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Recent Advances in the Genetics of Orthodontics

Yoko Tomoyasu, Tetsutaro Yamaguchi and Koutaro Maki
Department of Orthodontics, School of Dentistry, Showa University
Japan

1. Introduction

Consideration of genetic factors is an essential element of diagnosis that underlies orofacial traits. In particular, orthodontic clinicians may have an interest in craniofacial growth and tooth movement. These parts of the diagnostic process are important to understand the cause of the problem before attempting treatment. In this chapter, we present our studies on the genetic causes of external apical root resorption and mandibular morphology, and review related studies.

2. External apical root resorption (EARR)

External apical root resorption (EARR) is a common outcome following orthodontic treatment. The factors associated with this phenomenon are genetic background, the length of treatment, the magnitude of the orthodontic forces, the type of orthodontic movement, trauma and others (Brin & Bollen, 2011). Abnormal root shape is also a significant risk factor in root resorption (Kjaer, 1995). Allergy and asthma may also be high-risk factors for the development of excessive root resorption during orthodontic tooth movement (Nishioka et al., 2006).

Interleukin 1 beta IL-1B, a potent bone-resorptive cytokine, is a key component of the complex signaling pathways leading to root resorption. The proinflammatory cytokine IL-1 is a key mediator of the inflammatory response and regulates the proliferation of fibroblasts in the gingival and periodontal ligaments. The level of IL-1B notably increases in the human gingival crevicular fluid during orthodontic treatment (Uematsu et al., 1996). The levels of IL-1 correlate with individual differences in the amount of tooth translation (Iwasaki et al., 2001) and are thought to play a role in susceptibility to EARR (Davidovitch, 1991). Moreover, *IL-1B*-knockout mice demonstrate significantly greater root resorption than wild-type controls when undergoing experimental orthodontic treatments (Viecilli et al., 2009).

A C-to-T single nucleotide polymorphism (SNP) in *IL-1B*, rs1143634, may be causally associated with susceptibility to EARR. The TT genotype of this polymorphism has been associated with a 4-fold increase in IL-1B production (Pociot et al., 1992; di Giovine et al., 1995). Al-Qawasmi et al. (2003) reported an association of this polymorphism with the risk of EARR in the Caucasian population. Subjects homozygous for the C allele had a 5.6-fold

(95% confidence interval, 1.9–21.2) increased risk of EARR greater than 2 mm compared with those not homozygous for the C allele.

2.1 EARR and the Il-1B gene in the Japanese

Differences in tooth shape are used to characterize race and to provide an indication of racial affinity between human populations. For example, there are differences in the approximal root topography of teeth in the Chinese population compared with other populations (Ong & Neo, 1990). Sameshima & Sinclair (2001) reported that Asian patients experienced significantly less root resorption than Caucasian or Hispanic patients. We examined the association between a single polymorphism (rs1143634) in *IL-1B* and root resorption in 54 Japanese subjects (Tomoyasu et al., 2009a). Lateral cephalograms and panoramic radiographs were obtained from 54 Japanese subjects comprising 18 men and 36 women. The roots of three types of teeth were measured on pretreatment and posttreatment lateral cephalometric and panoramic radiographs. The roots of the maxillary and mandibular central incisors were measured from the pretreatment and posttreatment cephalometric radiographs. The mesial and distal roots of the left and right sides were measured on the panoramic radiographs. We amplified DNA by polymerase chain reaction, and genotyped the SNP by DNA sequencing. We found no significant difference between the genotype frequencies of the *IL-1B* SNP rs1143634 and the amount of root resorption in the Japanese population (Tables 1, 2).

