Characteristics of craniofacial morphology and factors affecting them in patients with isolated cleft palate

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Abstract

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44 **Background.** Myriad maxillo-mandibular occlusal relationships are observed in patients with

45 isolated cleft palate (ICP), unlike in patients with other cleft types, such as cleft lip and palate.

46 **Objectives.** This study aimed to categorise the characteristics of craniofacial morphology in

47 patients with ICP, and investigate the clinical factors affecting these categorised morphological

48 characteristics.

49 **Methods.** Thirty-six girls with ICP [age (mean ± SD): 5.36 ± 0.36 years] underwent

50 cephalometric measurement. Their craniofacial morphology was categorised using cluster

51 analysis. Profilograms were created and superimposed onto the standard Japanese profilograms

52 to visualise the morphological characteristics of each group (cluster). The mean values and

53 variations in the linear and angular measurements of each group were compared with the

54 Japanese standards and statistically analysed using Dunnett's test after the analysis of variance.

55 Fisher's exact test was used to analyse the differences between the cleft types (cleft in the hard

56 and/or soft palate) and skills of the operating surgeons in the groups.

57 **Results.** Cluster analysis of craniofacial morphologies in patients with ICP resulted in the

58 formation of three categories: the first cluster exhibited a relatively harmonious anteroposterior

59 relationship between the maxilla and the mandible (22.2 %); the second cluster exhibited

60 crossbite owing to a significantly smaller maxilla (33.3 %); and the third cluster exhibited a

61 smaller mandible with posterior rotation showing skeletal class II malocclusion (44.4 %).

62 Differences in cleft types and surgeons were not associated with the distribution of patients in

63 each cluster.

64 **Conclusions.** Patients with ICP exhibited characteristic morphological patterns, such as

65 bimaxillary retrusion or severe mandibular retrusion, besides the anterior crossbite frequently

66 found in patients with cleft lip and palate. Understanding the typical morphological

67 characteristics could enable better diagnostic categorisation of patients with ICP, which may

68 eventually improve orthodontic treatment planning.

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Introduction

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76   Cleft lip and/or palate (CL/P) is one of the most common congenital anomalies in the orofacial
77   area (Schutte & Murray, 1999). Patients with cleft palate including the isolated cleft palate (ICP)
78   and the cleft lip and palate (CLP) generally undergo palatoplasty at the age of 1–1.5 years to
79   obtain velopharyngeal competence and normal speech. The various palatoplasty techniques, such
80   as von Langenbeck's method (Langenbeck, 1861), Veau–Wardill–Kilner push-back method
81   (Wardill, 1937), intravelar veloplasty (Braithwaite & Maurice, 1968), and Furlow double
82   opposing Z-plasty (Furlow, 1986), have been introduced by different surgeons. Although there
83   are many variations of these techniques, the scar formed on maxillary oral and nasal mucosa by
84   palatoplasty is thought to impair maxillary growth, which is probably responsible for the high
85   frequency of anterior crossbite in patients operated for cleft palate. For example, a survey of 996
86   Japanese patients with CLP (Kouno, Suzuki & Watanabe, 1989) found that the reverse occlusion
87   involving at least one tooth was observed in 84.6 % of CLP cases. Vettore et al. also observed
88   that the frequencies of anterior crossbite and posterior crossbite in Brazilian patients with CLP
89   were 60.7 % and 39.3 %, respectively (Vettore & Sousa Campos, 2011). Sæle et al.
90   demonstrated that 61.4 % of Norwegian patients with CLP had Angle's class III malocclusion
91   (Sæle et al., 2017).

92   However, the suppression of maxillary bone growth due to palatoplasty is not necessarily a
93   problem in patients with ICP. Hermann et al. investigated unoperated patients with ICP and
94   suggested that children with ICP had a shorter maxilla, reduced maxillary posterior height,
95   shorter mandible, and reduced posterior height of the mandible with retrognathia, compared to
96   controls with unilateral isolated cleft lip (ICL) (Hermann et al., 2002). On the other hand, Fujita
97   et al. reported that the average maxillary length was shorter and the nasomaxillary complex was
98   generally positioned more posteriorly in operated patients with ICP than in controls with normal
99   occlusion; however, the craniofacial pattern exhibited a wide variation in patients operated for
100   ICP (Fujita et al., 2005). Nakasone et al. observed a variety of mandibular configurations and
101   jaw relationships, indicating the diversity of craniofacial morphologies in patients operated for
102   ICP (Nakasone et al., 2013). These reports imply that the characteristics of craniofacial
103   morphology are not sufficiently understood by simply comparing the cephalometric mean values

104 between patients operated for ICP and controls, such as those with unilateral ICL or the normal

105 population.

106 The objective of this study was to categorise the characteristics of craniofacial morphology in

107 patients operated for ICP, to elucidate the manifestation patterns before orthodontic treatment,

108 and to investigate the causal relationships between morphological categories and potential key

109 factors, such as the differences in cleft type (range of cleft) and skills of the operating surgeons.

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112 **Materials & Methods**

113 *1. Sample and data collection*

114 This study protocol was reviewed and approved by the Kyushu University Institutional Review

115 Board for Clinical Research (#27-135). A dedicated website was established with detailed

116 information on this clinical study in case patients wished to opt out of the investigation. For this

117 retrospective cohort study, the participants were selected from among patients with ICP who first

118 visited the Department of Orthodontics at Kyushu University Hospital between 2002 and 2014.

119 The inclusion criterion was: patients with overt ICP (*i.e.*, clefts of the hard and soft palate or

120 clefts of the soft palate) (n = 77). The exclusion criteria were: patients with syndromes affecting

121 the craniofacial morphology including the Pierre Robin sequence (n = 1), patients who

122 underwent palatoplasty other than push-back method (n = 7), missing diagnostic records

123 according to being transferred to other hospitals or the default of their appointment (n = 16), and

124 incomplete diagnostic records (*i.e.*, cephalogram taken with the mouth opened) or unwanted

125 developmental stages (*i.e.*, other than Hellman's dental stage IIA (Completion of the primary

126 dentition by the acquisition of second deciduous molars) (Hellman, 1935)) (n = 5). Of the 48

127 selected patients, 12 boys were excluded from the study sample because their numbers were not

128 sufficient for the categorisation and comparison of craniofacial morphology. Thirty-six girls,

129 who underwent lateral cephalography before orthodontic diagnosis, belonging to Hellman's

130 dental stage IIA were eventually included in the study. The 36 patients were aged 5.36 ± 0.36

131 years (mean ± SD). The participants were evaluated based on the cleft type (range of cleft): 23

132 patients had clefts of the hard and soft palate and 13 had clefts of the soft palate. All primary

133 surgeries were performed by a group of similarly trained oral surgeons, and using the modified

134 Wardill's push-back method at 1.55 ± 0.21 years (mean ± SD) of age.

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136   *2. Cephalometric measurements and cluster analysis*

137   All the cephalograms were taken on the same machine to account for the magnification factor.

138   The magnification factor in lateral cephalometric radiographs was 110 % at the midsagittal

139   plane. WinCeph 10.0 (Rise Corp., Sendai, Japan) was used to perform the cephalometric

140   measurements, according to previous studies (Iizuka, 1958; Sakamoto, 1959), using the reference

141   points represented in Figure 1. The explanations for all reference points are indicated in the

142   legend.

143   All cephalometric measurements were conducted by the same orthodontist to eliminate inter-

144   examiner errors. All measurements were recorded again after two months. Dahlberg's formula

145   (Dahlberg, 1940) was used to evaluate the reproducibility of the measurements. The

146   measurement error (distance) of the coordinates of 17 points used in the profilogram (Sakamoto,

147   1959) was 0.61 mm. The measurement error (angle) of the 10 representative angular

148   measurements (Facial angle, Convexity, A-B plane, Y-axis, FH to SN, SNA, SNB, ANB, N-Pog

149   to SN, and Nasal floor to SN) was 0.43 ˚.

