# The craniofacial characteristics of osteogenesis imperfecta patients

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SUMMARY The aim of this study was to identify the craniofacial characteristics of 16 osteogenesis imperfecta (OI) patients, 10 males and 6 females, aged 7–15 years. The control group comprised 863 Chinese children from 6 to 18 years of age. Eleven cephalometric reference points and 25 variables were measured on the lateral cephalometric radiographs. Cochrane's method of unequal variance *t*-test was used to differentiate the differences between two groups.

A Class III occlusal relationship was found in 62.5 per cent of the OI patients. The maxilla was more retrusive than the mandible in relation to the cranial base. Face heights, the effective maxilla and mandibular lengths, and anterior and posterior cranial base lengths were significantly shorter than the control subjects. The facial divergence, the cranial base (N-S-Ar, P < 0.001), and the gonial (Ar-Go-Gn, P < 0.001) angles were significantly enlarged, while the articular angle (S-Ar-Go, P < 0.001) was significantly reduced.

The findings showed that the OI patient had a more prominent Class III occlusal relationship, prognathic mandible, larger facial divergence, shorter face heights, defective sagittal growth of the maxilla and mandible, a flattened cranial base angle, impaired cranial base growth, and more forward counterclockwise rotation in mandibular growth compared with the controls.

## Introduction

Osteogenesis imperfecta (OI) is a hereditary connective tissue disorder caused by type I collagen defects (Byers, 1993). It occurs in all racial and ethnic groups. The detectable incidence in infancy is approximately one in 20 000 (Smith, 1995). The real incidence may be higher due to undiagnosed children with a mild expression (Engelbert et al., 1998). Most OI patients have mutations in COL1A1 on chromosome 17 and/or COL1A2 on chromosome 7, which are genes that encode type I collagen (Korkko et al., 1998). The clinical manifestations include fragile bones, blue sclera, early deafness, and other connective tissue defects. OI patients can be categorized into mild (type I), perinatal lethal (type II), progressive deforming (type III), and moderately severe (type IV) types, according to the classification of Sillence et al. (1979). Further subdivisions of the disorder with seven subtypes have been defined by the application of modern bone histology techniques (Glorieux et al., 2000, 2002; Ward et al., 2002).

OI is chiefly a disease of the mesoderm. The alterations in quality or quantity of type I collagen may induce morphological abnormality of facial bones resulting in an abnormal craniofacial complex growth, malformation of the upper and lower jaws, dental arches, and teeth (Isshiki, 1966). The different facial characteristics of various types of OI are related to their severity (Ormiston and Tideman, 1995). OI patients usually present with a triangular face, protrusive bitemporal bone and prominent frontal bone (Freedus *et al.*, 1976; Libman, 1981), an overhanging occiput (Freedus *et al.*, 1976), and a relatively larger head circumference (Lund *et al.*, 1999). Dental malocclusions are marked in many OI subjects and include a high incidence of Class III malocclusions (Engelbert *et al.*, 1998), anterior and/or posterior crossbite, and posterior open bite (Isshiki, 1966). These conditions are probably combined with the skeletal and dentoalveolar abnormality (O'Connell and Marini, 1999).

It is necessary to identify the craniofacial characteristics of OI patients to evaluate possible growth and development or the results of intervention. Very few studies have included details of the cephalometric measurements of the craniofacial characteristics of OI patients, especially children and adolescents. The aim of the present study was to compare the craniofacial complex characteristics on lateral cephalograms between normal Asian populations with Asian OI patients.

## Subjects and methods

The study group included 16 OI patients referred from the Pediatric Genetic Department of Chang Gung Children's Hospital for dental evaluation. Ten boys and six girls aged from 7 to 15 years were clinically and radiographically examined. They comprised five type I, three type III, and

eight type IV OI patients (Table 1). None of the subjects had previous posterior tooth extractions or orthodontic intervention. Informed consent was obtained for both the genetic and dental examinations from all subjects and their parents.

The control groups comprised 863 Chinese children (422 males and 441 females) aged from 6 to 18 years from a previous study (Fan, 1995). They met the requirements of acceptable occlusion, facial profile, and absence of previous orthodontic treatment.

Standardized lateral cephalograms of the OI patients were obtained and a cephalometric analysis comprising linear and angular measurements undertaken. The lateral cephalograms were taken in a rigid cephalostat (Gendex 900, Gx-Ceph, Milwaukee, Wisconsin, USA) with a filmfocus distance of 170 cm. The distance from the median sagittal plane to focus was 155 cm and the linear enlargement approximately 10 per cent for points situated in the median plane. The reference points and planes used are shown in Figure 1. Eleven cephalometric reference points and 25 variables were measured.