	Maxillary incisor (mm)				Mandibular incisor (mm)			
	n	Mean	S.D.	P	n	Mean	S.D.	P
CC	45	2.1	2	0.29	48	1.7	1.5	0.86
CT	6	2.9	1.3		6	1.7	1.8	
	Mandibular mesial incisor (mm)				Mandibular incisor (mm)			
	n	Mean	S.D.	P	n	Mean	S.D.	P
CC	46	0.5	1.4	0.39	46	0.5	0.7	0.27
CT	6	0.7	1		6	1.2	1.6	

Table 1. The relationship between the *IL-1B* SNP rs1143634 and the amount of root resorption of the maxillary incisor, mandibular incisor, mandibular mesial molar, and mandibular distal molar in Japanese subjects. No statistical significance of the differences between the *IL-1B* genotype and the amount of root resorption was found.

	Unaffected groups (<2.0mm)		Affected groups (≥2.0mm)		
IL-1B marker	CC	CT	CC	CT	P
Maxillary central incisor	22	2	23	4	0.47
Mandibular central incisor	31	3	17	3	0.48
Mandibular first molar, mesial root	45	5	1	1	0.08
Mandibular first molar, distal root	44	5	2	1	0.22

Table 2. Relationship between the unaffected and affected groups by genotype. Subjects were classified as unaffected (<2.0 mm) or affected (≥2.0 mm), according to the amount of root resorption. No statistical significance of the differences between the *IL-1B* genotype and the classification of root resorption was determined.

2.2 Accuracy of EARR measurements

In our study, we failed to replicate in the Japanese population the previously reported association between the *IL-1B* polymorphism and EARR. In our study, we used lateral cephalograms to measure the amount of root resorption. In the study by Al-Qawasmi et al. (2003), lateral cephalograms and panoramic radiographs were used to measure EARR. However, the intraoral radiograph is more useful for measuring the amount of root resorption than the panoramic radiograph or lateral cephalogram. McFadden et al. (1989) indicated that errors in measurement using electronic calipers on lateral cephalometric films were approximately 2.5 times more frequent than the errors using periapical radiographs. Sameshima & Asgarifar (2001) suggested that the use of panoramic radiographs to measure root resorption might overestimate the amount of root loss by 20% or more, and that they are not as precise or reliable as intraoral radiographs (Bastos Lages et al., 2009).

To solve this problem, Bastos Lages et al. (2009) used periapical radiographs to determine the presence and severity of EARR to reduce the bias related to the diagnosis of EARR by other types of radiographs. In this report, the positive association was replicated in the Brazilian population.

They described that errors will certainly continue to occur until an accurate three-dimensional imaging system is available, because the accuracy of periapical x-rays for EARR measurements is unlikely that any inconsistencies in evaluating root resorption by this method in our study seriously biased the estimates of EARR.

2.3 Ethnic differences in the frequency of the *IL-1B* polymorphism

It is well known that differences in SNP frequencies among human populations are ethnicity-dependent (Wang et al., 2008). Ethnic factors are also considered to be a major variable in evaluating predisposition to EARR (Sameshima & Sinclair, 2001).

We characterized the ethnic variation at the *IL-1B* locus by examining the allele frequencies of the *IL-1B* polymorphism among individuals with different ethnic backgrounds. DNA samples from 24 Han Chinese, 24 African Americans, 24 European Americans, and 24 Hispanics were obtained, but no craniofacial measurements taken, and were used as reference populations for the allele frequencies of the *IL-1B* SNP.

There were marked differences in the frequency of the T allele of rs1143634 among the various ethnic populations (Table 3). The highest frequency (29.2%) was observed in the European Caucasians. The African American and Hispanic populations carried the T allele at frequencies of 10.4% and 14.7%, respectively. In contrast, the Japanese and Han Chinese populations carried the T allele at the markedly lower frequencies of 5.6% and 2.5%, respectively.

	Japanese	Han Chinese	African American	European Caucasian	Hispanic
n	54	24	24	24	24
C	94.4%	97.5%	89.6%	70.8%	85.3%
T	5.6%	2.5%	10.4%	29.2%	14.7%

Table 3. Allele distribution of the *IL-1B* SNP rs1143634 among different ethnicities.

