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Geometric Morphometric Study on Distinguishing Metopic Craniosynostosis from Metopic Ridging

Yoshiaki Sakamoto, MD*
Hideki Amano, mEng†
Naomichi Ogihara, PhD†
Tomoru Miwa, MD‡
Ikkei Tamada, MD§
Makoto Hikosaka, MD¶
Keisuke Imai, MD‖

Background: Craniosynostosis, a common congenital anomaly, results from premature fusion of the cranial sutures. One of the forms of craniosynostosis is premature fusion of the metopic suture, referred to as trigonocephaly, but the diagnosis of metopic suture synostosis remains controversial. The purpose of this study was to clarify, using geometric morphometric analysis, if a metopic ridge alone observed in cases of mild trigonocephaly represents a pathological phenomenon.
Methods: Three different cranial morphologies were compared among patients up to 2 years old who were categorized into the true group, the mild group, and the normal group, based on the presence or absence of specific symptoms, history of cranioplasty for trigonocephaly, or lack of any abnormality on computed tomography. Using the obtained computed tomography images, 235 anatomical landmarks and semi-landmarks were plotted on the entire cranial surface for analysis of neurocranial morphology, and the cranial shapes represented by landmarks were analyzed using geometric morphometrics. Principal components of shape variations among specimens were then computed, based on the variance–covariance matrix of the Procrustes residuals of all specimens, and statistically analyzed.
Results: The principal component analyses of the variations in endocranial shape, frontal bone shape, and occipital bone shape did not show any significant differences in cranial morphology between mild trigonocephaly and normal skulls; however, true trigonocephaly was found to differ significantly from mild trigonocephaly and normal skulls.
Conclusions: These findings suggest that in assessments of cranial morphology, the presence of a ridge alone cannot be diagnosed as fundamentally pathological, and may represent normal morphology. *(Plast Reconstr Surg Glob Open 2024; 12:e6034; doi: 10.1097/GOX.0000000000006034; Published online 7 August 2024.)*

INTRODUCTION

Craniosynostosis is a common congenital anomaly resulting from premature fusion of the cranial sutures. Among the various forms, the occurrence of trigonocephaly as the premature fusion of the metopic suture has been increasing worldwide in recent years.[1] However, trigonocephaly can be confused with "physiological" closure of the metopic suture, with complete closure typically occurring by the age of 9–11 months.[2,3] In some cases, fusion can occur as early as 3 months of age.[4] Physiological closure of the metopic suture is often associated with a palpable midline ridge over the forehead,[5] which can be misinterpreted as the ridging associated with premature closure. The diagnosis of metopic synostosis on the basis of findings from computed tomography (CT) alone can thus prove misleading.

In Japan, some researchers define a metopic ridge with depressed temples, heel-shaped rather than keel-shaped forehead, and slight hypotelorism as "mild trigonocephaly" and believe this finding is associated with developmental delay.[6] However, controversy remains regarding this concept and the indications for cranioplasty.

Craniosynostosis, not only in trigonocephaly, causes deformity of the entire cranium due to growth retardation

*From the *Department of Plastic and Reconstructive Surgery, Keio University School of Medicine, Tokyo, Japan; †Laboratory of Human Evolutionary Biomechanics, Department of Biological Sciences, The University of Tokyo, Tokyo, Japan; ‡Department of Neurosurgery, Keio University School of Medicine, Tokyo, Japan; §Department of Plastic and Reconstructive Surgery, Tokyo Metropolitan Children's Hospital, Tokyo, Japan; ¶Department of Plastic and Reconstructive Surgery, National Center for Child Health and Development, Tokyo, Japan; and ‖Department of Plastic and Reconstructive Surgery, Osaka City General Hospital, Osaka, Japan.*

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caused by premature fusion of sutures and compensatory growth in the vicinity of other intact sutures.[7–9] In this study, we compared three cranial morphologies using geometric analysis: normal cranium; so-called mild trigonocephaly in which only the metopic ridge is observed; and true metopic synostosis in which a triangular cranium is involved. The aim was to verify whether true metopic synostosis can be diagnosed more clearly, and whether mild trigonocephaly is a pathological finding using geometric morphometric analysis.

Takeaways

Question: Is a slightly elevated metopic ridge in the forehead a symptom of trigonocephaly or simply a temporary feature of spontaneous closure?

Findings: Using geometric morphometric analysis, the principal component analyses of the variations in endocranial shape, frontal bone shape, and occipital bone shape did not show any significant differences in cranial morphology between mild trigonocephaly and normal skulls; however, true trigonocephaly was found to differ significantly from mild trigonocephaly and normal skulls.

Meaning: These findings suggest that in assessments of cranial morphology, the presence of a ridge alone cannot be diagnosed as fundamentally pathological, and may represent normal morphology.

PATIENTS AND METHODS

Subjects of the present study were patients who showed the following signs: a keel-shaped forehead; esotropia due to pseudohypotelorism, interorbital narrowing by visual examination; an Ω-sign, "omega"-shaped invagination intracranially[5]; a raccoon deformity that is caused by upper orbital narrowing[10]; and a frontal bone tangent intersecting the orbital midline or more medially when viewed from above[11] by CT scan. These were diagnosed by both a craniofacial surgeon and pediatric neurosurgeon in each unit.