150   Cluster analysis was performed to categorise the characteristics of craniofacial morphology

151   using JMP Pro14 (SAS Institute Inc. Cary, NC, USA). The variables used for cluster analysis

152   were based on a previous study (Yamanouchi et al., 1995) and included the lower anterior facial

153   height [anterior nasal spine to menton (ANS-Me)], length of the maxilla [point A-

154   pterygomaxillary fissure (A'-Ptm')], length of the mandible [condylion-gonion (Cd-Gn)],

155   anteroposterior position of the maxilla [sella, nasion, point A (SNA)], anteroposterior

156   relationship of the maxilla and mandible (ANB), facial profile (facial angle), mandibular shape

157   (gonial angle), and mandibular rotation [ramus plane to the sella-nasion line (SN)]. The linear

158   measurements were normalised based on the upper anterior facial height [nasion to ANS (N-

159   ANS)] before the cluster analysis, to eliminate the effect of the differences in the size of each

160   individual (Yamanouchi et al., 1995). A best-suited model of 3 clusters was obtained using the

161   Ward's method, defining the distances between groups and establishing the least possible

162   dispersion within groups to ensure the greatest homogeneity for each cluster (Fig. 2) (de Frutos-

163   Valle et al., 2020).

164   Average profilograms of each cluster were obtained and superimposed over the standard

165   Japanese age matched female profilogram (Sakamoto, 1959) to visualise the characteristics of

166   craniofacial morphology of each cluster. Furthermore, the mean linear or angular measurements

167   of each cluster were statistically compared to the Japanese female standard of linear

168   measurements (Sakamoto, 1959) or to the Japanese standard of angular measurements obtained

169   from combined male and female subjects (Iizuka, 1958), respectively.

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171   *3. Statistical analysis*

172   Multiple comparisons were performed using Dunnett's test following an analysis of variance

173   (ANOVA) by Prism 7 (GraphPad Software, San Diego, CA, USA). Moreover, Fisher's exact test

174   was performed to determine whether the differences in cleft type (cleft in the soft palate and/or

175   hard palate) or surgeons (who performed the palatoplasty) affected the craniofacial morphology

176   in each cluster by R (the R Foundation, https://www.r-project.org). Post-hoc power (1-β)

177   analysis for the ANOVA and Fisher's exact test was performed by G*power 3.1 (Faul et al.,

178   2009). *P* < 0.05 was considered statistically significant.

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181   **Results**

182   *1. Qualitative assessment of craniofacial morphology of each cluster categorised by cluster*

183   *analysis*

184   Participants were categorised into the following three clusters based on the results of the

185   cluster analysis: cluster A (n=8), cluster B (n=12), and cluster C (n=16) (Fig. 2).

186   Cluster A exhibited no difference in the maxillary position compared to the standard, when

187   the average profilograms of each cluster were superimposed over the standard profilogram;

188   however, the mandibular body and anterior facial height were larger than those in the standard

189   profilogram. The anteroposterior relationship of the maxilla and mandible was harmonious in

190   cluster A (Fig. 3A). Cluster B exhibited significant maxillary retrusion and a tendency towards

191   lingual inclination of the lower incisors, a shorter mandibular ramus, and a larger gonial angle

192   than those of the standard. Anterior crossbite was observed. (Fig. 3B). Cluster C exhibited

193   mandibular and maxillary retrusion, large ramus inclination, and clockwise rotation of the

194   mandible (Fig. 3C).

195   Superimposition of the profilograms of all clusters over the standard profilogram revealed that

196   the anterior-most maxillary position was observed the most in the standard, followed by that in

197   clusters A, C, and B, while the most anterior mandibular position was observed the most in

198   cluster A, followed by that in the standard, cluster B, and cluster C (Fig. 4).

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200   *2. Quantitative assessment of facial morphology in each cluster*

201   The mean linear and angular measurements of each cluster were compared to their standard

202   counterparts (Iizuka, 1958; Sakamoto, 1959) to clarify the morphological characteristics of each

203   cluster (Tables 1 and 2). Cluster A exhibited a significantly longer Gn-Cd (mandibular length)

204   and larger A-B plane angle than the standard, and significantly smaller FH to SN and L1 to

205   mandibular plane angles. These results indicate that the characteristics of cluster A included a

206   larger mandible and slight lingual inclination of the lower incisors. Cluster B exhibited a

207   significantly larger A-B plane and occlusal plane to FH, and significantly smaller SNA, L1 to

208   mandibular plane, convexity, ANB, and anterior incisal height (Is-Is') than the standard. These

209   results indicate that the characteristics of cluster B included a tendency towards a skeletal class

210   III relationship with maxillary retrusion. Cluster C exhibited a significantly larger Y-axis, nasal

211   floor to SN, nasal floor to FH, mandibular plane to FH, ramus to SN, ramus to FH, occlusal

212   plane to SN, and occlusal plane to FH, and a significantly smaller facial angle, SNB, and N-Pog

213   to SN than the standard. These results indicate that the characteristics of cluster C included

214   clockwise rotation of the occlusal unit, including the maxilla and mandible, resulting in a profile

215   exhibiting mandibular retrusion with a skeletal class II relationship.

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217   *3. Relationships between craniofacial morphology and the differences in cleft type and surgeons*

218   Patients with ICP in this study included those with clefts of the hard and soft palate and cleft

219   of the soft palate only, and were operated on by four different surgeons (surgeons A-D). Thus,

220   the respective relationships of craniofacial morphology with differences in cleft type and

221   surgeons were also analysed. The results of Fisher's exact test for cleft type [$P (\chi^2) = 0.27$]

222   indicated no bias in patients' distribution. The results of Fisher's exact test for surgeons [$P (\chi^2) =$

223   0.69] also did not indicate any bias. Taken together, these findings indicate that the

224   morphological differences in ICP were not significantly affected by the cleft type or skills of the

225   operating surgeon (Table 3).

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Discussion

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229   Patients with ICP, unlike those with other cleft types (e.g. CLP), present with a wide variety of

230   maxillo-mandibular occlusal relationships (Fujita et al., 2005; Nakasone et al., 2013).

231   Understanding the typical morphological features is crucial for the correct orthodontic diagnosis

232   and treatment planning. Cluster analysis of craniofacial morphologies in patients with ICP in the

233   present study resulted in their categorisation into three groups: a cluster with a relatively

234   harmonious anteroposterior relationship between the maxilla and the mandible (22.2 %), a

235   cluster with crossbite caused by a significantly smaller maxilla (33.3 %), and a cluster with a

236   smaller mandible with posterior rotation showing skeletal class II relationship (44.4 %). These

237   results suggest a significant difference from the craniofacial morphology of patients with CLP.

238   We selected cluster analysis for categorising craniofacial morphologies in this study. Cluster

239   analysis is a method of collecting and classifying items with similar characteristics from a group

240   containing a mixture of differing characteristics (Finkelstein, Lavelle & Hassard, 1989). Cluster

241   analysis was considered more suitable for categorising characteristics compared to other methods

242   of analysis, which require prior information about the potential groups, owing to the diversity of

243   craniofacial morphology in patients with ICP.

244   Several previous studies have used the principal component analysis to determine the variates

245   to be used before conducting the cluster analysis of craniofacial morphologies (Bui et al., 2006;

246   Uribe et al., 2013; de Frutos-Valle et al., 2020). However, it is necessary to understand the

247   clinical significance of the principal components, and sometimes it is even difficult to understand

248   the significance of obtained principal components. Therefore, the variates used for cluster

249   analysis in this study were based on Yamanouchi et al.'s study, which reported that the

250   characteristics of facial morphology were well characterised by linear measurements of the lower

251   anterior facial height (ANS-Me) and lengths of the maxilla and mandible (A'-Ptm' and Cd-Gn)

252   and angular measurements including the anteroposterior position of the maxilla (SNA),

253   anteroposterior relationship of the maxilla and mandible (ANB), facial profile (facial angle),

254   mandibular shape (gonial angle), and mandibular rotation (ramus to SN) (Yamanouchi et al.,

255   1995). They also reported that these skeletal factors were not significantly affected by local

256   dental factors.