The marked allelic diversity between different ethnic groups at this locus may explain our failure to identify any association between rs1143634 and EARR in the Japanese. We observed that Asian populations have a higher frequency of the C allele than other ethnic groups. In our data, only six Japanese subjects had a T allele. The failure to detect an association between the rs1143634 and root resorption in the Japanese may be due to the study being underpowered to detect a polymorphism that occurs at a relatively low frequency. In contrast, in the populations in which positive associations with EARR were identified, namely Caucasians and Brazilians, the T allele occurs at a higher frequency (Caucaisans: C; 70.8%, T; 29.2%, Tomoyasu et al., 2009a) (Brazilians: C; 43.4%, T; 56.6%, Bastos Lages et al., 2009), respectively. Further studies evaluating the genetic determinants of root resorption susceptibility are required.

3. Mandibular morphology and the growth hormone receptor gene

Craniofacial morphology has a strong genetic component but it is also influenced by environmental factors, making it a complex trait to study. Growth hormone (GH) is a craniofacial morphological determinant; it plays a major role in the growth and development of the craniofacial complex by directly and indirectly modulating the size and the angular relationships of the craniofacial structures (Ramirez-Yanez et al., 2005). Children with deficient or excess GH have been reported to develop unique craniofacial configurations (Pirinen et al., 1994). Disproportionate growth of the cranial base structures and jaws results in facial retrognathia, which entails a proportionately smaller posterior than anterior facial height in persons of short stature with GH deficiency (Kjelberg et al., 2000). GH therapy for children with short stature or Turner syndrome results in characteristic patterns of craniofacial growth (Van Erum et al., 1988; Simmons, 1999). Responses to systemic GH therapy are time- and site-dependent in the craniofacial region, and are associated with an increase in cartilage growth, particularly within the mandibular ramus (Van Erum et al., 1988; Simmons, 1999). Children who receive long-term GH replacement therapy show exaggerated growth of the craniofacial skeleton, especially with respect to the height of the mandibular ramus (Funatsu et al., 2006; Forsberg et al., 2002). A comparison of children with Turner syndrome who received recombinant human GH treatment and a large cross-sectional control group showed a statistically significant increase in ramus growth associated with mandibular ramus height, but not with mandibular body length, maxillary length, or anterior cranial base length (Rongen-Westerlaken et al., 1993).

Growth hormone receptors (GHRs) have been shown by molecular genetic analysis to be present in the mandibular condyle (Lewinson et al., 1994). Analysis of the *Ghr* knockout mouse has revealed that the GH→GHR→insulin-like growth factor 1 system is important in postnatal growth and that GHR plays a role in maintaining proportional skeletal growth (Sjogren et al., 2000). In *Ghr* knockout mice, the height of the mandibular ramus is significantly reduced (Ramirez-Yanez et al., 2005), and disproportionate skeletal growth is reflected by decreased femur:crown-rump and femur:tibia ratios (Sjogren et al., 2000). There are diverse mutations and polymorphisms in the *GHR* gene in humans. Reports have shown a relationship between *GHR* and idiopathic short stature (Goddard et al., 1995) and Laron syndrome (growth hormone insensitivity syndrome), which is marked by a characteristic facial appearance. Interestingly, patients with GHR deficiency showed significantly

decreased vertical facial growth (Schaefer et al., 1994). Therefore, GHR is suggested to have site-, area-, or region-specific effects (Hartsfield, 2005).

3.1 Relationship between the *GHR* gene and mandibular morphology in the Japanese

We quantitatively evaluated the relationship between craniofacial morphology and the P561T variant in exon 10 of the *GHR* gene in the non-syndromic Japanese population (Yamaguchi et al., 2001). DNA and cephalograms were obtained from 50 Japanese men and 50 Japanese women. To analyze craniofacial morphology, measurements were made on tracings of lateral cephalograms under standardized conditions. We measured cranial base length (nasion–sella; N–S), maxillary length (point A-pterygomaxillary fissure; A'–PTM'), overall mandibular length (gnathion–condylion; Gn–Co), mandibular corpus length (pogonion–gonion; Pog'–Go), and mandibular ramus height (condylion–gonion; Co–Go) (Figure 1). Body height was also measured. We identified a significant association of the polymorphic GHR gene (P561T, rs6184) with mandibular ramus height (P = 0.0181) (Table 4).

