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Three-dimensional craniomaxillary characteristics of the mouse with spontaneous malocclusion using micro-computed tomography

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SUMMARY The aim of this study was to clarify the morphological characteristics of craniomaxillary deviations in BALB/c-*bm*/*bm* mice with a spontaneous malocclusion (incisal transverse crossbite) using three-dimensional (3D) morphological measurements.

Sixty female mice aged 13 and 25 weeks were divided into the following groups: control (BALB/c-+/+ mice, $n = 20$), norm (BALB/c-*bm*/*bm* mice with a normal occlusion, $n = 20$), and mal (BALB/c-*bm*/*bm* mice with a malocclusion, $n = 20$). Various points in the skull were selected and the distances between two points were measured using 3D micro-computed tomography (CT) images. Statistically significant differences in measurement values among the three groups were evaluated by one-way analysis of variance with a probability level of $P < 0.05$ considered statistically significant.

At both ages, the lengths of almost all measurements in the norm and mal groups were significantly shorter than those in the control group. Comparison between the shifted and non-shifted sides in the mal group showed that significant lateral deviation at the maxilla and nasal bone had occurred.

Using 3D micro-CT images, the results of this study quantitatively showed that the craniomaxillary complex of BALB/c-*bm*/*bm* mice was significantly smaller than that of BALB/c-+/+ mice and that BALB/c-*bm*/*bm* mice have a spontaneous transverse crossbite due to lateral deviation of the maxilla and nasal bone.

Introduction

Brachymorphic (*bm*) (O'Brien *et al.*, 1994; Rusiniak *et al.*, 1996) mice were discovered in an inbred mahogany stock (Lane and Dickie, 1968). BALB/c-*bm*/*bm* mice (Hirabayashi *et al.*, 2003) are generated by crossing BALB/c mice and C57BL-*bm*/*bm* mice (Kurima *et al.*, 1998). BALB/c-*bm*/*bm* mice show specific characteristics: a dome-shaped skull, a short thick tail, and shortened but not widened limbs (Tsukamoto *et al.*, 2006, 2008). Malocclusion (incisal transverse crossbite) (Tsukamoto *et al.*, 2006) spontaneously occurs in about 10 per cent of BALB/c-*bm*/*bm* mice, though malocclusion does not spontaneously occur in mice with the same *bm* mutation as that in C57BL-*bm/bm* mice and in non-brachymorphic mice such as BALB/c-+/+ mice and BALB/c-*bm*/+ (*bm* heterozygotes) mice.

It is not clear why a transverse crossbite spontaneously occurs in some BALB/c-*bm*/*bm* mice. Experimental studies have been carried out to understand the cause of malocclusion. Tsukamoto *et al.* (2008) reported that columns of chondrocytes of BALB/c-*bm*/*bm* mice were histologically irregular in arrangement and that undersulphated glycosaminoglycans might cause a disturbance of endochondral growth at the cranial base with spheno-occipital synchondrosis and intersphenoid synchondrosis. Kajii *et al.* (2006) found no significant differences in the concentrations of sulphated glycosaminoglycans on condyles between the mandibular shifted and non-shifted sides in BALB/c-*bm*/*bm* mice with a spontaneous malocclusion. In a preliminary experiment (Kajii *et al.*, 2004) using two-dimensional (2D) headfilms, maxillary transverse deviation was found to be larger than mandibular deviation in BALB/c-*bm*/*bm* mice with malocclusions.

To date, morphological measurements of animals with malocclusion have been carried out using radiographs and/or photographs (Gebhardt and Pancherz, 2003; Yagi *et al.*, 2003; Kajii *et al.*, 2004). For evaluating rotated morphology, which is difficult to identify with 2D headfilms, computed tomography (CT) allows the use of three-dimensional (3D)

morphology (Papadopoulos *et al.*, 2005; Pelo *et al.*, 2006; Muramatsu *et al.*, 2008) (Figure 1).