257   Soma reported that the differences in the absolute sizes of the jaw or face makes it difficult to

258   compare craniofacial patterns simultaneously and that isometric processing (normalisation of

259 linear measurements) is an effective method for the analysis of craniofacial patterns (Soma,

260 1977). In the present study, normalisation of linear measurements was achieved by dividing the

261 values with the anterior facial height (N-ANS), which is one of the most reliable measurements.

262 This normalization is important to eliminate the effect of individual variation in absolute length

263 on the cluster analysis (*i.e.*, a larger individual may have a greater absolute length compared to a

264 smaller individual when, in fact, the length may be smaller if normalized for size). We believe

265 that the normalisation of linear measurements successfully eliminated the influence of size and

266 better clarified the trends in the characteristics of each sample.

267   Determination of the number of clusters is subjective and can result in variability between

268 studies. We deemed it appropriate to classify the participants into three cluster groups, which

269 could be understood easily without over-segmentation, based on the dendrogram created by

270 cluster analysis using the Ward's method (Fig. 2). The comparison of the mean values of each

271 cluster (obtained from cephalometric analysis) with the standard values showed that the large

272 mandibular size in cluster A was compensated (dentally) by a slight lingual inclination of the

273 lower incisors. Cluster B had a retruded maxilla and lingual inclination of the lower incisors,

274 which were similar to the dental compensation observed in cluster A. Cluster C had a retruded

275 mandible with clockwise rotation of the palatal plane, occlusal plane, mandibular plane, and

276 ramus plane. These results, based on cephalometric analyses, were faithfully represented in the

277 superimposed profilograms. Clusters A, B, and C constituted 22.2%, 33.3%, and 44.4% of the

278 total study population, respectively, suggesting that several patients with ICP have mandibular

279 hypoplasia (retruded mandible; cluster C), in whom the suppression of maxillary growth post-

280 palatoplasty would not lead to major disharmony in the anteroposterior relationship of the jaw.

281 We speculated that the craniofacial morphology in patients with ICP may have formed

282 congenitally or acquired by mechanisms that differ from those in patients with CLP because the

283 craniofacial morphological characteristics of patients with ICP differ from those of patients with

284 CLP, who often exhibit anterior crossbite (Kouno, Suzuki & Watanabe, 1989; Vettore & Sousa

285 Campos, 2011; Sæle et al., 2017).

286   Several studies that compared ICP with ICL (as the control group) found that patients with ICP

287 had smaller mandibles than those of the controls (Hermann et al., 2002; Eriksen et al., 2006),

288 which strongly indicates a link between mandibular hypoplasia occurring during mandibular

289 development and ICP. Price et al. reviewed 930 papers including clinical and basic research on

290   the relationship between cleft palate and mandibular hypoplasia, and concluded that mandibular

291   hypoplasia triggers cleft palate formation (Price, Haddad & Fakhouri, 2016). Pierre Robin

292   sequence is characterised by a spectrum of anatomical anomalies including mandibular

293   hypoplasia, glossoptosis, life-threatening obstructive apnoea, and feeding difficulties. Typically,

294   a wide U-shaped cleft palate is associated with Pierre Robin sequence (Lehman, Fishman &

295   Neiman, 1995); however, a narrow V-shaped cleft is associated with other cleft types. From this

296   perspective, there could be two important causes of ICP: primary failure of palatal fusion

297   (similar to other cleft types), and secondary failure of palatal fusion owing to a small mandible as

298   seen in Pierre Robin sequence. A previous study suggested that the width of the cleft at the

299   posterior end of the hard palate and the total length of the cleft are significantly related to the

300   severity of Pierre Robin sequence (Godbout et al., 2014). Unfortunately, the cleft shape or width

301   before palatal closure could not be evaluated in our study because our surgical records were not

302   tailored for the purpose of this study. Therefore, the relationships between the cleft shape/width

303   before surgery and craniofacial morphology could not be determined. Indeed, we did not find

304   any patients with typical manifestations of Pierre Robin sequence such as glossoptosis, life-

305   threatening obstructive apnoea, and feeding difficulties in their earliest infancy in this study.

306   However, patients with mild Pierre Robin sequence cannot be completely distinguished from

307   those with ICP with a small mandible. Therefore, it is conceivable that the number of

308   participants with a relatively wide U-shaped cleft by mild Pierre Robin sequence may have

309   affected the distribution of patients in the three categorised groups.

310   In a previous study, compensatory growth of the mandible was not observed at least during the

311   first 2 years of life in patients with Pierre Robin sequence (Hermann et al., 2003). Moreover,

312   none of the patients with Pierre Robin sequence exhibited significant improvements in the

313   skeletal pattern that could be construed as a gradual correction of the initial severe skeletal class

314   II relationship after the age of 5 years (Daskalogiannakis, Ross & Tompson, 2001). These studies

315   also support the notion that this sampling age would be suitable for identifying the typical

316   morphological characters of ICP, even if a certain number of patients with mild Pierre Robin

317   sequence are included in the study.

318   Nakasone et al. found that while the average severity of maxillary growth suppression was

319   mild in patients with ICP, individual cases displayed a wide variety of facial morphologies, from

320   mandibular protrusion to maxillary protrusion, and that averaging the characteristics of several

321   cases resulted in values that resembled the standard value (Nakasone et al., 2013). They also

322   indicated that although the mean value of measurements related to the mandible was similar to

323   the standard value, a large variation was found in mandibular measurements, suggesting the

324   existence of a wide variety of mandibular shapes or positions and maxillo-mandibular

325   relationships in patients with ICP. Therefore, although patients with ICP often present with

326   mandibular hypoplasia at birth, they can present a wide variety of phenotypes, possibly due to

327   the additive effect of the acquired influence of palatoplasty.

328   One of the limitations of this report is that only girls were selected for the present study.

329   Previous studies have shown that ICP is more common in girls than in boys (Mossey et al., 2009;

330   Martelli et al., 2012). Similarly, fewer boys with ICP were found than girls with this condition

331   between 2002 and 2014 during the study selection process, *i.e.* 12 boys and 36 girls. Therefore,

332   boys were excluded from the study sample because their numbers were not sufficient for the

333   categorisation and comparison of craniofacial morphology. Moreover, because of the gender

334   difference in incidence in the ICP, there might be gender-specific aetiology that would affect

335   craniofacial morphology of ICP, suggesting that a group consisting both genders would be

336   inappropriate to be analysed. It will be necessary to examine whether craniofacial morphologies

337   of boys with ICP are in line with the results of the present study.

338   Based on the appropriate statistical approach, we believe that the results obtained are clinically

339   useful for understanding the typical morphological characteristics of ICP. However, we admit

340   that the retrospective cohort with a relatively small sample may slightly undermine the results.

341   Further evaluation of the prospective cohort study with a large sample would be warranted.

342   A recent systematic review of the effects of functional appliances suggested that the skeletal

343   changes elicited by orthodontic treatment may be negligible or statistically insignificant

344   (Cacciatore et al., 2019). The ANB angle increased more effectively over a short period of time

345   in the treatment of skeletal class III malocclusion using maxillary protraction during the growth

346   period, compared to that in the untreated group; however, the effect become less pronounced

347   toward the end of growth period and the skeletal pattern became almost similar to that of the

348   untreated control group (Vaughn et al., 2005; Mandall et al., 2010, 2012, 2016). These reports

349   suggest that the skeletal pattern is not significantly altered by orthodontic treatment or residual

350   growth at least in participants without CLP or ICP. However, we selected younger patients in

351   Hellman's stage IIA before they underwent orthodontic intervention because we wished to

352 exclude the effects of orthodontic treatment on the skeletal pattern and thus on the determination

353 of typical morphological characteristics of ICP, which are encountered at the beginning of the

354 orthodontic treatment. Further studies with samples after growth complete will be required for

355 better evaluation and understanding of craniofacial morphology of ICP.