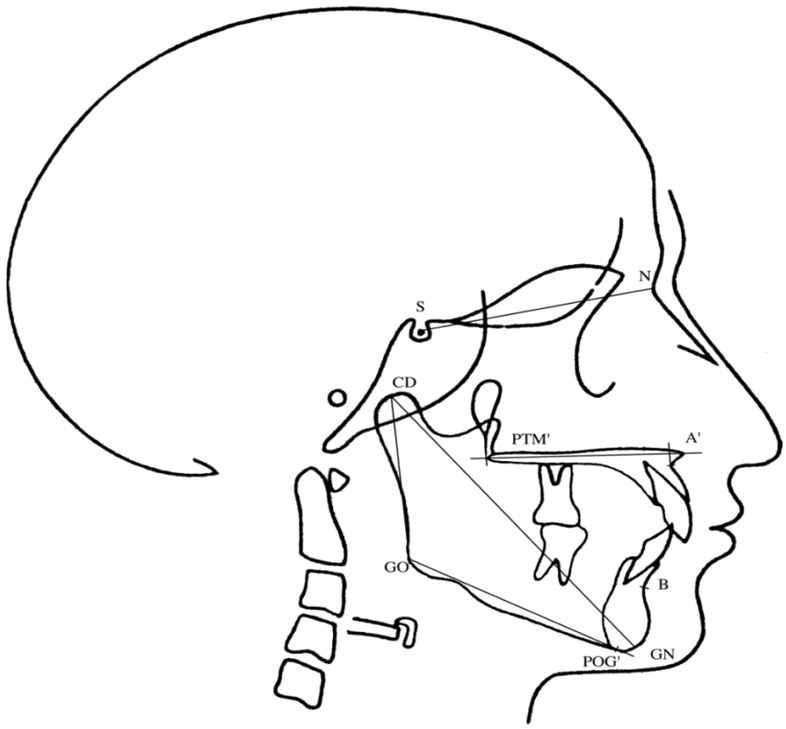


Fig. 1. Cephalometric reference points and lines used to assess the relationship between *GHR* gene variants. N–S, cranial base length; A'–PTM', maxillary length; Co–Go, mandibular ramus length; Pog'–Go; mandibular corpus length; Gn–Co, overall mandibular length.

	P561T	n	Body Height (cm)	N-S (mm)	A′-PTM′ (mm)	Gn-Co (mm)
Subjects	CC	86	165.2±7.8	71.0±3.6	50.9±3.3	126.3±9.5
(100)	CA	14	163.4±10.5	70.0±4.6	50.4±3.7	122.3±9.6
	P		0.32	0.6	0.47	0.12
Men	CC	44	171.0±5.5	72.6±3.6	52.1±3.1	131.6±7.0
(50)	CA	6	173.7±6.5	72.6±5.1	53.0±3.5	131.4±7.4
	P		0.4	0.55	0.53	0.98
Women	CC	42	159.2±4.6	69.3±2.7	49.6±3.0	120.7±8.6
(50)	CA	8	155.6±3.9	68.1±3.3	48.4±2.5	115.5±3.1
	P		0.38	0.32	0.26	0.06

	P561T	n	Pog′-Go(mm)	Co-Go(mm)	Height/Co-Go
Subjects	CC	86	81.2±6.0	63.5±6.9	2.7±0.2
(100)	CA	14	79.3±7.2	58.9±6.1	2.9±0.3
	P		0.32	.018*	.013*
Men	CC	44	84.3±4.7	68.5±4.4	2.5±0.2
(50)	CA	6	86.3±3.7	64.9±2.1	2.7±0.1
	P		0.37	.021*	.015*
Women	CC	42	78.0±5.6	58.3±4.9	2.8±0.3
(50)	CA	8	74.2±3.7	54.4±3.5	2.9±0.3
	P		0.07	.025*	.028*

Table 4. The relationship between *GHR* gene variants and linear measurements in 50 men and 50 women. *P < 0.05.