Patients with these symptoms who underwent cranioplasty for trigonocephaly were collected from four centers as the true group. Patients up to 2 years old who visited Keio University Hospital from 2015 or later with a complaint of metopic ridge but who did not show an Ω sign or raccoon deformity and were not operated on were included in the mild group. Patients up to 2 years old who visited the hospital after trauma and underwent CT but showed no abnormality were included as the control group (normal group).

Patients with syndromic craniosynostosis or multiple craniosynostosis were excluded from the present study. In addition, only patients with CT data with a slice thickness less than 1.5 mm were included in the present study. The study protocol was approved by the institutional research ethics board of Keio University Hospital (approval no. 202110872).

From a series of consecutive cross-sectional images, cranial bones were segmented by thresholding, and the three-dimensional (3D) surface of cranial bones was generated as a triangular mesh model using a marching cubes algorithm in Mimics 22.0 software (Materialise, Leuven, Belgium). A total of 40 anatomical landmarks on the cranial surface (Table 1) were digitized using Geomagic XOR software (3D Systems, Rock Hill, S.C.; Fig. 1). For individuals with an open anterior fontanel in whom the bregma could not be placed, the bregma was defined as the average of two points on the lateral contour of the frontal bone and the anterior end of the sagittal suture. To define landmarks on the neurocranial surface, a total of 29 equally spaced points along the midsagittal curves from nasion to bregma, bregma to lambda, and lambda to opisthion, and curves along the coronal and lambda sutures were calculated and defined as anatomical landmarks.[12] In addition, to capture the smooth shape of the neurocranium where no anatomical landmarks could be defined, semi-landmarks were introduced. For this, a template specimen with a total of 166 semi-landmarks located between anatomical landmarks was created, and these template landmarks were mapped onto target specimens based on anatomical landmarks so as to minimize the bending energy of spatial transformation.[13] This resulted in a total of 235 anatomical landmarks and semi-landmarks defined

Table 1. Definition of Anatomical Landmarks Used in the Present Study

Number	Type	Definition
1	M	Nasion
2	M	Bregma
3	M	Lamda
4	M	Opisthion
5	M	Basion
6	M	Sphenobasion
7	M	Most posterior point on the medial palatine suture
8	M	Rhinion
9	M	Zygoorbitale
10	B	Most superior point on the orbital margin
11	B	Frontomalare-orbitale
12	B	Intersection of the nasofrontal, nasomaxillary, and maxillofrontal sutures
13	B	Zygomaxilare
14	B	Zygoorbitale
15	B	Most posterior point on the margin of the temporal fossa
16	B	Porion
17	B	Most lateral point on the margin of the foramen magnum
18	B	Intersection of the occipitomastoid suture and occipital bone edge
19	B	Alare
20	B	Most posterior point on the margin of the pterygopalatine fossa
21	B	Intersection of the coronal, sphenofrontal, and sphenoparietal suture
22	B	Intersection of the lambda parietomastoid and occipitomastoid
23	B	Most posterior point on the margin of the jugular foramen
24	B	Most inferior point on the zygomaticotemporal suture

B, bilateral landmark; M, midsagittal landmark.

