Tooth size and its proportional variability in Japanese males with agenesis in permanent dentition

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Abstract  We studied the relationship of tooth agenesis with tooth size and its proportional variability (PV) based on mesiodistal crown diameters of 276 Japanese males including 49 individuals for reference. Tooth agenesis was classified into third molar agenesis, hypodontia, and multiple agenesis. In addition, third molar agenesis was classified into four types according to the number of congenitally missing third molars. PV was measured by standard deviation of log-transformed data. The size of remaining teeth was generally larger in the agenesis groups than in the reference group, and largest in individuals with hypodontia, followed by those with multiple agenesis and those with third molar agenesis. The findings suggest the existence of two types of tooth agenesis differing in nature, where remaining teeth tend to enlarge in the ‘moderate type’ and reduce in the ‘degenerative type.’ The former is dominant in (tooth agenesis of) the Japanese, whereas the latter seems to be more prevalent in European descendants, which is in accordance with recent findings in genetics. The ‘moderate type’ might be advantageous for survival in human microevolution because of its improved function and reduced risk of dentoskeletal discrepancies. The PV of tooth size was greater in the agenesis groups than in the reference group except for premolars and second molars. Among those with third molar agenesis, the greatest increase in PV was exhibited by those with all third molars missing, followed by those with two third molars missing. Among remaining teeth, canines and first molars tended to exhibit a greater increase of PV in agenesis groups, whereas their magnitude of PV did not exceed that of other teeth. These results can be explained by the genetic stability of canines and first molars and an increased variation due to common factors across remaining teeth associated with tooth agenesis.

Key words: tooth size, proportional variability, tooth agenesis, canine, first molar

Introduction

In human populations, reduction of teeth has occurred in terms of both their number and size. The congenital absence of permanent teeth is observed most frequently in third molars, which develop last and therefore are presumed to be the most vulnerable to environmental factors such as timing of eruption and nutrition (Garn and Lewis, 1962; Garn et al., 1962, 1963b; Keene, 1966; Yamada and Hanamura, 1993; Yamada et al., 2004). The prevalence of third molar agenesis in human populations varies from 2.6% in West Africans to 49.0% in Hungarians (Hellman, 1936).

Tooth agenesis seems to represent an extreme expression of the effects of various factors where the degree of expression varies according to the timing of tooth formation. In particular, third molar agenesis is known to be associated with crown size reduction in remaining teeth (Garn et al., 1963a; Baum and Cohen, 1971a; McKeown et al., 2002), reduction in the number of other teeth (Garn and Lewis, 1962; Garn et al., 1962), more spacing and less crowding (Keene, 1965), delayed somatic development (Garn et al., 1963b; Garn and Lewis, 1970), and developmental immaturity at birth (Keene, 1966). Garn et al. (1963b) reported that mesiodistal tooth diameters tended to be smaller in individuals lacking one or more third molar teeth. On the other hand, it has been stated that the neighboring teeth tend to increase in size to compensate the space caused by the tooth agenesis (Grüneberg, 1965; Sofer et al., 1971a, b; Mizoguchi, 1983; Yamada et al., 2005). Hence, two opposing opinions have been advanced about the size of the remaining teeth: whether they become smaller due to general tooth reduction (Garn et al., 1963b; Baum and Cohen, 1971a, b), or larger due to compensatory interaction (Grüneberg, 1965; Sofer et al., 1971a, b; Mizoguchi, 1983; Yamada et al., 2005). For third molar agenesis, however, enlargement of the remaining teeth has not been reported except by Asakura (1975), Mizoguchi (1983), and Yamada et al. (2005).

Garn and Lewis (1970) reported an association between dental agenesis and increased variability in the size of re-
remaining teeth. Similar results have been reported by various authors (Garn et al., 1964; Baum and Cohen, 1971a, b; Asakura, 1975; Brook et al., 2009; Yamada et al., 2010).