The objective of this study was to determine the morphological characteristics of craniomaxillary deviations in BALB/c-*bm*/*bm* mice using 3D morphological measurements.

Materials and methods

The procedures were reviewed and approved by the animal care and use committees of Nagoya Bunri University and Hokkaido University, and this study was performed according to the Guidelines for Animal Experiments of Hokkaido University.

Female mice aged 13 (adolescent, $n = 30$) and 25 (adult, $n = 30$) weeks were used in this study. The mice were divided into the following three groups for each age: (1) BALB/c-+/+ mice (control group, $n = 10$), (2) BALB/c-*bm*/*bm* mice with normal occlusion (norm group, $n = 10$), and (3) BALB/c-*bm*/*bm* mice with incisal transverse crossbite (mal group, $n = 10$). BALB/c-+/+ mice were obtained from Nippon Clea, Tokyo, Japan. By outbreeding between *bm* mice of the C57BL strain and normal mice of the BALB/c strain, the *bm* gene was successfully transferred to BALB/c strain mice (BALB/c-*bm*/+ mice). BALB/c-*bm*/*bm* mice were generated by crossbreeding between BALB/c-*bm*/+ mice.

The body weights of the mice in the three groups were determined at 13 and 25 weeks of age. In the mal group, five upper incisors were shifted to the right at 13 weeks of age and six at 25 weeks of age and five upper incisors were shifted to the left at 13 weeks of age and four at 25 weeks of age.

Dry skulls of each group were prepared using a standard protease method (Hachiya and Ohtaishi, 1994). Images of the dry skulls using 3D micro-CT (Arai *et al.*, 2007) (R_mCT, Rigaku, Tokyo, Japan) were obtained under the following conditions: tube voltage, 90 kV; tube current, 120 μA; and slice width, 0.4 mm. The obtained CT images were morphologically reconstructed using image reconstruction software (i-VIEW-R, Morita, Kyoto, Japan).

Six points were selected (Figure 2A–C). The 3D distances of Oc–Tb, Oc–S2, Oc–S1, Oc–Pr, Oc–A, Tb–S2, Tb–S1, Tb–Pr, Tb–A, S2–S1, S2–Pr, S2–A, S1–Pr, and S1–A were measured on both sides using iVIEW-R. The distances were compared among the three groups. Furthermore, the distances in the mal group were compared between the shifted and non-shifted sides in the same regions.

Statistical analysis

To determine measurement error, the same distance was measured on two occasions with a time interval of 2 weeks by the same investigator (FS). The correlation coefficient between the first and second measurements of 60 mice showed a significant correlation for all distances ($P < 0.001$).

Statistically significant differences in measurement values among the three groups were evaluated using the Statistical Package for Social Science version 13.0 (SPSS Inc., Chicago, Illinois, USA) by one-way analysis of variance (ANOVA), with a probability level of $P < 0.05$ considered statistically significant.