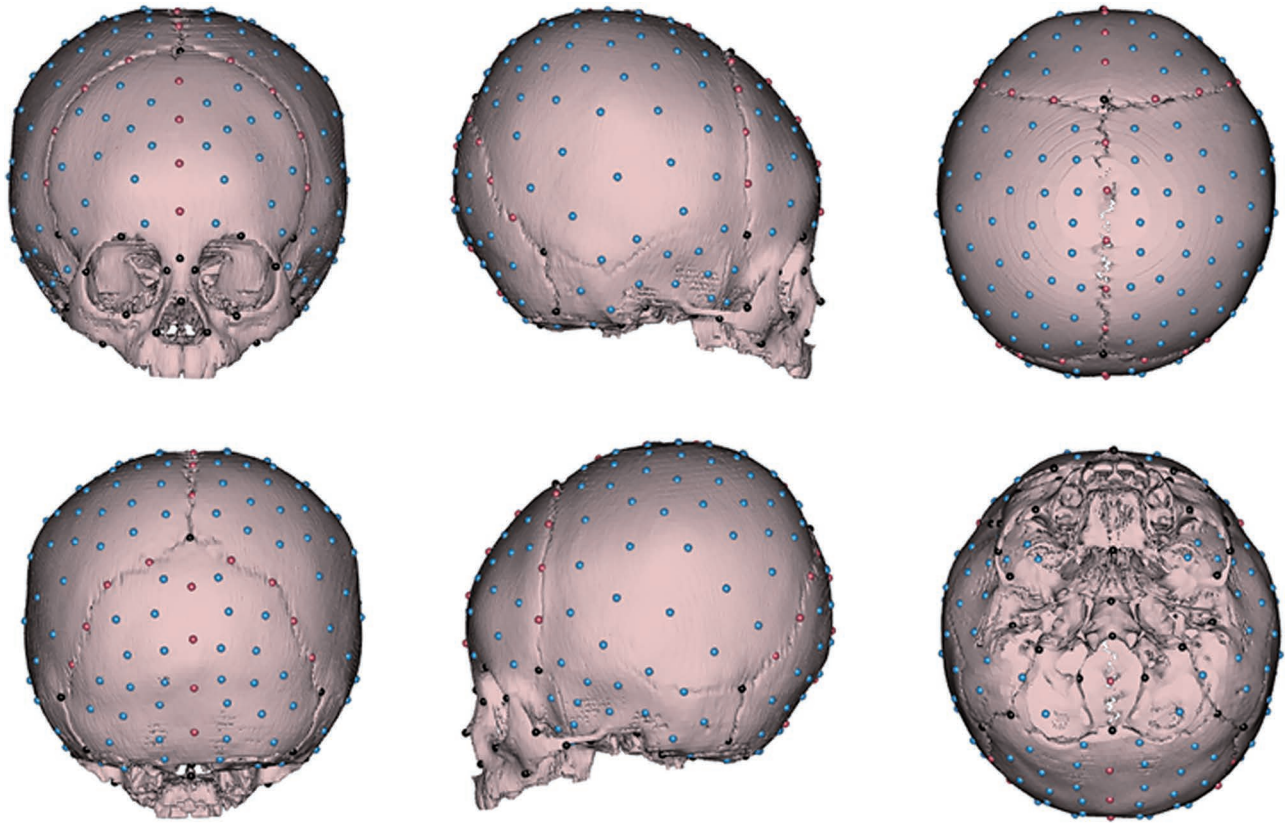

Fig. 1. A total of 235 anatomical landmarks and semi-landmarks. Black: anatomical landmark; red: equally spaced points along cranial sutures; blue: sliding landmark.

on the entire cranial surface to analyze differences in neurocranial morphology among subjects (Fig. 1).

In the present study, the cranial shape variabilities of the patients were analyzed using geometric morphometrics. Geometric morphometrics is a statistical method for analyzing shape variability in biological organisms. Unlike conventional morphometrics, which uses simple measurements like lengths, widths, and ratios, geometric morphometrics uses a set of coordinates of anatomically homologous landmarks defined on the organism to capture and analyze its shape.

Firstly, the landmark coordinates were transformed (translated and rotated) to minimize differences and align all specimens as closely as possible using the least-squares method (generalized Procrustes analysis[14]). Additionally, to focus purely on cranial shape variability, the size of each cranium was normalized using a measure called centroid size, defined as the square root of the sum of all squared distances from each landmark to the centroid of the shape.

The differences in the coordinates of the landmarks after alignment represent shape variations among the specimens. However, the dimensionality required to describe shape differences becomes very large with an increasing number of landmarks. To analyze this high-dimensional data, principal component analysis was used[15,16] to reduce the number of dimensions while retaining the variation in the data. Specifically, the eigenvalues and eigenvectors of the variance–covariance matrix of the aligned landmark coordinates were calculated. The eigenvectors, ordered by their corresponding eigenvalues from largest to smallest, are called principal components (PCs). The first principal component (PC1) accounts for the most variance, the second (PC2) for the next most, and so on.

In this study, we selected the PCs of shape variations that accounted for more than 5% of total variance to be meaningful. Differences in the PC scores (the values that each specimen takes on the axes of the PCs) in the lower-dimensional space created by the selected PCs were statistically analyzed to extract differences in cranial shape among the patients. Shape variations represented by each PC were visualized by warping the wireframe connecting cranial landmarks along the PCs.

These geometric morphometric analyses, including the calculation of semi-landmarks, were implemented in R, version 4.1.2 software (R Core Team, 2023) and the "Morpho," version 2.9 package.[17,18] For more detailed information, refer to the reference by Slice.[19]

RESULTS

Subjects included nine patients (one girl, eight boys) in the true group, eight patients (two girls, six boys) in the mild group, and 11 patients (four girls, seven boys) in the normal group (Table 2).

The percentage of morphological variance accounted for first six PCs were 19.8%, 18.9%, 16.0%, 9.3%, 7.2%, and 5.2%, respectively. Among PCs, only the first two PCs

Table 2. Demographic Characteristics of the Subjects

Group	True	Mild	Normal
No. (male)	9(8)	8(6)	11(7)
Age, mo (Ave)	4–23 (10.7 ± 5.2)	6–24 (13.5 ± 5.2)	4–20 (9.8 ± 4.9)