The variability of tooth size in recent human populations has been studied mainly in relation to heredity and dental development. Dempsey and Townsend (2001), who examined crown measurements of about 600 twins, stated that 80–90 percent (except about 60 percent for upper first molar) of variation of human tooth size could be explained by additive genetic factors and the rest by environmental factors unique to each tooth. Dahlberg (1945) and Sofiaer et al. (1971b) observed that the last developing tooth in each morphogenetic field tended to exhibit the greatest variability. Dahlberg (1945) explained this by the decreased control of the field of each morphological class in later developing teeth, whereas Sofiaer et al. (1971b) explained it by the greater variability of space left for the last developing tooth to compensate.

A scale-free measure would be suitable to study the genetic variability of tooth size as well as to examine Dahlberg’s (1945) explanation. Although a scale factor seems to have been considered in the explanation by Sofiaer et al. (1971b), Mizoguchi (1983) indicated that the size factor may have to be removed to detect the possible compensatory effect in dental development. Therefore, a scale-free measure is required to extract meaningful information from the variability of tooth size in any case. The proportional variability (PV) represented by the standard deviation of a log-transformed measurement satisfies this requirement. Its squared value (variance of the log-transformed measurement) reflects the hereditary variation of an additive genetic character (Lande, 1979).

The present study aims to investigate the relationship of size and its PV of remaining teeth with the type and degree of tooth agenesis in Japanese males.

Materials and Methods

The materials consisted of the plaster casts made from alginate impressions of dentitions of 276 Japanese males who were born between 1949 and 1970. These models are stored at Aichi-Gakuin University, Nagoya, Japan. Tooth agenesis was defined as radiographically proven agenesis of one or more permanent teeth. Individuals with any medical history of previous tooth loss due to trauma, dental caries, periodontal disease, or orthodontic extractions, and those with systemic illness or genetic medical conditions, were excluded from the sample.

The mesiodistal crown diameters of the permanent teeth from central incisor to second molar on the right and left sides of both jaws were measured on the plaster casts by the first author (H.Y.) using a sliding caliper with an accuracy of 0.05 mm employing the method of Fujita (1949). The average of right and left side measurements was used for the analysis, but a single measurement was accepted if the tooth on the other side was congenitally missing or impossible to measure. The total tooth size (TTS), defined as the sum of all 14 measurements, was also used as a measure of overall tooth size of an individual.

The sample was divided into the following three groups according to the type of agenesis: (1) Third molar agenesis (or M3 agenesis) consisting of 144 individuals with agenesis only in third molar(s). (2) Hypodontia consisting of 36 individuals with agenesis except in third molars (all of them had four third molars). (3) Multiple agenesis consisting of 47 individuals with both types of agenesis above.

The group consisting of all the individuals with tooth agenesis will be referred to as the pooled agenesis (group names will be italicized hereinafter: third molar agenesis, hypodontia, and multiple agenesis). The distribution of the number of affected teeth in hypodontia and multiple agenesis is shown in Table 1. The distribution is almost identical between these two groups, where the majority (89% and 87%, respectively) of individuals had only one or two missing teeth excluding third molars. The reference group consisted of 49 Japanese males with a full complement of 32 teeth. Furthermore, the third molar agenesis group was divided into the following four subgroups according to the number of congenitally missing third molars regardless of side or jaw: type 1 with only one third molar missing (35 individuals); type 2 with two third molars missing (59 individuals); type 3 with three third molars missing (16 individuals); and type 4 with all four third molars missing (34 individuals).

Group means and standard deviations were calculated for 14 mesiodistal dimensions, and their values of agenesis groups were compared with those of the reference group. The magnitude of PV was represented by the standard deviation of log-transformed data, and the notation ‘PV’ will be used for this statistic hereafter. The coefficient of variation (CV) has been broadly used for the same purpose. Under log-normal distribution, the population PV is determined by the population CV, and is close to it if the latter is below about 30 percent. Since CV is conventionally expressed as a percentage, we also express PV as a percentage, which should be intuitively acceptable when we note that the differential of \( \log(x) \) is \( 1/x \), and hence \( \Delta \log(x) \) is nearly equal to \( \Delta x/x \) for small \( \Delta x \).