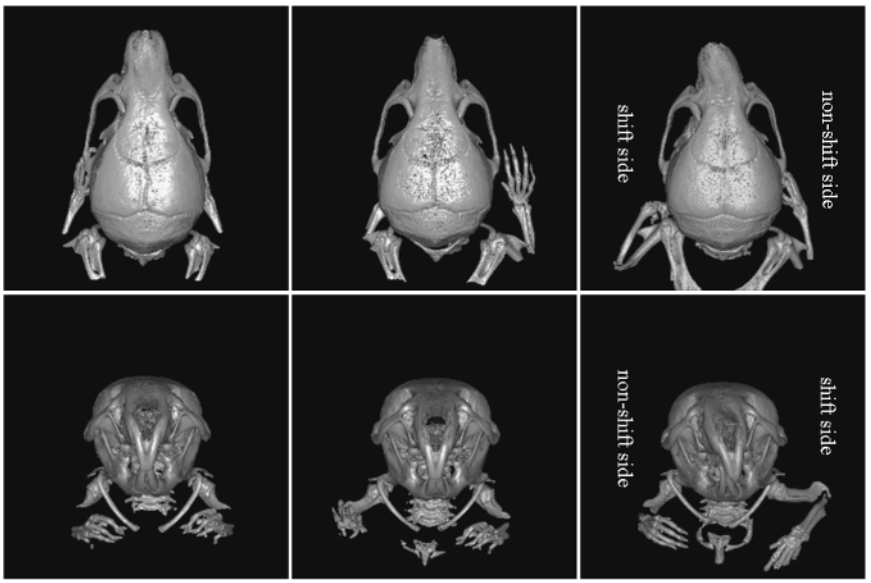

Figure 1 Three-dimensional micro-computed tomography (R_mCT) images. Left, BALB/c-+/+ mouse; centre, BALB/c-*bm*/*bm* mouse without a malocclusion; and right, BALB/c-*bm*/*bm* mouse with a malocclusion. Upper, dorsal view and lower, frontal view.

Pearson's correlation coefficient between deviations of Pr and A was also calculated using the SPSS software.

Results

Body weight

The mean body weights at the age of 13 weeks were 25.4 ± 2.3, 16.2 ± 1.4, and 15.1 ± 1.7 g in the control, norm, and mal groups, respectively, and at 25 weeks 28.4 ± 2.8, 18.1 ± 2.0, and 18.3 ± 1.3 g in the control, norm, and mal groups, respectively. At both 13 and 25 weeks of age, one-way ANOVA showed that there were significant differences in body weight among the three groups ($P < 0.001$). The body weight of the *bm* mice (norm and mal groups) was significantly less than that of the control group ($P < 0.001$). No significant difference in body weight was found between the norm and mal groups at either 13 or 25 weeks of age.

Thirteen weeks of age

For almost all measurements, there were significant differences among the control, norm, and shifted and non-shifted sides of the mal group ($P < 0.001$). Intergroup comparison showed that almost all measured lengths in the norm and mal groups (both shifted and non-shifted sides) were significantly shorter than those in the control group ($P < 0.05$) (Tables 1 and 2). The distances Oc–A, Tb–A,

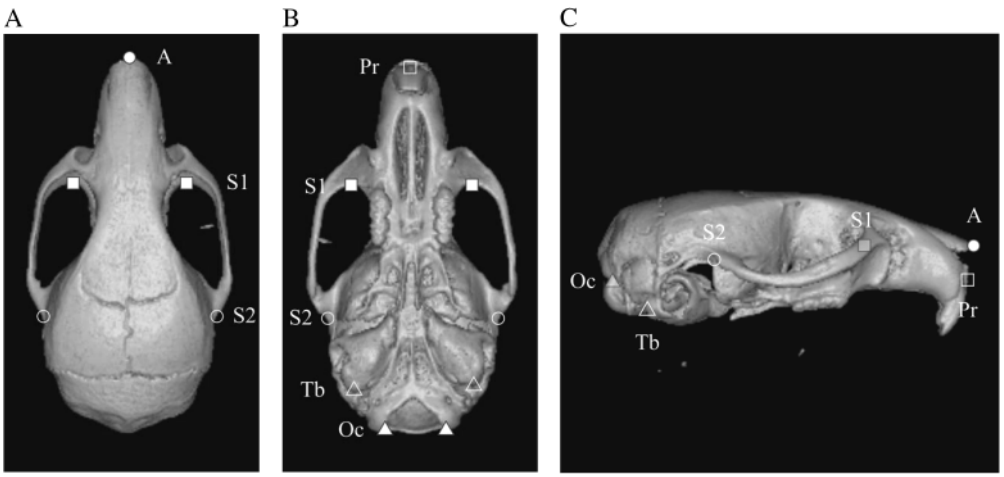

Figure 2 Dorsal (A) and ventral (B) views. Reference points: Oc, inner point of the occipital bone; Tb, posterior apex of the tympanic bulla; S2, transitional point between the squamous part and the zygomatic process in the temporal bone; S1, frontal point in the inner margin of the zygomatic arch; Pr, frontal apex of the alveolar process in the incisive; and A, frontal apex of the nasal bone. Lateral view (C) is shown to clarify the difference between points A and Pr.