A sliding calliper, accurate to 0.1 mm, was used to measure the distances between the reference points (marked with a pencil on a 0.003-inch acetate matte tracing paper) to the nearest half millimetre. The angular measurements were made to the nearest whole degree with a protractor. When there were two images of the structure, the reference point was placed in the midpoint between these images.

The lateral cephalograms of the OI patients were traced and measured twice by one author (PC). Each landmark location was reviewed by one of the other authors (SL) before cephalometric tracing. The interval between measurements was 3 months. The intraobserver error was analysed using the method suggested by Bland and Altman (1986). It was found, with four exceptions (Pg-Nv 3.9 per cent, S-Go/N-Me 5.3 per cent, A-Gn 3.34 per cent, and S-Ar-Go 5.12 per cent), that the error of the method was less than 3 per cent of the total biological variance.

Cochrane's method of unequal variance *t*-test was used to determine the difference between the two groups. A value of P < 0.05 was defined as statistically significant.

## Results

The results of the cephalometric measurements of the OI group and their controls are shown in Table 2.

## Intermaxillary relationship

The antero-posterior position of the maxilla relative to the anterior cranial base (SNA) in OI patients was smaller than that in the controls. In the OI group, the maxillo-mandibular base relationship in the sagittal plane (ANB) showed a significant (P < 0.001) retrusive tendency compared with the controls.

For the Frankfort horizontal plane, point A projection was relatively more retrusive than point B projection in the OI patients. The differences in these two measurements were highly significant (AH-BH, P < 0.001).

## Facial divergence

In the OI group, the angle between the mandibular plane and anterior cranial base (SN-MP) was significantly (P < 0.001) greater than that in the controls, and the facial divergence (SN-FH, P < 0.001) was larger by 10 degrees in the OI patients compared with the controls.

#### Face height measurements

All face height measurements, including posterior face height (S-Go), total anterior face height (N-Me), lower face

OI type DI (±, age in years)	Male, <i>n</i> = 10						Female, $n = 6$					
	Туре І		Type III		Type IV		Туре І		Type III		Type IV	
	(+)	(-)	(+)	(-)	(+)	(-)	(+)	(-)	(+)	(-)	(+)	(-)
7 8 9	1		1 1		1	1	1				1	2 1
10 11 12 13 14	1 1					1 1			1			
15 Total	3	1 1	2	0	1	3	1	0	1	0	1	3

 Table 1
 Osteogenesis imperfecta (OI) patients' data.

(+): with dentinogenesis imperfecta (DI); (-): without DI; Type I, mild type of OI; Type III, progressive deforming type of OI; Type IV, moderately severe type of OI.



Figure 1 The cephalometric points. Landmark—S = sella, the centre of sella turcica; N = nasion, the most anterior point on the frontonasal suture; Or = orbitale, the lowest point on the infraorbital margin; Po = porion, the uppermost point of the body of the external auditory meatus, usually regarded as coincidental with the uppermost point of the ear rods of the cephalostat. Point A = subspinale, the deepest midline point between anterior nasal spine and prosthion; point B = supramentale, the deepest point in the bony outline between infradentale and pogonion; Pog = pogonion, the most anterior point of the bony chin; Me = menton, the lowest point on the bony outline of the mandibular symphysis; Go = gonion, the most lateral external point at the junction of the horizontal and ascending rami of the mandible; Gn = gnathion, the most anterior and inferior point on the body outline of the chin, situated equidistant from Pog and Me; Ar = articulare, the point of intersection of the dorsal contours of the posterior border of the mandible and temporal bone. Planes—FH plane = Frankfort plane, a transverse plane through the skull represented by a line joining porion and orbitale; S-N = anterior cranial base length; Nv = nasion perpendicular, a vertical line existing downward from nasion perpendicular to the FH plane; Go-Gn = the mandibular pane (MP). Linear measurements-A-Nv, the distance from point A to nasion perpendicular; Pog-Nv, the distance from Pog to Nv; AH-BH, the vector from AH (point A projected to FH plane) to BH (point B projected to FH plane); S-Go, posterior face height (PFH); N-Me, anterior face height (AFH); N-A, upper face height (UFH); A-Me, lower face height (LFH); Ar-A, effective maxillary length; Ar-Gn, effective mandibular length; S-N, anterior cranial base length; S-Ar, posterior cranial base length. Angular measurements-SNA, the antero-posterior position of the maxilla relative to the anterior cranial base; SNB, the antero-posterior position of the mandible relative to the anterior cranial base; ANB, the magnitude of the skeletal jaw discrepancy; SN-FH, the divergence degree of the cranial base to the FH plane; SN-MP, the divergence degree of the cranial base to the mandibular plane (the mandibular plane angle); A-Ar-Gn, posterior angle; Ar-A-Gn, upper anterior angle; A-Gn-Ar, lower anterior angle; N-S-Ar, cranial base angle; S-Ar-Go, articular angle; Ar-Go-Gn, gonial angle. Ratio measurements-S-Go/N-Me, the ratio of PFH/AFH; N-A/A-Me, the ratio of UFH/LFH; Ar-A/Ar-Gn, the ratio of effective maxillary length/effective mandibular length.

height (A-Me), and the ratio (S-Go/N-Me) in the OI patients, were significantly smaller than those in the controls (all P < 0.001). However, the ratio (N-A/A-Me) in OI patients was significantly (P < 0.001) larger than that in the controls.