356 The present study population included patients with clefts of the soft palate and those with

357 clefts of the hard and soft palate. Surgeries for clefts of the soft palate are often less invasive

358 because they require lesser removal of mucosa from the nasal side than that required for clefts of

359 the hard and soft palate. Thus, this research was also aimed at confirming whether the

360 differences in the cleft type affect the degree of maxillary growth suppression. Moreover, the

361 differences between the skills of the four surgeons were also considered because they may affect

362 maxillary development. Table 3 shows the sample distribution for each category. Fisher's exact

363 test was used to examine the distribution of the small sample size. The data in Table 3A and B

364 exhibit P-values greater than 0.05 and relatively high power (1-β), indicating that the distribution

365 was not significantly different. These results suggest that differences in the cleft type (cleft

366 range) and skills of the operating surgeon were not significantly associated with the craniofacial

367 morphology of patients with ICP. Therefore, the characteristics of three clusters obtained from

368 this ICP population can be expected to represent the typical craniofacial morphologies

369 encountered in the clinical practice, which reflect the characteristics of ICP itself and the effects

370 of any subsequent surgeries. This information could be beneficial in orthodontic treatment

371 planning for patients with cleft palate.

372

373 **Conclusions**

374 Cluster analysis of craniofacial morphologies in patients with ICP resulted in the identification of

375 three clusters: a cluster with a relatively harmonious anteroposterior relationship between the

376 maxilla and the mandible; that with anterior crossbite caused by a significantly small maxilla;

377 and that with a smaller mandible with posterior rotation showing a skeletal class II relationship.

378 A total of 44.4 % of the patients were classified into the cluster characterised by a skeletal class

379 II relationship with a smaller mandible (cluster C). Differences in the cleft type (cleft range) and

380 skills of the surgeon were not associated with the distribution of craniofacial morphology. These

381 results suggest that the mechanisms responsible for craniofacial morphology of patients with ICP

382 are different from those in patients with CLP. Understanding the typical morphological

383 characteristics could enable better diagnostic categorisation of patients with ICP, which may

384 eventually improve orthodontic treatment planning.

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386

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498

499

500 **Figure legends**

501 **Fig. 1** Reference points for the cephalometric measurements

502   (A) N: nasion, the anterior-most point of the frontonasal suture; S: sella turcica, the estimated

503 centre of the hypophyseal fossa; Or: orbitale, the deepest point on the infraorbital margin; Po:

504 porion, the upper margin of the ear canal; Ba: basion, the anterior-most margin of the foramen

505   magnum; Cd; condylion, the most supradorsal point of the condylar head; Ar: articulare, the

506   intersection between the external contour of the cranial base and dorsal contour of the condylar

507   head and neck; Ptm: pterygomaxillary fissure, the inferior point of the fissure; PNS: posterior

508   nasal spine; ANS: anterior nasal spine; A: subspinale, the deepest point on the premaxilla

509   between the ANS and prosthion in the midline; U1 (Is) and U1a : upper incisor constructed

510   between the incisal tip of the anterior-most deciduous maxillary central incisor and its apex; Mo:

511   mid-point of the deciduous maxillary second molar; L1 (Ii) and L1a: lower incisor constructed

512   between the incisal tip of the most anterior deciduous mandibular central incisor and its apex;

513   Pog: pogonion, the anterior-most point of the bony chin; B: supramentale, the posterior-most

514   point in the concavity between the infradentale and Pog; Me: menton, the lowest point on the

515   symphyseal shadow; Gn: gnathion, the point on the chin determined by bisecting the angle

516   formed by the facial plane and mandibular plane; Go: gonion, the intersection between the ramus

517   plane and the mandibular plane; A': intersection of a perpendicular drawn from point A to the

518   palatal plane; Ptm': intersection of a perpendicular line from the Ptm to the palatal plane; Ms':

519   intersection of the perpendicular drawn from Mo to the palatal plane;

520   palatal plane: the square dotted line; mandibular plane: the dashed line

521   (B) U1 (Is): upper incisor constructed between the incisal tip of the most anteriorly placed

522   deciduous maxillary central incisor; Is': intersection of the perpendicular drawn from Is to the

523   palatal plane; L1 (Ii): lower incisor constructed between the incisal tip of the most anteriorly

524   placed deciduous mandibular central incisor; Ii': intersection of the perpendicular drawn from Ii

525   to the palatal plane; Mo: mid-point of the deciduous maxillary second molar; Ms': intersection of

526   the perpendicular drawn from Mo to the palatal plane; Mi': intersection of the perpendicular

527   drawn from Mo to the mandibular plane;

528   palatal plane: the square dotted line; mandibular plane: the dashed line

529

530   **Fig. 2** Dendrogram created by cluster analysis using Ward's method

531   Thirty-six girls were classified into three groups, *i.e.* clusters A, B, and C.

532

533   **Fig. 3** Averaged profilograms of each cluster and their superimposition over the Japanese

534   standard profilogram

535   Points S, N, Or, ANS, A, U1, L1, B, Pog, Me, Go, Ar, PNS, and Mo were connected on the

536   profilograms to visualise the facial pattern [according to a previous study (Sakamoto, 1959)].

537   The superimposition was performed at point S, parallel to the Frankfurt horizontal (FH) plane.

538   The square dotted line, dashed line, dash-dotted line, and solid line represent clusters A, B, C,

539   and the Japanese standard, respectively. (A) Cluster A exhibited no difference in maxillary

540   position compared to the standard. The mandible and maxilla showed a balanced anteroposterior

541   relationship. (B) Cluster B exhibited significant maxillary retrusion and tendencies towards

542   lingual inclination of the lower incisors, a shorter mandibular ramus, and a larger gonial angle,

543   with crossbite. (C) Cluster C exhibited mandibular and maxillary retrusion, a larger ramus angle,

544   and clockwise rotation of the mandible.

545   The ANB in the averaged profilograms of clusters A, B, and C was + 3.1 ˚, + 0.7 ˚, and + 4.8 ˚,

546   respectively.

547   Abscissa: FH-parallel line through S; Ordinate: FH-perpendicular line through S.

548   ANS, anterior nasal spine; A, subspinale; S, sella turcica; N, nasion; Or, orbitale; U1, incisor tip

549   of the most anteriorly placed deciduous maxillary central incisor; L1, lower incisor tip of the

550   most anteriorly placed deciduous mandibular central incisor; B, supramentale; Pog, pogonion;

551   Me, menton; Go, gonion; Ar, articulare; PNS, posterior nasal spine; Mo, mid-point of the

552   deciduous maxillary second molar

553

554   **Fig. 4** Superimposition of all the clusters over the Japanese standard profilogram

555   The superimposition was performed at point S, parallel to the Frankfurt horizontal (FH) plane.

556   The square dotted line, dashed line, dash-dotted line, and solid line represent clusters A, B, C,

557   and the Japanese standard, respectively.