The mean of each agenesis group was compared with that of the reference group using the percentage of deviation (dev%) from the reference group defined as \( (m - m_0) / m_0 \times 100 \), where \( m \) is the mean of an agenesis group and \( m_0 \) is that of the reference group. A formula of the same form was also used for comparison of PV.

The statistical significance of difference in mean tooth
size between the agenesis groups and the reference group was examined by Student’s t-test, and that of difference in PV was examined by Levene’s F-statistic based on log-transformed data. SPSS version 21 was used for statistical calculations.

The comparisons of the agenesis groups with the reference group for each variable were regarded as a set of multiple comparisons, and Benjamini and Hochberg’s method (BH method) was applied to control the false discovery rate of multiple tests (FDR), whose value is conventionally denoted by \( q \). We adopted \( q < 0.05 \) as the level of statistical significance in order to control the familywise error rate (FWER) to some extent; FDR becomes equal to FWER when only one comparison is diagnosed as statistically significant.

**Results**

**Size of remaining teeth**

Table 2 and Figure 1 give descriptive statistics of mesiodistal crown measurements in each group and \( t \)-values for testing the difference of group means from those of the reference group. The remaining teeth of the agenesis groups tended to be larger than those of the reference group. The group means of TTS in the agenesis groups were greater than that of the reference group, and the difference was statistically significant in pooled agenesis and multiple agenesis \( (q < 0.05) \). Out of 14 measurements examined by \( t \)-test, statistically significant increases \( (q < 0.05) \) were exhibited by measurements of eight teeth in pooled agenesis, of seven teeth in hypodontia, of four teeth in multiple agenesis, and of three teeth in third molar agenesis. No significant difference was exhibited by UI2, UP1, UP2, and LC.

Among the four types of third molar agenesis, i.e., subgroups of third molar agenesis (Table 3, Figure 2), the greatest size difference from reference was exhibited by type 4 followed by type 2. In type 4, significant differences from reference were exhibited by total value \( (q < 0.05) \) and by measurements of four out of 14 teeth \( (q < 0.01) \). In type 2, significant differences from reference were exhibited by measurement of two teeth \( (q < 0.05) \). No significant difference from reference was detected in type 1 and type 3.

**Proportional variability in tooth size**

Table 4 and Figure 3 show the PV of each group and \( F \)-values to test statistical significance of difference in PV between the agenesis groups and the reference group. In pooled agenesis, all the teeth except upper first premolar exhibited increased PV compared with reference, where increases of upper and lower canines were statistically significant \( (q < 0.05) \). The average percentage increase of PV over 14 teeth was 15.2% in pooled agenesis, 16.0% in third molar agenesis, 16.3% in multiple agenesis, and 4.6% in hypodontia. No statistically significant decrease of PV was detected in agenesis groups. In multiple agenesis, the PV increased in 12 out of 14 teeth, with an average increase of 16.3%, but the PV of TTS decreased by 24.9%, although the change was not statistically significant.

Of the four subgroups of third molar agenesis, the greatest average increase of PV was exhibited by type 2 (19.1%)...
Figure 1. Percentage deviation (from the reference group) of mean tooth size in three agenesis groups. The false discovery rate $q$ for multiple comparisons was calculated by the Benjamini–Hochberg method based on the results of $t$-tests.

Figure 2. Percentage deviation (from the reference group) of mean tooth size in four types of third molar agenesis. The false discovery rate $q$ for multiple comparisons was calculated by the Benjamini–Hochberg method based on the results of $t$-tests.

Table 3. Basic statistics of mesiodistal crown diameters in four types of third molar agenesis and $t$-values for testing difference from reference data. The Benjamini–Hochberg method was used to control the false discovery rate ($q$) in multiple comparisons of each variable.