Table 1 Mean and standard deviation (SD) for each distance measured at 13 weeks of age in the three groups.

	Control		Norm		Mal (non-shifted)		Mal (shifted)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Oc–Tb	3.27	0.37	3.04	0.31	3.08	0.31	2.89	0.17
Oc–S2	7.41	0.59	6.06	0.45	6.25	0.26	6.23	0.30
Oc–S1	14.61	0.36	11.84	0.46	11.57	0.52	11.39	0.46
Oc–Pr	21.56	0.34	17.45	0.43	17.06	0.69	16.81	0.69
Oc–A	22.42	0.38	18.05	0.53	17.38	0.86	17.15	0.83
Tb–S2	5.31	0.56	4.66	0.19	4.69	0.23	4.71	0.14
Tb–S1	12.22	0.33	9.89	0.33	9.70	0.51	9.60	0.28
Tb–Pr	19.24	0.37	15.48	0.36	15.29	0.65	14.97	0.52
Tb–A	20.33	0.37	16.37	0.43	15.92	0.78	15.64	0.61
S2–S1	8.06	0.67	7.31	0.54	6.67	0.42	6.40	0.33
S2–Pr	15.94	0.63	14.12	0.66	13.50	0.52	12.82	0.56
S2–A	16.47	0.69	14.28	0.64	13.46	0.64	12.88	0.62
S1–Pr	8.15	0.08	7.13	0.30	7.19	0.26	6.65	0.38
S1–A	8.62	0.11	7.14	0.26	7.07	0.36	6.63	0.50

Table 2 *P* values of one-way analysis of variance among control (1), norm (2) and mal [shifted (3) and non-shifted (4) sides] groups at the age of 13 weeks.

	P value					
	1 versus 2	1 versus 3	1 versus 4	2 versus 3	2 versus 4	3 versus 4
Oc–Tb	0.332	0.507	0.036*	0.989	0.678	0.486
Oc–S2	0.000**	0.000**	0.000**	0.770	0.801	1.000
Oc–S1	0.000**	0.000**	0.000**	0.534	0.135	0.819
Oc–Pr	0.000**	0.000**	0.000**	0.421	0.065	0.734
Oc–A	0.000**	0.000**	0.000**	0.143	0.027*	0.878
Tb–S2	0.000**	0.001**	0.001**	0.996	0.980	0.998
Tb–S1	0.000**	0.000**	0.000**	0.672	0.301	0.917
Tb–Pr	0.000**	0.000**	0.000**	0.831	0.112	0.464
Tb–A	0.000**	0.000**	0.000**	0.298	0.032*	0.692
S2–S1	0.011*	0.000**	0.000**	0.035*	0.002**	0.654
S2–Pr	0.000**	0.000**	0.000**	0.105	0.000**	0.067
S2–A	0.000**	0.000**	0.000**	0.037*	0.000**	0.207
S1–Pr	0.000**	0.000**	0.000**	0.967	0.002**	0.001**
S1–A	0.000**	0.000**	0.000**	0.962	0.009**	0.030*

*$P < 0.05$, **$P < 0.01$.

Table 3 Mean and standard deviation (SD) for each distance measured at 25 weeks of age in the three groups.