558   Abscissa: FH-parallel line through S; Ordinate: FH-perpendicular line through S.

559   S: sella turcica

560

561

562   **Table 1** Comparison between the mean angular measurements of the Japanese standard and each

563   cluster

564   **Table 2** Comparison between the mean linear measurements of the Japanese standard and each

565   cluster

566   **Table 3** Relationships of craniofacial morphology with the differences in cleft type and surgeons

567   A) Patient distribution according to the cleft type

568   B) Patient distribution according to the operating surgeon

Figure 1

Reference points for the cephalometric measurements

(A) N: nasion, the anterior-most point of the frontonasal suture; S: sella turcica, the estimated centre of the hypophyseal fossa; Or: orbitale, the deepest point on the infraorbital margin; Po: porion, the upper margin of the ear canal; Ba: basion, the anterior-most margin of the foramen magnum; Cd; condylion, the most supradorsal point of the condylar head; Ar: articulare, the intersection between the external contour of the cranial base and dorsal contour of the condylar head and neck; Ptm: pterygomaxillary fissure, the inferior point of the fissure; PNS: posterior nasal spine; ANS: anterior nasal spine; A: subspinale, the deepest point on the premaxilla between the ANS and prosthion in the midline; U1 (Is) and U1a : upper incisor constructed between the incisal tip of the anterior-most deciduous maxillary central incisor and its apex; Mo: mid-point of the deciduous maxillary second molar; L1 (Ii) and L1a: lower incisor constructed between the incisal tip of the most anterior deciduous mandibular central incisor and its apex; Pog: pogonion, the anterior-most point of the bony chin; B: supramentale, the posterior-most point in the concavity between the infradentale and Pog; Me: menton, the lowest point on the symphyseal shadow; Gn: gnathion, the point on the chin determined by bisecting the angle formed by the facial plane and mandibular plane; Go: gonion, the intersection between the ramus plane and the mandibular plane; A': intersection of a perpendicular drawn from point A to the palatal plane; Ptm': intersection of a perpendicular line from the Ptm to the palatal plane; Ms': intersection of the perpendicular drawn from Mo to the palatal plane; palatal plane: the square dotted line; mandibular plane: the dashed line (B) U1 (Is): upper incisor constructed between the incisal tip of the most anteriorly placed deciduous maxillary central incisor; Is': intersection of the perpendicular drawn from Is to the palatal plane; L1 (Ii): lower incisor constructed between the incisal tip of the most anteriorly placed deciduous mandibular central incisor; Ii': intersection of the

perpendicular drawn from Ii to the palatal plane; Mo: mid-point of the deciduous maxillary second molar; Ms': intersection of the perpendicular drawn from Mo to the palatal plane; Mi': intersection of the perpendicular drawn from Mo to the mandibular plane; palatal plane: the square dotted line; mandibular plane: the dashed line

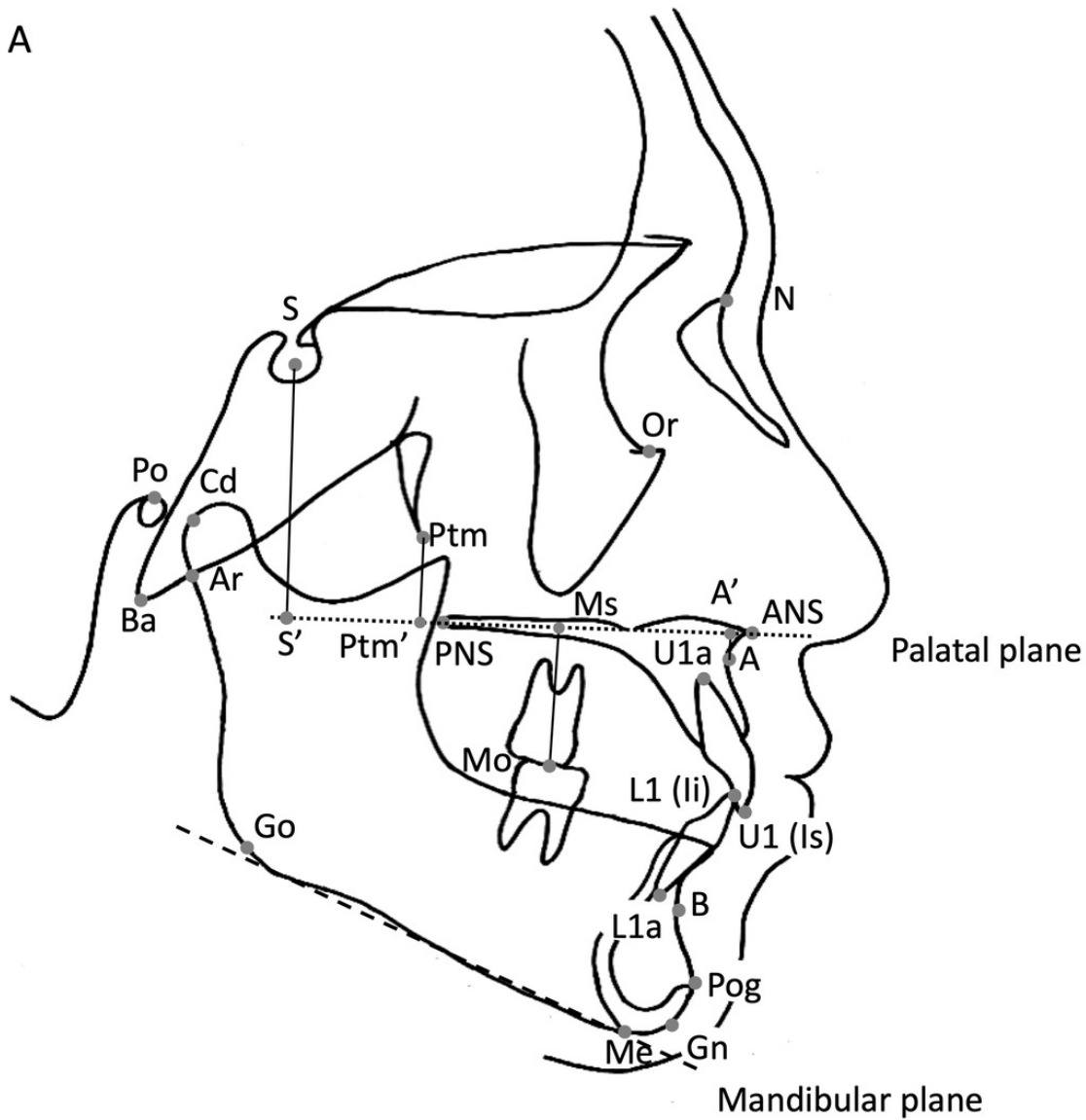
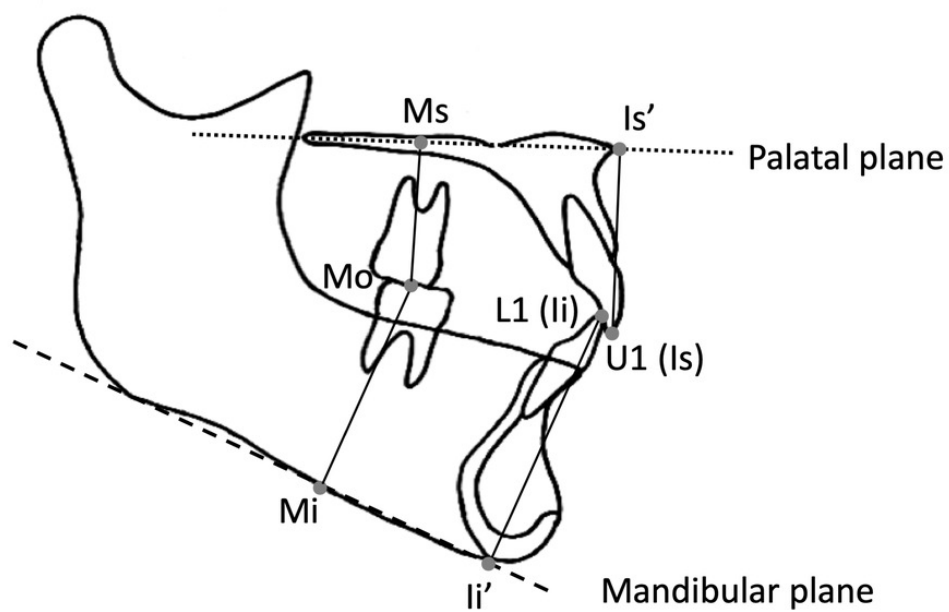



Figure 2

Dendrogram created by cluster analysis using Ward's method

Thirty-six girls were classified into three groups, *i.e.* clusters A, B, and C.