<table>
<thead>
<tr>
<th>Tooth</th>
<th>Type 1</th>
<th>Type 2</th>
<th>Type 3</th>
<th>Type 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean</td>
<td>dev%</td>
<td>SD</td>
</tr>
<tr>
<td>UI1</td>
<td>32</td>
<td>8.57</td>
<td>0.1</td>
<td>0.37</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>33</td>
<td>7.24</td>
<td>0.1</td>
<td>0.61</td>
</tr>
<tr>
<td>UC</td>
<td>35</td>
<td>8.13</td>
<td>0.9</td>
<td>0.37</td>
</tr>
<tr>
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<td>1.0</td>
<td>0.41</td>
</tr>
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<td>33</td>
<td>7.13</td>
<td>0.4</td>
<td>0.38</td>
</tr>
<tr>
<td>UM1</td>
<td>32</td>
<td>10.69</td>
<td>0.2</td>
<td>0.51</td>
</tr>
<tr>
<td>UM2</td>
<td>32</td>
<td>10.13</td>
<td>0.4</td>
<td>0.72</td>
</tr>
<tr>
<td>LC</td>
<td>35</td>
<td>5.48</td>
<td>-0.7</td>
<td>0.23</td>
</tr>
<tr>
<td>LP1</td>
<td>33</td>
<td>7.10</td>
<td>0.4</td>
<td>0.31</td>
</tr>
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<td>LP2</td>
<td>33</td>
<td>7.57</td>
<td>1.6</td>
<td>0.44</td>
</tr>
<tr>
<td>LM1</td>
<td>30</td>
<td>11.84</td>
<td>0.9</td>
<td>0.62</td>
</tr>
<tr>
<td>LM2</td>
<td>30</td>
<td>11.49</td>
<td>1.9</td>
<td>0.52</td>
</tr>
<tr>
<td>TTS</td>
<td>23</td>
<td>116.61</td>
<td>0.7</td>
<td>4.05</td>
</tr>
</tbody>
</table>

1) $t$-value without assumption of equal variances. $+q<0.10$, $*q<0.05$, $**q<0.01$ (BH method).
followed by type 4 (16.0%), type 1 (10.8%), and type 3 (4.7%) as shown in Table 5 and Figure 4, although a statistically significant increase was detected only for LM2 in type 3.

**Discussion**

Congenital tooth loss can be regarded as an extreme expression of tooth size reduction. In individuals with missing teeth, the remaining teeth, in general, tend to diminish in size in comparison with that of individuals with a full complement of 32 teeth (Garn and Lewis, 1963a, 1970; Le Bot and Salmon, 1977). Moreover, the teeth affected by congenital absence show a gradient in size reduction, where the extent of reduction regularly decreases from incisors to molars (Keene, 1965; Garn and Lewis, 1970; Lavelle et al., 1970; Baum and Cohen, 1971a, b; Christensen and Melsen, 1974; Brook et al., 2002). On the other hand, Grüneberg (1965) stated that if the first molar of a mouse was reduced to be the smallest, then the second and the third molars tended to grow even larger than in normal mice, and Sofaer (1973) also stated that the later developing molars grew to compensate a whole dentition of certain length in normal mice. When UI2 was congenitally missing on one side, the UI1 adjacent to the missing UI2 was larger than the UI1 on the other side in a survey of students in Hawai‘i (Sofaer et al., 1971b). Mizoguchi (1983), who conducted a path analysis of Japanese odontometric data, concluded that there was no or little compensatory growth of the later developing teeth except for the third molars, which grew to compensate the

Table 4. Proportional variability of tooth size in the agenesis and reference groups. Difference of PV from reference was tested by pairwise Levene’s test (*F*). The Benjamini–Hochberg method was used to control the false discovery rate (q) in multiple comparisons of each variable. Averages of CV and PV are based on 14 teeth.