To confirm these findings, we extended our previous study, genotyping approximately 1.7-times more non-syndromic Japanese individuals than analyzed in a previous report. Genomic DNA and lateral cephalograms were obtained from 167 Japanese subjects comprising 50 men and 117 women. The male subjects were the same as those we reported previously. We genotyped these individuals for five SNPs in the coding region of GHR (exon 10): C422F (rs6182, GG and GT genotype), S473S (rs6176, CC and CT genotype), P477T (rs6183, CC and CA genotype), I526L (rs6180, AA, AC and CC genotype), and P561T (rs6184, CC and CA genotype). We identified a significant relationship between the P56IT and C422F genotypes with mandibular ramus height in the Japanese population ($P < 0.05$; Table 5). These two polymorphisms are in linkage disequilibrium (Tomoyasu et al., 2009b).

			Body height (cm)			N-S (mm)		
		n	Mean	S.D.	P	Mean	S.D.	P
C422F	GG	135	161.6	7.9	0.16	69.7	3.4	0.66
	GT	16	164.6	10.2		69.3	4.4	
S473S	CC	137	161.9	8.4	0.95	69.6	3.5	0.32
	CT	11	161.1	6.1		70.5	2.8	
P477T	CC	146	161.6	8.3	0.47	69.6	3.5	0.58
	CA	4	163.8	9.1		69.5	4.8	
I526L	AA	77	162.7	8.8	0.47	69.5	3.5	0.56
	AC	44	161	7.9		70.2	4	
	CC	32	161.4	6.9		69.4	2.6	
P561T	CC	135	161.6	7.9	0.16	69.7	3.4	0.66
	CA	16	164.6	10.2		69.3	4.4	

			A′-PTM′ (mm)			Gn-Co (mm)		
		n	Mean	S.D.	P	Mean	S.D.	P
C422F	GG	135	50	4.8	0.95	122.9	9.3	0.63
	GT	16	49.9	3.1		121.7	8.5	
S473S	CC	137	49.9	4.8	0.71	122.9	9.2	0.89
	CT	11	49.8	2.1		123	9.7	
P477T	CC	146	49.9	4.7	0.54	122.7	9.1	0.15
	CA	4	51.3	3.5		130.5	11.4	
I526L	AA	77	50.1	3.2	0.06	124.2	9.7	0.19
	AC	44	50.7	3.1		121.6	8.7	
	CC	32	48.1	7.9		121.4	7.7	
P561T	CC	135	50	4.8	0.95	122.9	9.3	0.63
	CA	16	49.9	3.1		121.7	8.5	

			Pog′-Go (mm)			Co-Go (mm)		
		n	Mean	S.D.	P	Mean	S.D.	P
C422F	GG	135	79.5	5.6	0.78	61.6	6.5	0.02*
	GT	16	79.9	7.2		57.9	6.1	
S473S	CC	137	79.9	5.9	0.31	61.5	6.5	0.54
	CT	11	78.5	6.4		60.9	5.6	
P477T	CC	146	79.8	6	0.23	61.3	6.4	0.17
	CA	4	83.3	5.7		65.6	4.5	
I526L	AA	77	80.1	5.8	0.82	62.4	6.7	0.13
	AC	44	79.6	5.5		61.1	6.8	
	CC	32	79.5	6.8		59.7	5.4	
P561T	CC	135	79.5	5.6	0.78	61.6	6.5	0.02*
	CA	16	79.9	7.2		57.9	6.1	

Table 5. Relationship between 5 SNPs in the GHR and 6 linear measurements of body height and craniofacial morphology in 167 Japanese subjects. *P < 0.05.