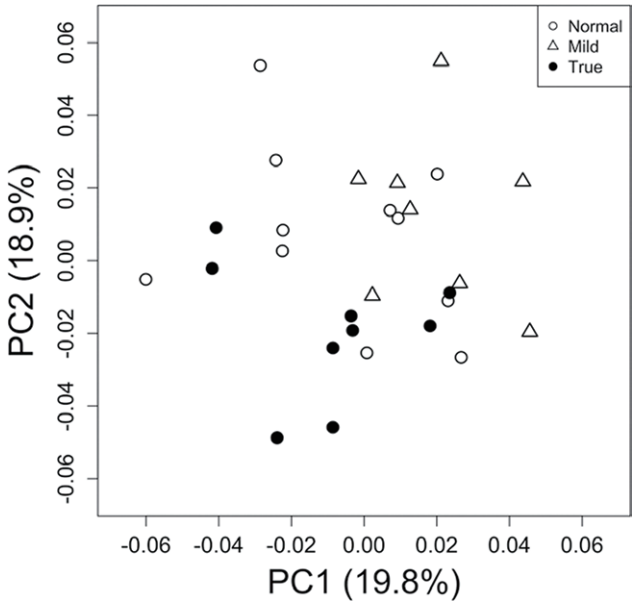

Fig. 2. Results from PC analysis of endocranial shape variation. PC1 (*x*-axis) vs PC2 (*y*-axis).

were considered dominant, because no clear separations among the three groups were observed in the remaining components. So the results of PC analysis concerning morphological variability in the cranial surface of patients with true trigonocephaly, mild trigonocephaly, and normal cranium are presented in Figure 2, as a plot of the first principal component (PC1) versus the second principal component (PC2).

The mean and SD of PC scores are shown in Figure 3. The results of multiple testing showed that PC1 differed significantly between the mild and true groups ($P < 0.05$). However, no significant difference was evident between the normal and mild groups ($P = 0.06$), or between the normal and true groups ($P = 0.94$). The results of multiple testing showed that PC2 differed significantly both between the mild and true groups and between the normal and true groups ($P < 0.05$ each). However, no significant difference was noted between the normal and mild groups ($P = 0.85$).

With an increase in PC1, relative elongation of the endocranial length, relative contraction of the endocranial breadth, and more posteroinferior protrusion of the cerebellar region were noted. In contrast, a decrease in PC1 resulted in relative contraction of the endocranial length, flattening of the posterior cranium, and more posterosuperior protrusion of the parietal region (Fig. 4).

With an increase in PC2, relative elongation of the endocranial length, relative contraction of the endocranial breadth, and more posteroinferior protrusion of the cerebellar region were seen. In contrast, with a decrease in PC2, relative contraction of the endocranial length, flattening of the posterior cranium, and more posterosuperior protrusion of the parietal region became evident (Fig. 5).

In addition, a decrease in PC2 resulted in relative shortening of the interorbital distance, relative contraction of frontal bone breadth, and more anterior and posterior protrusion of the frontal and posterior regions (Fig. 5).

Evaluation of the entire cranium would inevitably weaken the impact of the distortion. From the results of PC1 and PC2, changes were observed in the frontal and occipital regions, so further analysis focusing on these areas was conducted.

The results of PCs concerning morphological variability in the frontal region were 40.9%, 14.5%, 13.7%, and 6.5% for PC1, PC2, PC3, and PC4, respectively. This suggested that PC1 was greatly involved (Fig. 6). Multiple testing showed that PC1 differed significantly between the normal and true groups, and between the mild and true groups ($P < 0.05$ each). However, no significant difference

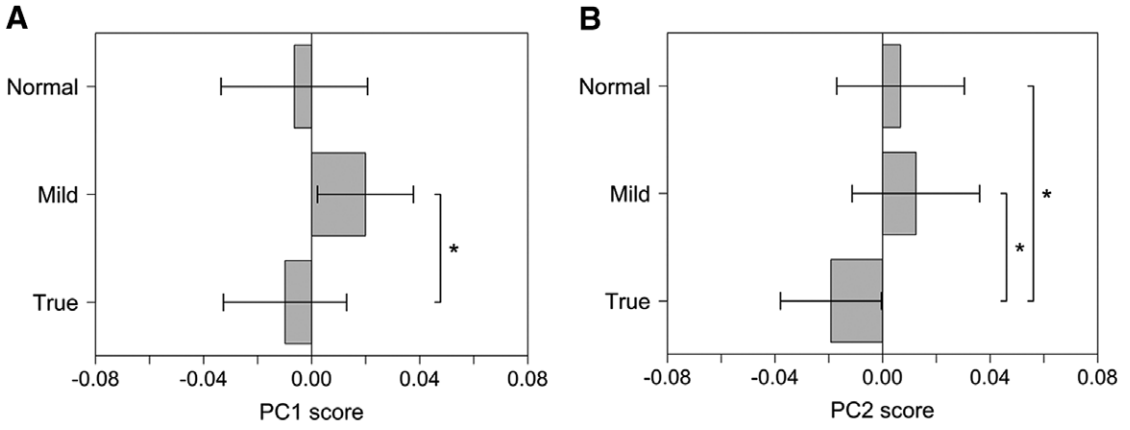

Fig. 3. Mean and SD of PC scores for endocranial shape variation. A, PC1; B, PC2.

