression of growth hormone receptor by immunocytochemistry in rat molar root formation and alveolar bone remodeling. *Calcif Tissue Int*. 1992;50:541–546.
34. Pentinpuro RH, Lähdesmäki RE, Niinimaa AO, Pesonen PR, Alvesalo LJ. Crown heights in the permanent teeth of 45,X and 45,X/46,XX females. *Acta Odontol Scand*. 2014;72:908–916.
35. Pentinpuro RH, Lähdesmäki RE, Alvesalo LJ. Root lengths in the permanent teeth of 45,X females. *Acta Odontol Scand*. 2013;71:778–785.
36. Zorba E, Vanna V, Moraitis K. Sexual dimorphism of root length on a Greek population sample. *Homo*. 2014;65:143–154.
37. Lähdesmäki R, Alvesalo L. Root growth in the permanent teeth of 45,X/46,XX females. *Eur J Orthod*. 2006;28:339–344.
38. Lazos JP, Senn LF, Brunotto MN. Characterization of maxillary central incisor: novel crown-root relationships. *Clin Oral Investig*. 2014;18:1561–1567.
39. Black GV. *Descriptive Anatomy of the Human Teeth*. Philadelphia, Pa: S.S. White Dental Manufacturing Company; 1902.
40. Suwa G, Fukase H, Kono RT, Kubo D, Fujita M. Mandibular tooth root size in modern Japanese, prehistoric Jomon, and Late Pleistocene Minatogawa human fossils. *Anthropol Sci*. 2011;119:159–171.
41. Brook AH, Griffin RC, Townsend G, Levisianos Y, Russell J, Smith RN. Variability and patterning in permanent tooth size of four human ethnic groups. *Arch Oral Biol*. 2009;54(suppl 1):S79–S85.
42. Huang SY, Kang T, Liu DY, Duan YZ, Shao JL. Variability in permanent tooth size of three ancient populations in Xi'an, northern China. *Arch Oral Biol*. 2012;57:1467–1473.

43. Hanihara T, Ishida H. Metric dental variation of major human populations. *Am J Phys Anthropol*. 2005;128:287–298.
44. Othman SA, Harradine NW. Tooth-size discrepancy and Bolton's ratios: a literature review. *J Orthod*. 2006;33:45–51; discussion 29.
45. Sumi K, Kawakubo Y, Yamashita Y, Goto M, Kuraoka A. Generational differences in tooth size in the Japanese population: analysis of cohorts with a generation gap of four to five decades. *Fukuoka Igaku Zasshi*. 2014;105:225–233.