		Body height(cm)			N-S (mm)		
	n	Mean	S.D.	P	Mean	S.D.	P
d3/fl-GHR							
fl/fl	92	171.2	7.2	0.24	75.3	3.8	0.92
fl/d3	24	169.7	6.3		75.6	3.8	
d3/d3	9	173.7	3.9		75.4	4.4	
C422F/P561T							
GG/CC	124	170.6	7.1	0.49	75.2	3.8	0.7
GT/CA	24	169.6	6.7		75.2	3.7	
S473S							
CC	145						
CT	3						
P477T							
CC	145						
CA	3						
I526L							
AA	62	171.5	7.2	0.19	75.8	3.7	0.24
AC	61	170	7.2		74.8	3.3	
CC	24	169	6.3		75.1	4.5	

		A′-PTM′(mm)			Gn-Co (mm)		
	n	Mean	S.D.	P	Mean	S.D.	P
d3/fl-GHR							
fl/fl	92	52	3.2	0.79	139.6	8.3	0.21
fl/d3	24	52.2	3.4		137.8	6.9	
d3/d3	9	51.3	2.5		142.7	10.4	
C422F/P561T							
GG/CC	124	52.1	3.3	0.32	138.7	8	0.38
GT/CA	24	51.3	2.9		137.7	8.6	
S473S							
CC	145						
CT	3						
P477T							
CC	145						
CA	3						
I526L							
AA	62	52.6	3.2	0.24	139.1	8.7	0.71
AC	61	51.7	3.2		137.9	7.8	
CC	24	51.7	3.7		139.2	7.9	

		Pog′-Go(mm)			Co-Go(mm)		
	n	Mean	S.D.	P	Mean	S.D.	P
d3/fl-GHR							
fl/fl	92	84.8	5.5	0.12	72	7.6	0.59
fl/d3	24	82.8	5.2		70.7	6.3	
d3/d3	9	84.5	4.5		72.5	6.6	
C422F/P561T							
GG/CC	124	83.9	5.5	0.77	71.9	7.1	0.02*
GT/CA	24	84.2	5.3		68.5	5.5	
S473S							
CC	145						
CT	3						
P477T							
CC	145						
CA	3						
I526L							
AA	62	84.3	5.7	0.82	72	7.6	0.68
AC	61	83.5	5.3		71.2	6.5	
CC	24	84.2	84.2		71.1	7.4	

Table 6. The relationship between six SNPs in GHR and six linear measurements of body height and craniofacial morphology in 159 Korean subjects. *$P < 0.05$.

3.2 Relationship between the *GHR* gene and mandibular morphology in Asian populations

Following our report of an association between an exon 10 SNP in the *GHR* gene and mandibular ramus height in the Japanese (Yamaguchi et al., 2001), Zhou et al. (2005) reported the association of another exon 10 *GHR* polymorphism, I526L, with mandibular height in 95 Han Chinese subjects. We did not replicate this finding in 167 Japanese subjects (Tomoyasu et al., 2009b).

We also evaluated the association of *GHR* polymorphisms with mandibular ramus height in the Korean population (Kang et al., 2009). Genomic DNA samples and lateral cephalograms were obtained from 159 Korean subjects, comprising 100 men and 59 women. We tested the five aforementioned exon 10 SNPs plus a common polymorphism *d3/fl-GHR* that results in genomic deletion of exon 3 (Urbanek et al., 1992; Pantel et al., 2000). Two common isoforms of GHR, one full-length (fl-GHR) and the other lacking the extracellular domain encoded by exon 3 (d3-GHR), are associated with differences in responsiveness to GH. Children carrying at least one *d3-GHR* allele show a 1.7- to 2-fold greater response to GH than do *fl-GHR/fl-GHR* homozygotes (Dos-Santos et al., 2004). This common polymorphism has also been associated with the degree of height increase in response to GH therapy in French children of short stature who were born small for gestational age or with idiopathic short stature (Dos-Santos et al., 2004), as well as in German Turner syndrome patients (Binder et al., 2006), and Brazilian GH-deficient children (Jorge et al., 2006).