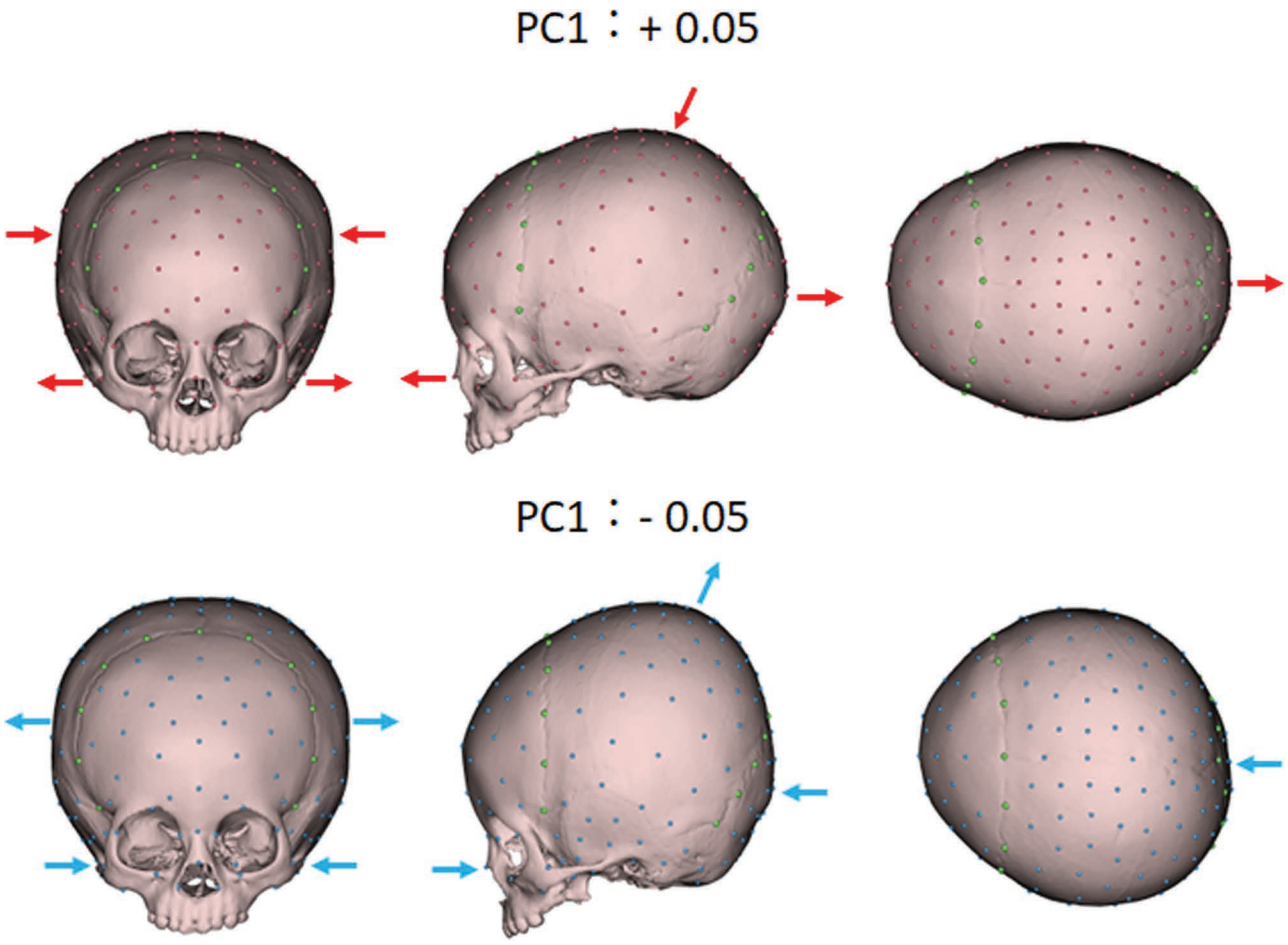

Fig. 4. Variations in total cranial shape represented by PC1.

was noted between the normal and mild groups ($P = 0.94$; Fig. 7).

Figure 8 shows 3D shape variabilities along PC1 by warping the endocranial shape represented by the wireframe that connected the landmarks.

With an increase in PC1, the center of the forehead generally protruded more anteriorly and forehead width was reduced. Apex and caudal points of the forehead were deviated posterosuperiorly and inferiorly, respectively.

The results for PCs concerning morphological variability in the occipital region were 22.2%, 19.9%, 11.3%, 9.9%, 8.1%, and 5.9% for PC1, PC2, PC3, PC4, PC5, and PC6, respectively. Results are shown for PC1 and PC2, which showed particularly high values (Fig. 9). Multiple testing showed that PC2 differed significantly between the normal and true groups ($P < 0.05$). However, no significant difference was noted between the normal and mild groups ($P = 0.79$) or between the mild and true groups ($P = 0.09$; Fig. 10).

Figure 11 shows 3D ectocranial shape variabilities along PC2 with warping of the cranial shape represented by the wireframe that connected the landmarks. With an increase in PC2, the inion protruded posteriorly, the upper part of the occipital bone was wider, and the lower part was narrower.