<table>
<thead>
<tr>
<th>Tooth</th>
<th>M3 agenesis</th>
<th>Hypodontia</th>
<th>Multiple agenesis</th>
<th>Pooled agenesis</th>
<th>Reference group</th>
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<tr>
<td></td>
<td>N</td>
<td>CV</td>
<td>PV dev%</td>
<td>F</td>
<td>N</td>
</tr>
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<td>UI1</td>
<td>137</td>
<td>5.38</td>
<td>5.37</td>
<td>12.0</td>
<td>1.29</td>
</tr>
<tr>
<td>UI2</td>
<td>138</td>
<td>8.34</td>
<td>8.52</td>
<td>19.2</td>
<td>1.82</td>
</tr>
<tr>
<td>UC</td>
<td>143</td>
<td>5.18</td>
<td>5.20</td>
<td>27.8</td>
<td>3.14</td>
</tr>
<tr>
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<td>5.16</td>
<td>-3.3</td>
<td>0.02</td>
</tr>
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<td>1.39</td>
</tr>
<tr>
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<td>137</td>
<td>4.85</td>
<td>4.82</td>
<td>26.3</td>
<td>3.76</td>
</tr>
<tr>
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<td>139</td>
<td>5.91</td>
<td>5.97</td>
<td>27.9</td>
<td>2.47</td>
</tr>
<tr>
<td>LI1</td>
<td>144</td>
<td>5.51</td>
<td>5.52</td>
<td>7.4</td>
<td>0.54</td>
</tr>
<tr>
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<td>143</td>
<td>5.84</td>
<td>5.90</td>
<td>14.6</td>
<td>1.48</td>
</tr>
<tr>
<td>LC</td>
<td>144</td>
<td>5.62</td>
<td>5.64</td>
<td>27.5</td>
<td>3.19</td>
</tr>
<tr>
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<td>144</td>
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<td>5.47</td>
<td>4.4</td>
<td>0.01</td>
</tr>
<tr>
<td>LP2</td>
<td>138</td>
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<td>5.97</td>
<td>19.0</td>
<td>1.00</td>
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<td>4.70</td>
<td>4.68</td>
<td>24.2</td>
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</tr>
<tr>
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<td>5.70</td>
<td>5.75</td>
<td>11.3</td>
<td>0.95</td>
</tr>
<tr>
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<td>4.06</td>
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<tr>
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<td>5.67</td>
<td>16.0</td>
<td>5.13</td>
<td>5.11</td>
</tr>
</tbody>
</table>

* q < 0.05, ** q < 0.01 (BH method).

Figure 3. Percentage deviation (from the reference group) of proportional variability of tooth size in three agenesis groups. The false discovery rate q for multiple comparisons was calculated by the Benjamini–Hochberg method based on the results of pairwise Levene’s tests.
space caused by an agenesis at any site in a whole dentition. In the present study, we try to review the cases of individuals with congenital tooth agenesis with regard to the following three points: (i) the size of remaining teeth, (ii) the PV of remaining teeth, and (iii) the stability of canines and first molars in their size and PV.

Size of remaining tooth

Summary of findings

Among individuals with tooth agenesis, the size of the remaining teeth tended to be greater than the reference group. Statistically, many teeth exhibited significant enlargement in different agenesis groups, whereas no significant reduction was found in the size of the remaining teeth. Among individuals with third molar agenesis, those lacking four third molars (Type 4) showed the greatest enlargement, whereas four dimensions of upper and lower molars exhibited statistically significant enlargement (Table 3, Figure 2). These results are quite different from those of Garn and Lewis (1970). To account for this disagreement, we first examine two factors that differ between the studies, i.e. the extent of severity of tooth agenesis in the sample, and the ancestry of population studied, and then propose a new classification of tooth agenesis in order to comprehensively understand the phenomena of contradictory appearance.

Severity of agenesis: In our sample, the majority had only one or two missing teeth (excluding third molars) and they constituted 89% of hypodontia and 87% of multiple agenesis (Table 1), whereas 73% of the dentitions studied by Baum and Cohen (1971a) were hypodontia, and the sample of McKeown et al. (2002) consisted of only dentitions with severe hypodontia where six or more teeth were congenitally missing. Although Garn and Lewis (1970) did not give the number of missing teeth for the 19 individuals with multiple

Table 5. Proportional variability of tooth size in third molar agenesis types. Difference of PV from reference was tested by pairwise Levene’s test ($F$). The Benjamini–Hochberg method was used to control the false discovery rate ($q$) in multiple comparisons of each variable. Averages of CV and PV are based on 14 teeth.