Cluster A
N=8

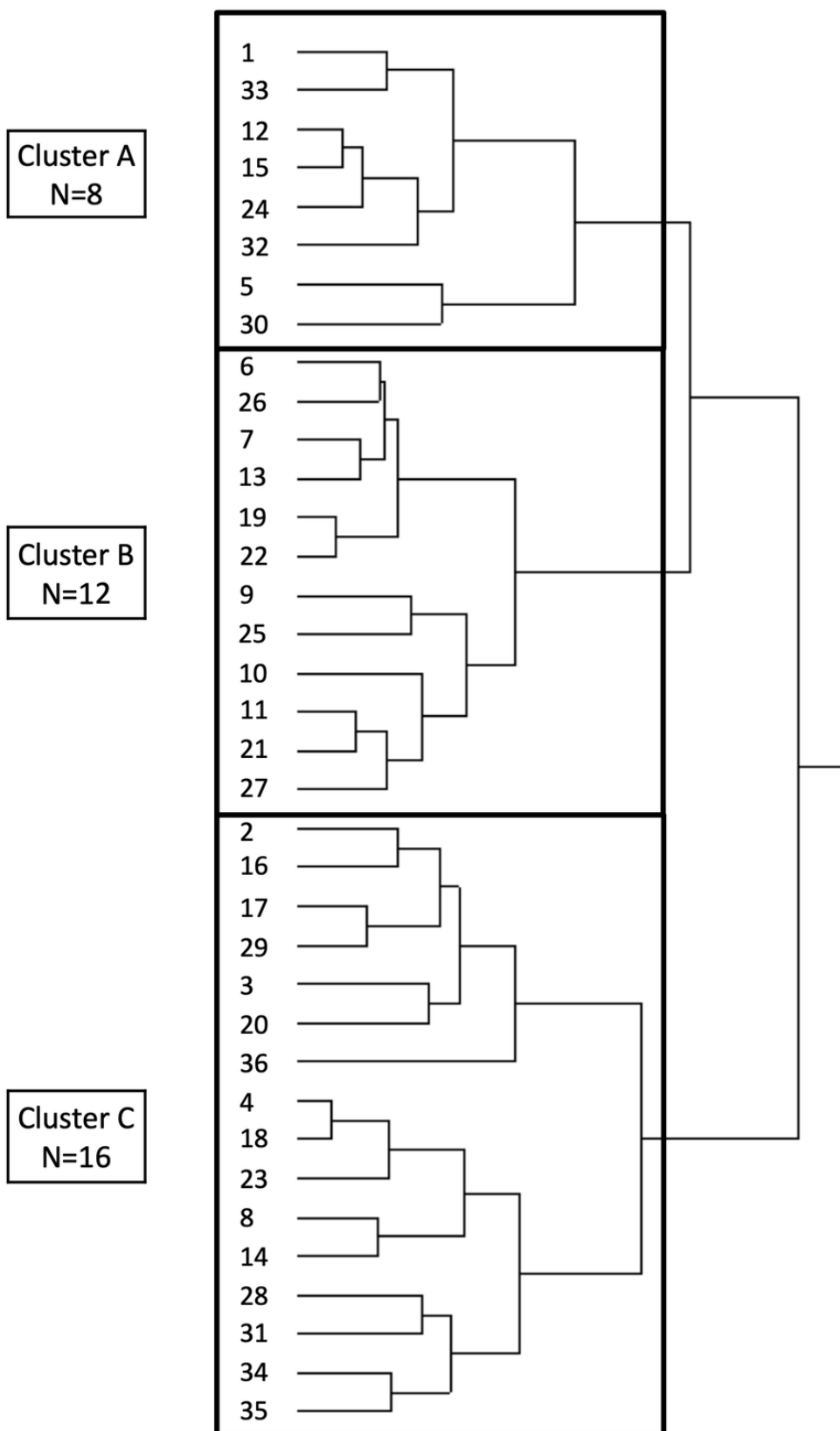
Cluster B
N=12

Cluster C
N=16

Figure 3

Averaged profilograms of each cluster and their superimposition over the Japanese standard profilogram

Points S, N, Or, ANS, A, U1, L1, B, Pog, Me, Go, Ar, PNS, and Mo were connected on the profilograms to visualise the facial pattern [according to a previous study (Sakamoto, 1959)]. The superimposition was performed at point S, parallel to the Frankfurt horizontal (FH) plane. The square dotted line, dashed line, dash-dotted line, and solid line represent clusters A, B, C, and the Japanese standard, respectively. (A) Cluster A exhibited no difference in maxillary position compared to the standard. The mandible and maxilla showed a balanced anteroposterior relationship. (B) Cluster B exhibited significant maxillary retrusion and tendencies towards lingual inclination of the lower incisors, a shorter mandibular ramus, and a larger gonial angle, with crossbite. (C) Cluster C exhibited mandibular and maxillary retrusion, a larger ramus angle, and clockwise rotation of the mandible. The ANB in the averaged profilograms of clusters A, B, and C was $+ 3.1 °$, $+ 0.7 °$, and $+ 4.8 °$, respectively. Abscissa: FH-parallel line through S; Ordinate: FH-perpendicular line through S. ANS, anterior nasal spine; A, subspinale; S, sella turcica; N, nasion; Or, orbitale; U1, incisor tip of the most anteriorly placed deciduous maxillary central incisor; L1, lower incisor tip of the most anteriorly placed deciduous mandibular central incisor; B, supramentale; Pog, pogonion; Me, menton; Go, gonion; Ar, articulare; PNS, posterior nasal spine; Mo, mid-point of the deciduous maxillary second molar