Table 6 shows the frequencies of the six *GHR* genotypes and the relationships between these genotypes and six linear measurements of body height and craniofacial morphology in 159 Korean subjects. Heterozygosity for S473S and P477T (genotypes CT and CA, respectively) was found in only three subjects. Therefore, statistical analysis was not performed for S473S or P477T. Genotype-specific association analysis revealed that mandibular ramus height only was significantly correlated with the P561T (a C-to-A transversion) and C422F (a G-to-T transversion) variants (P = 0.024). The *d3/fl-GHR* polymorphism was not associated with any measurement. These data replicated our findings in the Japanese population, but were different from the findings reported for the Han Chinese population.

We confirmed an association between polymorphisms P561T and C422F and mandibular ramus height. Individuals with the genotype CC for polymorphism P561T and the genotype GG for polymorphism C422F had a significantly greater mandibular height than those with genotypes CA and GT, respectively.

3.3 Ethnic differences in the *GHR* SNP allele frequencies

A clue to understanding ethnic differences in the association between the *GHR* locus and mandibular ramus height might be gained by determining the allelic frequencies of the five SNPs among 24 Han Chinese, 24 African Americans, 24 European Americans, and 24 Hispanics. we examined the allelic frequencies of the five SNPs among 24 Han Chinese, 24 African Americans, 24 European Americans, and 24 Hispanics. We found that the allele frequencies vary considerably (Table 7).

The reason for the difference between Japanese/Koreans and Chinese remains unclear; however, we did find widely discordant allele frequencies in the *GHR* exon 10 SNPs between some of the different ethnic groups. Indeed, the association of *GHR* is different depending on ethnicity in other cases, such as Laron syndrome (Hopp et al., 1996; Shevah et al., 2004) and idiopathic short stature (Blum et al., 2006; Hujeirat et al., 2006; Bonioli et al.,

2005; Sjoberg et al., 2001; Sanchez et al., 1998; Johnston et al., 2000). These differences might imply the need for independent studies on the association of *GHR* with craniofacial morphology in each ethnic group. The mandibular size of Japanese people appears to be slightly smaller than that of European-Americans (Miyajima et al., 1996) or Caucasians (Ishii et al., 2001; Ishii et al., 2002; Ishizuka et al., 1989).

		Japanese (n=167)	Han Chinese (n=24)	African American (n=24)	European American (n=24)	Hispanic (n=24)
C422F	G	94.1%	79.4%	100.0%	100.0%	100.0%
	T	5.9%	20.6%	0.0%	0.0%	0.0%
S473S	C	96.3%	97.3%	100.0%	97.5%	100.0%
	T	3.7%	2.6%	0.0%	2.5%	0.0%
P477T	C	98.7%	100.0%	100.0%	100.0%	100.0%
	A	1.3%	0.0%	0.0%	0.0%	0.0%
I526L	A	46.7%	38.2%	64.3%	58.3%	62.4%
	C	53.3%	61.8%	35.6%	41.6%	37.5%
P561T	C	94.7%	80.0%	100.0%	100.0%	100.0%
	A	5.2%	19.9%	0.0%	0.0%	0.0%

Table 7. Allele distribution of 5 SNPs in exon10 of the GHR

On average, the allele frequencies for populations from different continents differ by 16–19%, and for populations within a continent, such as Koreans and Japanese, they differ by 5–10% (Miller et al., 2005). These differences may be sufficiently large, even among the closely related Korean, Japanese, and Chinese populations, to cause substructural problems for case–control genetic studies of complex traits. Indeed, our findings in the Japanese and Korean populations were not replicated in the Han Chinese. A haplotype-based study based on HapMap data is required to assess the differences among Asian populations, and a larger-scale study with the ethnicities kept distinct is required to obtain a conclusive result (Roeder et al., 2006; Ambrosius et al., 2004; Schork et al., 2002; Longmate et al., 2001). Our work emphasizes the importance of close matching of ethnic groups, especially when measuring craniofacial morphology, which is known to vary by ethnicity (Miyajima et al., 1996; Ishii et al., 2001; Ishii et al., 2002; Ioi et al., 2007).