 Table 2
 Cephalometric measurements in the osteogenesis imperfecta (OI) group and the controls.

Variable	Mean		P value	
	OI group	Control group		
Intermaxillary relationship				
SNA	74.86	82.69	***	
SNB	76.63	78.13	NS	
ANB	-1.77	3.61	***	
A-Nv	-2.70	-0.55	*	
Pg-Nv	-2.14	-7.79	***	
AH-BH	-1.25	6.43	***	
Facial divergence				
SN-FH	16.84	6.89	***	
SN-MP	36.84	32.26	***	
Face heights				
S-Go	62.63	75.38	***	
N-Me	105.46	116.91	***	
S-Go/N-Me	59.46	64.41	***	
A-Me	51.06	59.75	***	
N-A/A-Me	108.45	97.17	***	
Jaw triangle				
Ar-A	76.28	83.51	***	
Ar-Gn	96.50	103.92	***	
A-Gn	49.94	56.75	***	
Ar-A/Ar-Gn	79.45	80.52	NS	
A-Ar-Gn	33.16	33.01	NS	
Ar-A-Gn	95.84	93.6	NS	
A-Gn-Ar	50.28	53.4	***	
Posterior angles				
N-S-Ar	130.72	122.64	***	
S-N	63.87	66.63	***	
S-Ar	29.04	33.11	***	
S-Ar-Go	134.22	146.12	***	
Ar-Go-Gn	129.78	123.49	***	

\*P < 0.05; \*\*\*P < 0.001; NS, not significant.

#### Jaw triangle measurements

The effective maxillary (Ar-A) and mandibular lengths (Ar-Gn) and the intermaxillary length (A-Gn) were significantly (P < 0.001) shorter in the OI patients than in the controls.

The angular measurements (A-Ar-Gn) and (Ar-A-Gn) between the control and OI groups were not significantly different, but the angular measurement (A-Gn-Ar) was significantly (P < 0.001) smaller in the OI group.

#### Posterior angle

Anterior (S-N) and posterior (S-Ar) cranial base lengths were significantly (P < 0.001) smaller in the OI patients than in the controls.

Cranial base (N-S-Ar) and gonial angles (Ar-Go-Gn) were significantly (P < 0.001) larger in the OI patients than in the controls. However, articular angle (S-Ar-Go) in the OI group was significantly (P < 0.001) smaller than that in the control group.

## Occlusal relationship between upper and lower jaws

A Class III occlusal relationship was found in 62.5 per cent of the OI patients in this study.

## Discussion

Osteoblasts in OI patients may produce insufficient or defective type I collagen. The most prominent clinical features of these consequences are deformed and fragile bones. However, all parts of the body containing type I collagen are affected, including bones, dentine, dermis, tendons, organ capsules, fascia, meninges, cornea, and sclera (Tsipouras *et al.*, 1986; Junquera *et al.*, 1989; Cohn and Byers, 1990; Byers, 1993). OI patients usually have a unique facial profile which is different from the normal population (Moore *et al.*, 1983), but little is known about the cephalometric craniofacial characteristics in young OI patients. This study investigated the craniofacial complex characteristics in 16 OI patients.

Since one previous study comprised craniofacial characteristics of 863 normal Chinese children, this group served as the control. Cochrane's unequal variance *t*-test was used, as this method can be applied to different sample distributions.

While the findings between type I, III, and IV OI craniofacial characteristics would be interesting, this comparison was not possible due to the small number of subjects in each subgroup.

A Class III occlusal relationship was found in 62.5 per cent of the OI patients in this study. This is similar to the findings of Schwartz and Tsipouras (1984) and it might be hypothesized that the early loss of vertical dimensions and the unstable occlusion could make the mandible habitually move forward. Isshiki (1966) measured the dental arches of 10 unclassified OI patients and undertook a cephalometric analysis of seven subjects. Six patients had mandibular prognathism. Stenvik *et al.* (1985) reported a negative jaw relationship in 27 OI patients and an inverted incisor relationship in six. Jensen and Lund (1997) found a negative jaw relationship in type III OI patients. These studies show that OI patients have a higher frequency of Class III occlusal relationships compared with the 3–8 per cent in the normal population (Mills, 1966).