DISCUSSION

The diagnosis of metopic suture synostosis remains controversial.[20] Although some reports have stated that the metopic ridge alone is not pathological,[5,21–23] others have suggested that the intracranial volume of the forehead area is small and that surgery is indicated.[24] However, all previous studies have focused on the anterior forehead and orbits. However, the entire skull is thought to be affected in all types of craniosynostoses due to the premature closure of sutures and the resulting compensatory changes.[7–9] This study was therefore conducted to clarify whether a metopic ridge alone observed in mild trigonocephaly represents a pathological phenomenon by examining the entire cranium, as metopic suture synostosis must also have altered the morphology of the entire skull. To the best of our knowledge, this represents the first study to examine the entire cranium using geometric morphometric analyses. The results showed no significant differences in cranial morphology between mild trigonocephaly and normal skulls. On the other hand, true

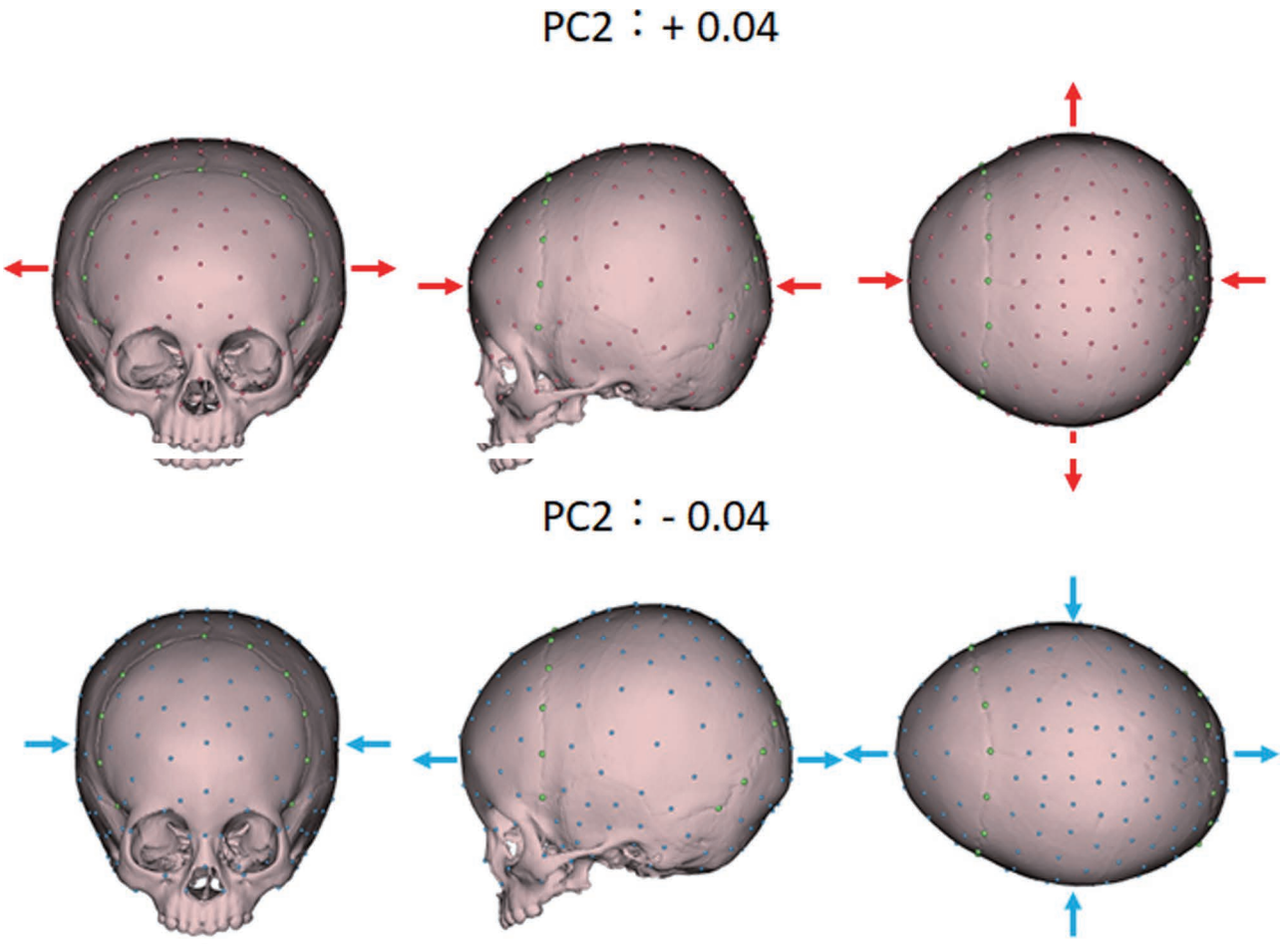

Fig. 5. Variations in total cranial shape represented by PC2.