<table>
<thead>
<tr>
<th>Tooth</th>
<th>Type 1</th>
<th>Type 2</th>
<th>Type 3</th>
<th>Type 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>CV</td>
<td>PV</td>
<td>dev%</td>
</tr>
<tr>
<td>UI1</td>
<td>32</td>
<td>4.34</td>
<td>4.35</td>
<td>–9.2</td>
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<tr>
<td>UI2</td>
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<td>8.49</td>
<td>8.40</td>
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<td>UC</td>
<td>35</td>
<td>4.52</td>
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</tr>
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<td>4.23</td>
<td>4.23</td>
<td>–17.7</td>
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<td>5.08</td>
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<td>5.52</td>
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<tr>
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<tr>
<td>Average</td>
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<td>10.8</td>
<td>5.78</td>
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</table>

+ $q < 0.10$, * $q < 0.05$ (BH method).

Figure 4. Percentage deviation (from the reference group) of proportional variability of tooth size in four types of third molar agenesis. The false discovery rate $q$ for multiple comparisons was calculated by the Benjamini–Hochberg method based on the results of pairwise Levene’s tests.
tooth agenesis, we estimated it to be about 4.6 on average (excluding third molars) from the number of missing measurements. This difference in sample composition should partly explain the disagreement of results, which may also reflect the difference between the populations to some extent. In particular, the sample of multiple tooth agenesis studied by Garn and Lewis (1970) should have been collected without bias because it was included in the sample of 658 individuals they regarded as a reference group.

**Ancestry of population:*** Garn and his colleagues used the samples collected from inhabitants of Ohio of European ancestry. It has been reported that the tooth size became reduced in hypodontia for the English (Lavelle et al., 1970), European Americans (Baum and Cohen, 1971a), and European descendants (Christensen and Melsen, 1974; Brook et al., 2002, 2009; McKeown et al., 2002). In Japanese dentition, Ozaki et al. (1967) described that there were no significant differences in the mesiodistal dimensions of first and second molars between those with and without third molars. Asakura (1975) found that Japanese females congenitally lacking all four third molars exhibited a tendency of enlargement in the remaining teeth. Moreover, Yamada et al. (2005) showed that the mean mesiodistal diameters of upper and lower molars were significantly larger in those with all four third molars congenitally missing. Therefore, the general tendency in the size of remaining teeth appears to considerably differ between the Japanese and the populations of European ancestry.

**Existence of two types of agenesis:** What accounts for these different tendencies in the size of remaining teeth between populations? Yamada et al. (2010), who studied the relationships between the number of missing teeth and the size of remaining teeth in hypodontia, reported that the remaining teeth were enlarged in those with one or two teeth congenitally missing but reduced in those with three or more teeth congenitally missing. On the other hand, Anderson and Popovich (1977) observed enlargement of first molar associated with third molar agenesis in European Canadians. Since their study focused on dental health, their materials are not likely to have included severe cases of agenesis. These observations indicate that the milder cases of tooth agenesis are somewhat different in nature from the severer cases. The conventional trichotomy into ‘hypodontia,’ ‘oligodontia,’ and ‘anodontia’ does not work for biological purposes because there exists no corresponding natural clustering and most non-syndromic cases fall into ‘hypodontia.’ Therefore, we classify tooth agenesis here into the following two types with reference to the relationship between severity of agenesis and the size of remaining teeth: (1) Degenerative tooth agenesis (DTA or ‘degenerative type’), which exhibits size reduction in most remaining teeth and tends to have a greater number of congenitally absent teeth (perhaps three or more excluding third molars); (2) Moderate tooth agenesis (MTA or ‘moderate type’), which exhibits enlargement or no reduction in most remaining teeth and tends to have a smaller number of congenitally absent teeth (perhaps up to two excluding third molars).

Using these terms, the disagreement between our results and those of Garn and Lewis (1970) can be explained by the difference in the proportion of DTA and MTA between the samples. Although no precise information is available about the representativeness of samples except for Garn and Lewis (1970), it is likely that MTA is dominant in Japanese tooth agenesis and DTA is more prevalent in tooth agenesis of European descendants than in the Japanese.

Therefore, we can summarize the findings so far reported as follows.

1. **Tooth agenesis can be classified into two types differing in nature:** DTA with a tendency of size reduction in the remaining teeth, and MTA without a tendency of size reduction in the remaining teeth; the latter is often accompanied by enlargement of the remaining teeth.