For the intermaxillary relationship, SNA and ANB angular measurements were significantly reduced and the AH-BH linear measurement was also much smaller in the OI group. This suggests that the maxilla is more retrusive than the mandible in relation to anterior cranial base. Waltimo-Siren *et al.* (2005) hypothesized that the sella region was depressed by the weight of the brain which resulted in a downward bending of the skull base. If the more ventrally situated sella point causes a decrease in SNA, then SNB would also be reduced, but it was not significantly different between the two groups in this study, which implies that mandibular growth rotation could be in a forward counterclockwise direction.

The A-Nv and Pg-Nv linear measurements were smaller in the OI group indicating that growth of the maxilla and mandible in the sagittal plane was impaired in the OI subjects. Facial divergence (SN-FH and SN-MP) was larger in the OI group, which is reasonable if the sella point is situated more ventrally (Waltimo-Siren *et al.*, 2005). The hyperdivergence of the mandibular plane indicated a skeletal open bite tendency (Sassouni and Nanda, 1964; Figure 2). It was hypothesized that the mandible grew in a forward counterclockwise rotation and was compatible with a clinically prognathic mandible.

The overall somatic size, i.e. average standing height, was reduced in OI patients due to the defective type I collagen formation. The body heights of all OI patients were all less than the third percentile. It was therefore not surprising that vertical linear face height measurements, including posterior face height (S-Go), total anterior face height (N-Me), and lower face height (A-Me), were shortened. The smaller ratio of S-Go/N-Me can be related to the deep midface region, which was more affected in the OI group. However, the larger ratio of upper anterior and lower face heights (N-A/A-Me) indicated more retarded vertical growth of the lower face in OI patients. This was supportive of a closing rotation mandible growth pattern to compensate for the shortened lower anterior face with a prognathic expression.

For the jaw triangle, the effective maxillary and mandibular lengths (Ar-A and Ar-Gn) were shorter in the OI group, confirming defective maxillary and mandibular anterior growth. The reduced effective mandibular length found in this study was different from that reported by Isshiki (1966) and Schwartz and Tsipouras (1984). The

Figure 2 Cephalogram showing the skeletal pattern of an 11-year-old male patient with osteogenesis imperfecta.



difference may be due to the small sample size, various distributions of age, and different OI types. Severe tooth attrition or enamel fractures could have contributed to the reduced intermaxillary length (A-Gn).

The osteoporotic cervical bone of OI patients is not strong enough to withstand the mechanical stress from the weight of the head (Jensen and Lund, 1997). Scoliosis and spinal deformity commonly occurred in OI subjects (Engelbert *et al.*, 1998). Among the postural variables, the position of the head in relation to the cervical column demonstrated the largest set of correlations with craniofacial morphology (Solow and Tallgren, 1976). Although the associations between cranial base flexure and head posture are known, the natural head position is difficult to produce due to the short neck, high thorax, and short stature in OI patients and was thus not applied in this investigation.

The posterior angles included the cranial base, the articular, and the gonial angles. In the OI group, a larger cranial base angle was found which was similar to the result of Jensen and Lund (1997). It was hypothesized that cranial base flattening occurs because the thin osteoporotic bone is not sufficiently strong to withstand the mechanical stress from the weight of the head. The anterior and posterior cranial base lengths were also shorter in the OI group, indicating that growth of the cranial base region was impaired. The small articular angle (S-Ar-Go) in the OI group also indicated prognathic changes (Rakosi, 1982). This could explain the clinically skeletal Class III profiles in the OI group. The gonial angle had a marked relationship on the direction of growth, profile changes, and even the position of the lower incisors. A larger gonial angle indicated an increased skeletal open bite tendency, but in this study, the OI patients actually showed a deep bite.

In the OI group, linear measurements of anterior (S-N) and posterior (S-Ar) cranial base lengths were shorter than those in the control group, indicating impaired growth in the cranial base area.

Although currently there is no cure for OI, several treatments, such as physiotherapy (Root, 1984), surgical repair (Benson *et al.*, 1978; Harrison and Rankin, 1998), growth hormone therapy (Antoniazzi *et al.*, 1996), and intravenous bisphosphonate treatment (Glorieux *et al.*, 1998; Plotkin *et al.*, 2000; Rauch *et al.*, 2003; Zeitlin *et al.*, 2003), are available. Gene therapy (Marini and Gerber, 1997) and stem cell research (Horwitz *et al.*, 1999) are being investigated, thus ensuring a promising and effective cure for patients affected by OI. Especially in growing children, in order to evaluate the improvement of any treatments in the craniofacial complex of OI patients, baseline data of the craniofacial complex should be established.

## Conclusion

OI patients usually have a unique facial profile which is different from the normal population. Malocclusions became more dominant with increased age. OI patients have retarded vertical dimensions, a flattened cranial base angle, relative prognathism, larger facial divergence, and more forward counterclockwise mandibular growth.

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