A   Cluster A

ANB = 3.1˚

.... Cluster A
———— Japanese standard

B   Cluster B

ANB = 0.7˚

— — — — Cluster B
———— Japanese standard

C   Cluster C

ANB = 4.8˚

— · — · Cluster C
———— Japanese standard

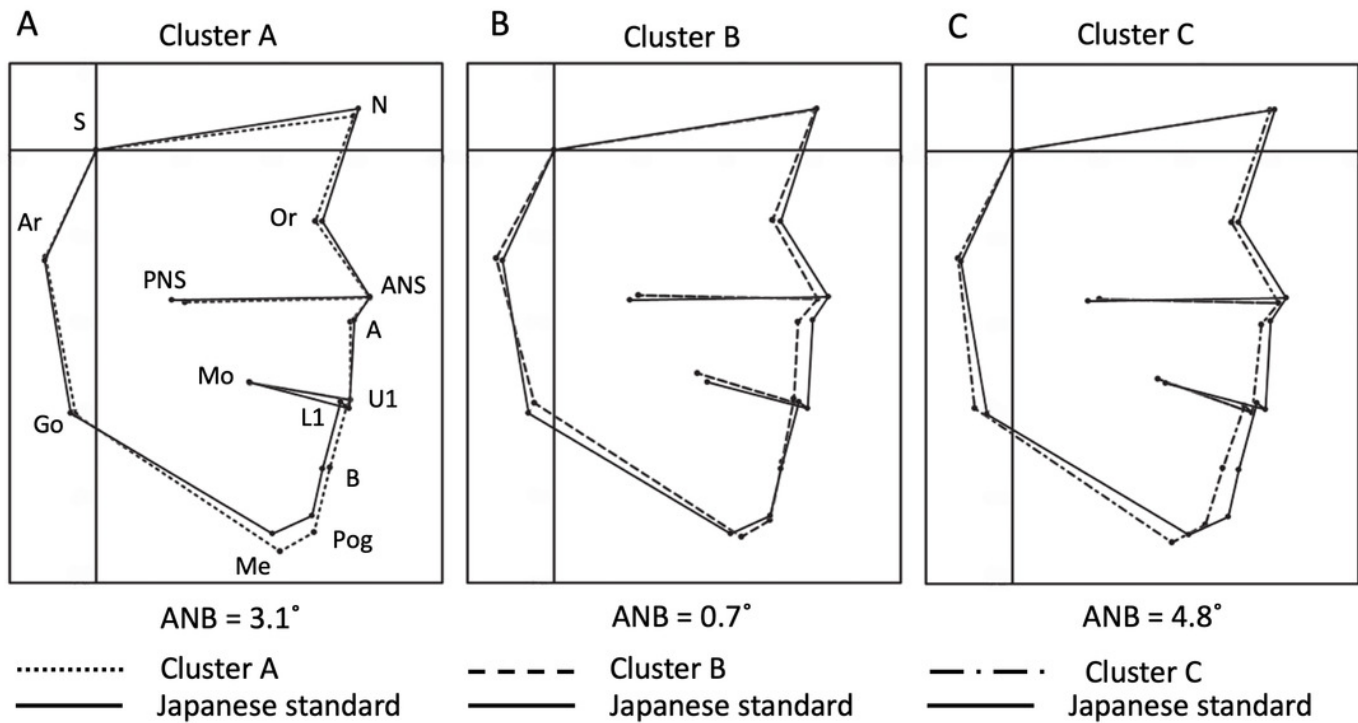



Figure 4

Superimposition of all the clusters over the Japanese standard profilogram

The superimposition was performed at point S, parallel to the Frankfurt horizontal (FH) plane. The square dotted line, dashed line, dash-dotted line, and solid line represent clusters A, B, C, and the Japanese standard, respectively. Abscissa: FH-parallel line through S; Ordinate: FH-perpendicular line through S. S: sella turcica

Comparison between the mean angular measurements of the Japanese standard and each cluster

P < 0.05, **P* < 0.01 by Dunnett' s multiple comparison test. SD, standard deviation.

1   **Table 1** Comparison between the mean angular measurements of the Japanese standard and each cluster

Angular measurements (°)	Japanese standard		Cluster A			Cluster B			Cluster C			Post-hoc power (1-β)
	Mean (± SD)	95% CI	Mean (± SD)	95% CI	P-value	Mean (± SD)	95% CI	P-value	Mean (± SD)	95% CI	P-value	
Facial angle	84.5 (± 3.2)	(83.3 to 85.7)	84.5 (± 1.3)	(83.5 to 85.6)	1.000	83.7 (± 1.3)	(82.9 to 84.5)	0.737	81.8 (± 3.0)	(80.2 to 83.4)	0.005**	0.620
Convexity	10.6 (± 2.7)	(9.6 to 11.6)	8.9 (± 5.9)	(4.0 to 13.9)	0.664	3.3 (± 5.9)	(-0.5 to 7.0)	0.000**	11.9 (± 4.8)	(9.3 to 14.5)	0.656	1.000
A-B plane	-5.7 (± 2.4)	(-6.6 to -4.8)	-2.7 (± 2.7)	(-5.0 to -0.5)	0.032*	-0.1 (± 4.1)	(-2.7 to 2.5)	0.000**	-5.9 (± 2.7)	(-7.4 to -4.4)	0.993	1.000
Y-axis	61.5 (± 3.4)	(60.2 to 62.8)	62.9 (± 1.6)	(61.5 to 64.2)	0.548	62.1 (± 1.9)	(60.9 to 63.3)	0.906	64.6 (± 3.5)	(62.7 to 66.4)	0.006**	0.674
FH to SN	10.1 (± 3.0)	(9.0 to 11.2)	7.5 (± 1.3)	(6.4 to 8.6)	0.039*	8.7 (± 2.1)	(7.4 to 10.1)	0.300	9.5 (± 2.5)	(8.1 to 10.8)	0.760	0.450
∠SNA	80.1 (± 3.4)	(78.8 to 81.4)	81.6 (± 3.5)	(78.7 to 84.5)	0.502	76.6 (± 2.6)	(74.9 to 78.3)	0.005**	78.1 (± 2.7)	(76.7 to 79.6)	0.121	0.890
∠SNB	76.0 (± 3.5)	(74.7 to 77.3)	78.5 (± 1.5)	(77.3 to 79.8)	0.091	75.9 (± 1.9)	(74.7 to 77.1)	0.999	73.3 (± 2.8)	(71.8 to 74.8)	0.012*	0.842
∠ANB	4.1 (± 3.5)	(2.8 to 5.4)	3.1 (± 2.3)	(1.2 to 5.0)	0.716	0.7 (± 2.6)	(-0.9 to 2.3)	0.003**	4.8 (± 2.1)	(3.7 to 5.9)	0.754	0.769
N-Pog to SN	75.3 (± 3.8)	(73.9 to 76.8)	77.0 (± 1.0)	(76.2 to 77.8)	0.348	75.0 (± 1.7)	(73.9 to 76.1)	0.977	72.3 (± 2.6)	(70.9 to 73.7)	0.006**	0.736
Nasal floor to SN	7.7 (± 3.6)	(6.3 to 9.1)	6.2 (± 2.1)	(4.4 to 7.9)	0.412	10.0 (± 1.9)	(8.8 to 11.2)	0.061	10.8 (± 2.2)	(9.7 to 12.0)	0.003**	0.850
Nasal floor to FH	-1.0 (± 3.5)	(-2.3 to 0.3)	-1.3 (± 2.7)	(-3.6 to 0.9)	0.988	1.3 (± 2.4)	(-0.2 to 2.8)	0.083	1.4 (± 2.6)	(0.0 to 2.8)	0.035*	0.604
Mandibular plane to SN	39.2 (± 4.4)	(37.5 to 40.9)	39.9 (± 3.1)	(37.4 to 42.5)	0.956	40.4 (± 4.4)	(37.6 to 43.1)	0.785	42.3 (± 5.0)	(39.6 to 45.0)	0.073	0.430
Mandibular plane to FH	29.5 (± 3.4)	(28.2 to 30.8)	32.4 (± 3.2)	(29.7 to 35.1)	0.230	31.6 (± 4.4)	(28.8 to 34.4)	0.353	32.9 (± 6.0)	(29.7 to 36.1)	0.041*	0.825
Ramus plane to SN	89.2 (± 5.5)	(87.1 to 91.3)	89.0 (± 4.6)	(85.2 to 92.9)	0.999	86.0 (± 2.2)	(84.6 to 87.4)	0.104	94.9 (± 3.3)	(93.1 to 96.6)	0.000**	0.965
Ramus plane to FH	79.9 (± 5.2)	(77.9 to 81.9)	81.5 (± 4.3)	(77.9 to 85.2)	0.673	77.3 (± 2.9)	(75.5 to 79.1)	0.201	85.4 (± 3.5)	(83.6 to 87.2)	0.000**	0.956
Gonial angle	130.0 (± 5.3)	(128.0 to 132.0)	130.9 (± 7.3)	(124.8 to 137)	0.963	134.3 (± 4.8)	(131.3 to 137.4)	0.081	127.5 (± 6.3)	(124.1 to 130.8)	0.355	0.795
U1 to SN	87.2 (± 6.5)	(84.7 to 89.7)	92.0 (± 7.7)	(85.6 to 98.4)	0.209	89.1 (± 6.2)	(85.2 to 93.1)	0.759	85.2 (± 7.8)	(81.0 to 89.3)	0.672	0.532
U1 to FH	96.6 (± 6.5)	(94.1 to 99.1)	99.5 (± 6.9)	(93.8 to 105.2)	0.592	97.9 (± 6.6)	(93.7 to 102.0)	0.908	94.6 (± 7.7)	(90.5 to 98.7)	0.677	0.304
L1 to mandibular plane	85.7 (± 4.1)	(84.1 to 87.3)	78.9 (± 4.4)	(75.2 to 82.6)	0.041*	78.2 (± 7.5)	(73.4 to 83.0)	0.006**	82.0 (± 10.4)	(76.4 to 87.5)	0.200	1.000
Interincisal angle	148.4 (± 9.5)	(144.8 to 152)	149.2 (± 11.2)	(139.9 to 158.6)	0.994	152.3 (± 7.9)	(147.3 to 157.3)	0.538	150.5 (± 11.8)	(144.3 to 156.8)	0.837	0.151
Occlusal plane to SN	22.3 (± 3.9)	(20.8 to 23.8)	21.6 (± 2.1)	(19.9 to 23.3)	0.914	24.0 (± 3.0)	(22.1 to 25.9)	0.342	26.9 (± 3.1)	(25.2 to 28.6)	0.000**	0.932
Occlusal plane to FH	12.6 (± 3.0)	(11.5 to 13.7)	14.1 (± 1.9)	(12.5 to 15.7)	0.490	15.2 (± 3.2)	(13.2 to 17.3)	0.044*	17.5 (± 3.7)	(15.5 to 19.4)	0.000**	0.996

2   *$P < 0.05$, **$P < 0.01$ by Dunnett' s multiple comparison test. SD, standard deviation. 95% CI, 95% Confidence Interval.