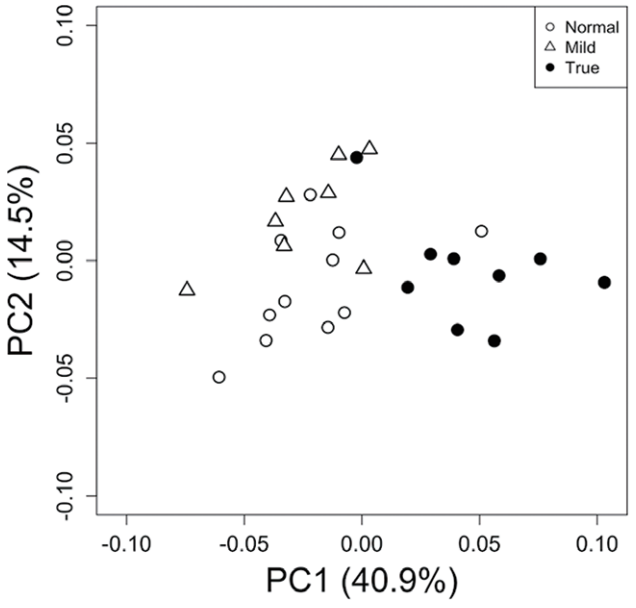

Fig. 6. Results from principal component (PC) analysis of frontal bone shape variation. PC1 (*x*-axis) vs PC2 (*y*-axis).

trigonocephaly was found to differ significantly from mild trigonocephaly and normal skulls.

True trigonocephaly in this study was characterized by anterior elongation in the midline and reduced width of the frontal region, and narrowed interorbital distance in the upper facial region. Of particular interest was the occipital region contralateral to the fused side, in which posterior downward expansion was thought of as reflecting a compensatory change in brain growth in true trigonocephaly. However, one limitation of this study was a possible effect on occipital deformation due to sleeping position. Changes observed in PC1 of the entire cranium (occipital flattening, parietal protrusion and transverse widening of posterior portion) resemble changes observed in deformational brachycephaly,[24] and further investigation is therefore needed.

Another issue of particular interest was the length of the anterior skull base, which was greater than normal, suggesting that the frontoorbital bone piece in frontoorbital advancement may not need to be advanced in the midline.

The limitation of this study was the small number of samples. A power analysis was conducted, and we found that a sample size of 10 was required to achieve a power of

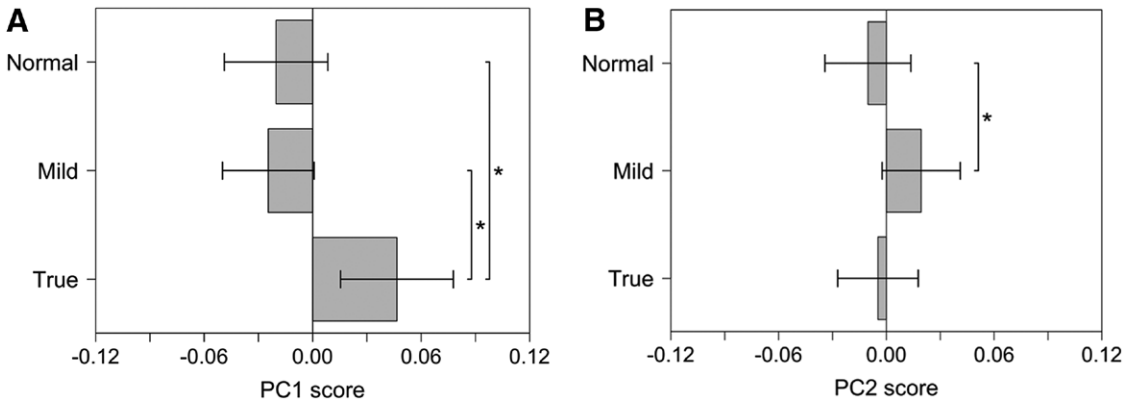

Fig. 7. Mean and SD of PC scores of frontal bone shape variation. A, PC1; B, PC2.

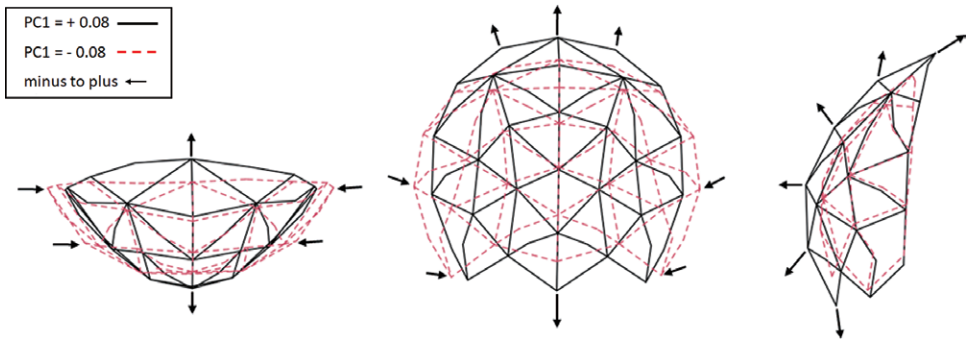

Fig. 8. Variations in frontal bone shape represented by PC1.