Growth hormone insensitivity syndrome of genetic origin has been linked to many different mutations of *GHR*, and is associated with a wide range of severities of clinical and biochemical phenotypes. Mandibular growth is also influenced by multiple factors, among which heterozygous *GHR* mutations appear to play a more or less important role, depending on the kind of mutation and on the overall genetic make-up of the individual. Although there is continuing interest in the functional importance of the P56IT and C422F variants, their precise roles remain unknown. The availability of an environmental factor (*i.e.*, orthopedic treatment) has made it possible to initiate therapeutic trials on children with short ramus height. Sasaki et al. (2007) reported a Japanese patient with ectodermal dysplasia, and proposed that the P561T variant could be a genetic marker for mandibular growth. Sasaki et al. (2009) reported that a difference in mandibular growth between P561T heterozygous and wild-type individuals could be demonstrated by cephalometric measurements during childhood. A heterozygous P561T mutation may affect mandibular growth during early childhood, as it is hypothesized to function as an inhibitory factor in the process of mandibular growth. *GHR* is considered a possible genetic marker for mandibular ramus height (Sasaki et al., 2007). This genetic factor might be considered along with other factors associated with mandibular growth when planning treatment to influence

mandibular height, such as Herbst appliances, functional appliances, headgear, and facemask therapy.

3.4 Mandibular prognathism

We previously reported a genome-wide linkage analysis with 90 mandibular prognathism sib-pairs from an Asian population, and identified three significantly linked chromosomal loci: 1p36, 6q25, and 19p13.2 (Yamaguchi et al., 2005). These do not include the *GHR* locus on chromosome 5. We did not find any *GHR* gene SNPs that were associated with mandibular corpus length or overall mandibular length; there was also no identified association in the Chinese population (Zhou et al., 2005).

Recently, there have been four reports describing mandibular prognathism-related genes or loci. Jang et al. (2010) reported that polymorphisms in matrilin-1 could be used as a marker for genetic susceptibility to mandibular prognathism. Xue et al. (2010) reported an association between genetic polymorphisms in the erythrocyte membrane protein band 4.1 gene and mandibular prognathism. Li et al. (2010, 2011) reported a novel suggestive linkage locus for mandibular prognathism in two Chinese pedigrees. The linked region, around SNP rs875864 on chromosome 4, contains candidate genes include *EVC* and *EVC2* (Li et al., 2010), and that on chromosome 4 between rs1468507 and rs7141857 contains candidate genes including transforming growth factor, beta 3 and latent transforming growth factor beta binding protein (Li et al., 2011). Further studies will be needed to find the rare variants causing mandibular prognathism.

3.5 Conclusion

While various environmental factors contribute to morphogenesis of the mandible, genetic factors play a substantial role (Chang et al., 2006). However, there are very few reports that have examined the correlation between craniofacial morphology and genotype. Our studies have succeeded in elucidating susceptibility locus-related non-syndromic craniofacial morphology. We have also found marked diversities in the allelic frequencies of GH receptor polymorphisms within a multi-ethnic study population, which might partly explain the differing craniofacial morphologies among different ethnicities. Recent advances in clinical genetics have increased our knowledge of the genetic impact on craniofacial phenotypes. Identifying the genetic susceptibility for specific craniofacial phenotypes would enable more effective diagnosis and treatment for patients while they were still growing.

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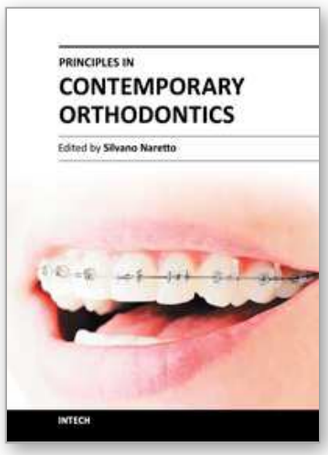
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51000 Rijeka, Croatia
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Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
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