Distances	Control		Norm		Mal (non-shifted)		Mal (shifted)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Oc–Tb	3.44	0.17	3.14	0.30	3.04	0.26	3.04	0.20
Oc–S2	7.58	0.22	6.18	0.32	6.42	0.16	6.29	0.25
Oc–S1	15.31	0.19	12.11	0.46	12.08	0.28	11.96	0.26
Oc–Pr	22.64	0.33	18.05	0.51	17.78	0.32	17.60	0.32
Oc–A	23.43	0.35	18.65	0.61	18.27	0.50	18.11	0.55
Tb–S2	5.31	0.15	4.77	0.36	4.87	0.19	4.85	0.19
Tb–S1	12.78	0.23	10.13	0.44	10.25	0.30	10.08	0.27
Tb–Pr	20.18	0.29	16.06	0.49	16.05	0.36	15.65	0.30
Tb–A	21.23	0.32	16.99	0.60	16.86	0.54	16.51	0.52
S2–S1	8.63	0.33	7.39	0.44	7.04	0.40	6.90	0.30
S2–Pr	16.90	0.32	14.54	0.48	14.18	0.46	13.66	0.41
S2–A	17.36	0.35	14.70	0.51	14.25	0.63	13.75	0.53
S1–Pr	8.56	0.24	7.46	0.19	7.58	0.25	7.06	0.24
S1–A	8.97	0.19	7.53	0.24	7.51	0.31	7.03	0.32

S2–Pr, S1–Pr, and S1–A on the shifted side in the mal group were significantly shorter than those in the norm group ($P < 0.05$). The distances S2–S1 and S2–A on both the shifted and non-shifted sides in the mal group were significantly shorter than those in the norm group ($P < 0.05$). Most of the other distances in the anterior region on the non-shifted side in the mal group were also shorter than those in the norm group, although the differences were not statistically significant.

Intragroup comparison showed that the distances S1–Pr and S1–A on the shifted side were significantly shorter than those on the non-shifted side in the mal group ($P < 0.05$; Tables 1 and 2). No significant differences were found in the other distances between the shifted and non-shifted sides, although almost all distances on the shifted side were shorter than those on the non-shifted side.

Twenty-five weeks of age

For all measurements, there were significant differences among the control and norm groups, and shifted and non-shifted sides of the mal group ($P < 0.001$). Intergroup comparison showed that all measured lengths in the norm and mal groups (both shifted and non-shifted sides) were significantly shorter than those in the control group ($P < 0.05$; Tables 3 and 4). The distances S2–S1, S2–Pr, S2–A, S1–Pr, and S1–A on the shifted side in the mal group were significantly shorter than those in the norm group ($P < 0.05$).

Table 4 *P* values of one-way analysis of variance among control (1), norm (2) and mal [shifted (3) and non-shifted (4) sides] groups at the age of 25 weeks.

	P value					
	1 versus 2	1 versus 3	1 versus 4	2 versus 3	2 versus 4	3 versus 4
Oc–Tb	0.030*	0.002**	0.003**	0.772	0.790	1.000
Oc–S2	0.000**	0.000**	0.000**	0.143	0.721	0.664
Oc–S1	0.000**	0.000**	0.000**	0.994	0.686	0.831
Oc–Pr	0.000**	0.000**	0.000**	0.416	0.058	0.711
Oc–A	0.000**	0.000**	0.000**	0.363	0.099	0.885
Tb–S2	0.000**	0.001**	0.001**	0.752	0.844	0.998
Tb–S1	0.000**	0.000**	0.000**	0.830	0.982	0.618
Tb–Pr	0.000**	0.000**	0.000**	1.000	0.076	0.093
Tb–A	0.000**	0.000**	0.000**	0.950	0.173	0.412
S2–S1	0.000**	0.000**	0.000**	0.161	0.027*	0.845
S2–Pr	0.000**	0.000**	0.000**	0.223	0.000**	0.044*
S2–A	0.000**	0.000**	0.000**	0.234	0.001**	0.143
S1–Pr	0.000**	0.000**	0.000**	0.664	0.002**	0.000**
S1–A	0.000**	0.000**	0.000**	0.999	0.001**	0.002**

*$P < 0.05$, **$P < 0.01$.

Most of the other distances in the anterior region on the non-shifted side in the mal group were also shorter than those in the norm group, although the differences were not statistically significant.