Comparison between the mean linear measurements of the Japanese standard and each cluster

P < 0.05, **P* < 0.01 by Dunnett' s multiple comparison test. SD, standard deviation.

1   **Table 2** Comparison between the mean linear measurements of the Japanese standard and each cluster

Linear measurements (mm)	Japanese standard		Cluster A			Cluster B			Cluster C			Post-hoc power (1-β)
	Mean (± SD)	95% CI	Mean (± SD)	95% CI	*P*-value	Mean (± SD)	95% CI	*P*-value	Mean (± SD)	95% CI	*P*-value	
N-S	61.5 (± 2.3)	(60.2 to 62.8)	60.2 (± 3.5)	(57.3 to 63.1)	0.515	61.0 (± 1.8)	(59.9 to 62.2)	0.940	60.6 (± 2.6)	(59.2 to 62.0)	0.673	0.245
N-ANS	43.7 (± 2.9)	(42.0 to 45.4)	42.2 (± 2.0)	(40.6 to 43.9)	0.344	43.7 (± 1.3)	(42.9 to 44.6)	1.000	44.8 (± 2.4)	(43.5 to 46.0)	0.440	0.368
ANS-Me	58.9 (± 3.3)	(57.0 to 60.8)	62.2 (± 4.0)	(58.9 to 65.6)	0.127	57.8 (± 3.5)	(55.6 to 60.1)	0.813	60.2 (± 4.2)	(57.9 to 62.4)	0.689	0.739
N-Me	100.0 (± 4.2)	(97.6 to 102.4)	102.1 (± 5.2)	(97.7 to 106.4)	0.629	100.2 (± 4.3)	(97.5 to 102.9)	0.999	102.3 (± 5.1)	(99.6 to 105.0)	0.407	0.345
S'-Ptm'	16.9 (± 2.1)	(15.7 to 18.1)	16.8 (± 2.5)	(14.7 to 18.9)	0.998	17.4 (± 1.4)	(16.5 to 18.3)	0.823	17.6 (± 1.5)	(16.8 to 18.4)	0.593	0.149
A'-Ptm'	41.9 (± 2.1)	(40.7 to 43.1)	41.1 (± 2.5)	(39.1 to 43.2)	0.798	39.8 (± 1.9)	(38.6 to 41.0)	0.061	41.0 (± 2.6)	(39.6 to 42.4)	0.573	0.665
Ptm'-Ms	17.6 (± 2.1)	(16.4 to 18.8)	17.6 (± 2.8)	(15.3 to 19.9)	1.000	16.8 (± 1.2)	(16.1 to 17.6)	0.623	17.7 (± 1.8)	(16.8 to 18.7)	0.995	0.150
A'-Ms	24.3 (± 1.3)	(23.6 to 25.1)	23.6 (± 1.4)	(22.4 to 24.8)	0.739	23.0 (± 2.3)	(21.5 to 24.4)	0.208	23.3 (± 2.3)	(22.0 to 24.5)	0.352	0.783
Is-Is'	25.5 (± 1.8)	(24.5 to 26.5)	25.7 (± 2.0)	(24.0 to 27.4)	0.990	24.1 (± 2.3)	(22.6 to 25.6)	0.161	25.1 (± 1.5)	(24.3 to 25.9)	0.903	0.485
Mo-Ms	18.6 (± 1.7)	(17.6 to 19.6)	19.0 (± 1.9)	(17.4 to 20.6)	0.887	17.8 (± 1.2)	(17.0 to 18.6)	0.376	18.1 (± 1.2)	(17.5 to 18.8)	0.702	0.289
Is-Mo	24.0 (± 1.3)	(23.3 to 24.8)	23.6 (± 2.6)	(21.4 to 25.8)	0.942	23.3 (± 2.3)	(21.8 to 24.8)	0.734	23.0 (± 2.1)	(21.9 to 24.1)	0.417	0.543
Gn-Cd	89.7 (± 3.6)	(87.6 to 91.8)	94.5 (± 5.4)	(89.9 to 99.0)	0.028*	93.2 (± 4.0)	(90.6 to 95.7)	0.089	90.3 (± 3.7)	(88.4 to 92.3)	0.956	0.924
Pog'-Go	59.3 (± 3.0)	(57.6 to 61.0)	61.3 (± 3.2)	(58.6 to 63.9)	0.309	60.7 (± 2.4)	(59.2 to 62.2)	0.486	59.6 (± 3.1)	(58.0 to 61.3)	0.980	0.331
Cd-Go	44.2 (± 3.0)	(42.5 to 45.9)	44.5 (± 2.8)	(42.2 to 46.9)	0.989	42.2 (± 2.7)	(40.4 to 43.9)	0.176	42.3 (± 2.8)	(40.8 to 43.8)	0.184	0.573
Ii-Ii'	34.2 (± 1.6)	(33.3 to 35.1)	36.5 (± 1.9)	(34.8 to 38.1)	0.064	33.5 (± 2.3)	(32.0 to 35.0)	0.767	35.3 (± 2.7)	(33.9 to 36.7)	0.404	0.978
Mo-Mi	27.9 (± 2.1)	(26.7 to 29.1)	29.0 (± 1.5)	(27.8 to 30.3)	0.499	26.8 (± 1.9)	(25.7 to 28.0)	0.456	29.0 (± 2.6)	(27.7 to 30.4)	0.347	0.695
Ii-Mo	21.1 (± 1.3)	(20.4 to 21.9)	21.9 (± 1.8)	(20.5 to 23.4)	0.502	21.8 (± 2.1)	(20.4 to 23.1)	0.603	21.1 (± 1.3)	(20.4 to 21.8)	1.000	0.378

2   *$P < 0.05$ by Dunnett's multiple comparison test. SD, standard deviation. 95% CI, 95% Confidence Interval.

Relationships of craniofacial morphology with the differences in cleft type and surgeons

(A) Patient distribution according to the cleft type (B) Patient distribution according to the operating surgeon

1 **Table 3** Relationships of craniofacial morphology with the differences in cleft type and surgeons
2
3 **(A)** Patients distribution according to the cleft type

	Cleft in hard & soft palate	Cleft in soft palate	Total
Cluster A	3	5	8
Cluster B	9	3	12
Cluster C	11	5	16
Total	23	13	36

4 $P (\chi^2) = 0.27$, Effect Size; $w = 0.457$, Post-hoc power; $(1-\beta) = 0.725$
5
6 **(B)** Patients distribution according to the operating surgeon

	Surgeon A	Surgeon B	Surgeon C	Surgeon D	Total
Cluster A	3	1	1	3	8
Cluster B	4	2	4	2	12
Cluster C	5	6	2	3	16
Total	12	9	7	8	36

7 $P (\chi^2) = 0.69$, Effect Size; $w = 0.775$, Post-hoc power; $(1-\beta) = 0.957$