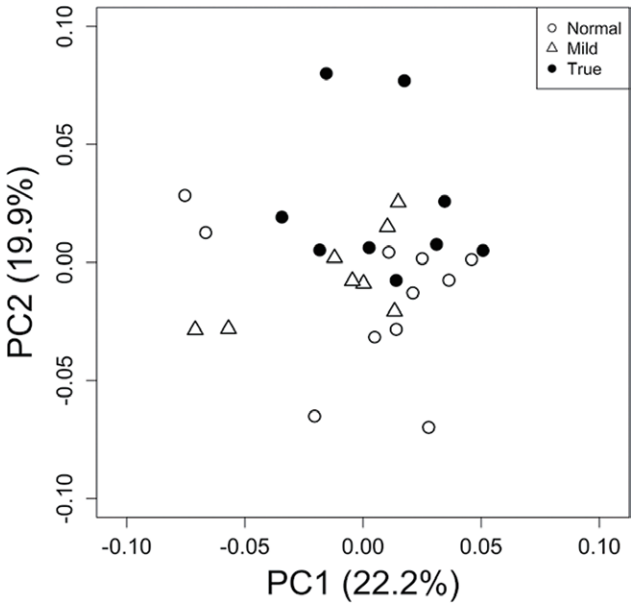

Fig. 9. Results of principal component (PC) analysis of occipital bone shape variation. PC1 (*x*-axis) vs PC2 (*y*-axis).

0.8, assuming an effect size of one. In this study, effect size was determined using Cohen d statistics when a significant difference was confirmed. In all instances, the effect size exceeded 0.8, indicating a large effect size. This suggests that the observed differences remained substantial despite the small sample size. However, trigonocephaly has severity,[25] we believe, that increased the number of samples and led to more robust results and conclusions.

In conclusion, if craniosynostosis is a disease that fundamentally affects cranial morphology, the presence of a ridge alone cannot be diagnosed as pathological, but rather represents a normal situation in terms of morphology.

Yoshiaki Sakamoto, MD
Department of Plastic and Reconstructive Surgery
Keio University School of Medicine
35 Shinanomachi, Shinjuku-ward
Tokyo 160-8582, Japan
E-mail: ysakamoto@z8.keio.jp

DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

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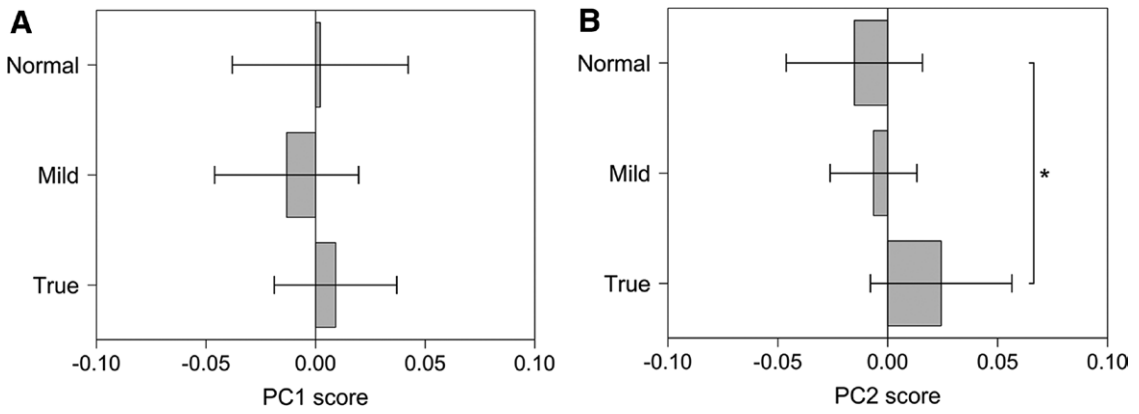

Fig. 10. Mean and SD of PC scores for occipital bone variation. A, PC1; B, PC2.

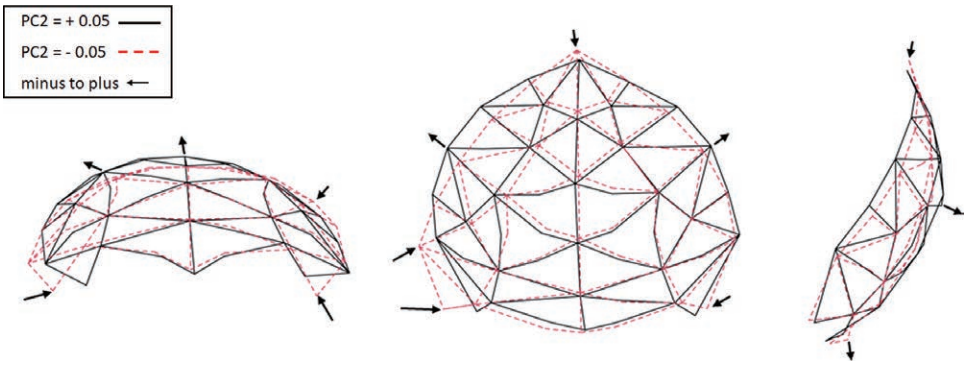

Fig. 11. Variations in occipital bone shape represented by PC2.

ETHICAL APPROVAL

The study protocol was approved by the institutional research ethics board of Keio University Hospital (approval no. 202110872).

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