Intragroup comparison showed that the distances S2–Pr, S1–Pr, and S1–A on the shifted side in the mal group were significantly shorter than those on the non-shifted side in the mal group ($P < 0.05$; Tables 3 and 4). No significant differences were found for any other distances between the shifted and non-shifted sides, although almost all distances on the shifted side were shorter than those on the non-shifted side.

Correlation coefficient between deviations of maxillary alveolar bone and nasal bone

In the mal group, Pearson's correlation coefficients between the deviation of Pr (distance of S1–Pr on the shifted side subtracted from that on the non-shifted side) and A (distance of S1–A on the shifted side subtracted from that on the non-shifted side) were 0.885 and 0.942 at the ages of 13 and 25 weeks, respectively (Figure 3A and 3B). A scatter diagram between deviations of Pr and A showed significant positive correlations at both ages ($P < 0.01$). Regression slopes obtained from the scatter diagrams were 0.956 and 0.697 at the ages of 13 and 25 weeks, respectively (Figure 3A and 3B).

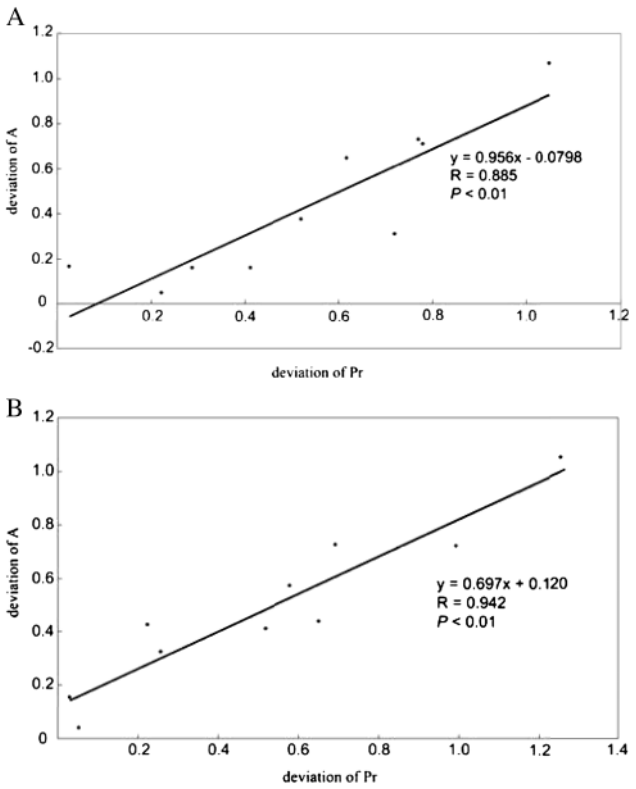

Figure 3 Scattergrams at the ages of 13 (A) and 25 (B) weeks between deviations of A and Pr in the malocclusion (mal) group. Deviation of Pr was calculated by subtracting the distance of S1–Pr on the shifted side from that on the non-shifted side. Deviation of A was similarly calculated by subtracting the distance of S1–A on the shifted side from that on the non-shifted side.

Discussion

Intergroup comparisons at both ages showed that the skulls of *bm* mice (norm and mal groups) were significantly shorter than those of control mice. The body weights of *bm* mice were also smaller than those of control mice. Therefore, it was quantitatively shown that *bm* homozygotes caused not only inferior body growth but also inferior craniomaxillary growth.

In BALB/c-*bm*/*bm* mice with a malocclusion (transverse crossbite), there was no significant difference between the shifted and non-shifted sides in the posterior region of the cranium at either age. Therefore, there was no notable deformity of the posterior neurocranium. On the other hand, S1–Pr (maxillary alveolar bone) and S1–A (nasal bone) on the maxillary shifted side were significantly shorter than those on the non-shifted side at both 13 and 25 weeks of age. It was shown three-dimensionally that the maxillary alveolus and nose were significantly bent in BALB/c-*bm*/*bm* mice with spontaneous malocclusions. The correlation coefficient between the deviation of the maxillary alveolus and that of the nose was investigated. The deviation of the nose was significantly related to the deviation of the maxillary alveolus at both 13 and 25 weeks of age ($P < 0.01$). The regression slopes were 0.956 and 0.697 at the ages of 13 and 25 weeks, respectively. At 13 weeks of age, the alveolar process and nasal bone were almost similarly deviated. However, at 25 weeks of age, the alveolar process was more deviated than the nasal bone. Thus, the degree of torsion between the maxillary alveolar process and nasal bone was larger in older BALB/c-*bm*/*bm* mice with malocclusions.

Growth is generally divided into three types: sutural, cartilaginous, and periosteal. Some studies have shown that the cartilage of the nasal septum plays an important role as a maxillary pacemaker in total growth (Sicher, 1949; Scott, 1954, 1959; Sarnat and Wexler, 1968; Latham, 1970). Tsukamoto *et al.* (2008) histologically reported that undersulphated glycosaminoglycans might cause a disturbance of endochondral growth at the cranial base by disparity of synchondrodial joints in BALB/c-*bm*/*bm* mice. It was suggested that the greater the undersulphated cartilage, the smaller endochondral growth. The results of the present and a previous study (Tsukamoto *et al.*, 2008) suggest that the skull of the craniomaxillary complex of the BALB/c-*bm*/*bm* mouse was similarly smaller due to undersulphated glycosaminoglycans than that of the BALB/c-+/+ mouse.

Kajii *et al.* (2006) reported that the concentration of sulphated glycosaminoglycans in the cartilage of the condyle of BALB/c-*bm*/*bm* mice with a malocclusion was significantly less than that in BALB/c-*bm*/*bm* mice without a malocclusion. Moreover, it was shown in the present study that the craniomaxillary complex of the BALB/c-*bm*/*bm* mouse with a malocclusion was also smaller than that of the BALB/c-*bm*/*bm* mouse without a malocclusion. Although the concentration of sulphated glycosaminoglycans in the craniomaxillary region of the BALB/c-*bm*/*bm* mouse was not measured, it was speculated that a genetic factor such as more undersulphation of glycosaminoglycans in BALB/c-*bm*/*bm* mice might induce more hypo-growth of the craniomaxillary region resulting in a malocclusion such as a transverse crossbite.

On the other hand, Kajii *et al.* (2004) reported that the degree of lateral deviation of incisors in BALB/c-*bm*/*bm* mice with a malocclusion was less if the incisors were shortened after the occurrence of the malocclusion. It was speculated that a genetic factor may be one cause of deformation and/or displacement of the maxilla and nasal bone in the BALB/c-*bm*/*bm* mice with malocclusion and that mechanical loads such as lateral functional occlusal force may enhance the deformity.

Although there have been some reports on malocclusion artificially induced using oral appliances (Fuentes *et al.*, 2003; Nakano *et al.*, 2003; Katsaros *et al.*, 2006; Liu *et al.*, 2007; Ishii and Yamaguchi, 2008), there has been no research on animals with spontaneously induced malocclusions, except for a cleft palate (Nagata *et al.*, 1997). The BALB/c-*bm*/*bm* mouse is therefore useful as a malocclusion model with maxillofacial deformity induced without oral appliances.

In this study, cross-sectional samples at the ages of 13 and 25 weeks represented adolescents and adults, respectively. However, it might be more obvious if living mice with a malocclusion were examined using longitudinal samples to determine when maxillofacial deviation started and how deviation occurred.

Conclusions

The following conclusions were obtained from the results of quantitative measurements using 3D micro-CT images.

1. The skull of the BALB/c-*bm*/*bm* mouse was significantly smaller than that of the BALB/c-+/+ mouse.
2. The BALB/c-*bm*/*bm* mouse had a spontaneous malocclusion (transverse crossbite) due to lateral deviation of the maxilla and nasal bone.
3. The degree of torsion between the alveolar process and nasal bone was greater in older BALB/c-*bm*/*bm* mice with a malocclusion.

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