2. **MTA was dominant in the Japanese tooth agenesis samples, whereas DTA was dominant in the tooth agenesis samples of European descendants.**

3. **This difference in sample composition may partly reflect the difference of frequencies of two types between populations even though some sampling bias may exist.**

In our sample, two of ten individuals tentatively classified as DTA by the number of congenitally absent teeth showed a tendency of enlargement of the remaining teeth. This may indicate the existence of intermediate forms. However, since evaluation of agenesis has to take into account various factors such as asymmetry, jaw, and the number and kind of missing teeth, as well as estimated causes, further studies may find more effective methods for classification of individual cases that make sense both for biological and clinical purposes.

**Possible interpretation of findings**

We examined some theories that would explain the change in tooth size associated with tooth agenesis. We first examined a developmental theory that was expected to provide us with clear hypotheses to be tested by our findings, and the result of this examination became the basis for selection of the two theories we examined further.

**Inhibitory cascade model:** Kavanagh et al. (2007) proposed a developmental mechanism called the ‘inhibitory cascade model’ (IC model) based on experiments on the mouse, where the removal of inhibition on posterior molars resulted in earlier initiation and larger size of posterior teeth, and, in contrast, an increase of inhibition lead to smaller posterior molars and eventually to the lack of third molars. Yamada (2010) demonstrated the existence of first molar agenesis where the second molar had been wrongly diagnosed as the first molar. For this rare agenesis, the IC model predicted the earlier eruption and the enlargement of second molar, both of which were actually observed. Therefore, application of the IC model to our findings will give us a useful suggestion for inference of the mechanism of this interesting phenomenon about tooth agenesis and the size of remaining teeth. We examined whether the IC model can explain the third molar agenesis and the associated enlargement of remaining teeth we observed.

1. **Third molar agenesis:** The IC model explains third molar agenesis as a result of dominance of inhibition over activation in the molar field. According to the IC model, however, the size of the second molar must be roughly one third of the total size of three molars. This rule of molar proportion has been observed in almost all mammals, and this
fact is regarded as a strong evidence for the IC model. Therefore, the IC model can explain only limited cases of tooth agenesis where the second molar is about half the size of the first molar or smaller, which seems to be rather rare in human third molar agenesis. In both the third molar agenesis and multiple agenesis groups in this study, the ratio of means of second molar to first molar was 0.95 in the upper dentition and 0.97 in the lower dentition.

(2) Enlargement of remaining teeth: There might be a possibility that a larger tooth tends to cause agenesis in its posterior tooth by stronger inhibition. This assumes that the larger a tooth becomes, the stronger inhibition it generates on its posterior tooth. In the IC model, however, the extent of inhibition by a tooth is assumed to be independent of its size. Although Kavanagh et al. (2007) did not explicitly write so, their formula for calculation of tooth size does not include the size of earlier developing anterior tooth as a variable, and it was this independence that allowed their formula to fit the macroevolutionary data where the tooth sizes were positively intercorrelated. This independence also allowed the inhibition cascaded through even the very reduced second molar to cause agenesis of third molar in their experiments. Therefore, it is also difficult to interpret the association of a larger tooth with agenesis or reduced size of its later-developed posterior tooth by the IC model.

These facts indicate not the non-existence of inhibitory effects but that we need some other factor(s), in addition to the inhibitory cascade, to explain the enlargement of teeth associated with tooth agenesis. Since the IC model denies the possibility that the agenesis of a tooth caused the enlargement of its anterior earlier-developed tooth, the only possible interpretation would be that the both resulted from single or linked causes. In other words, the logic and the formula of the IC model clearly indicate pleiotropic nature of the association of tooth agenesis with enlargement of remaining teeth. This leads us to examine the following two theories as candidates for explanation of our findings because both can explain pleiotropic phenomena in general.

Nutritional environment: Nutrition is a candidate for a factor affecting both the development and the size of teeth. Riesenfeld (1970) reported that higher nutrition enlarged the molars of rats. Therefore, nutrition could explain our findings if higher nutrition also tends to cause tooth agenesis. The frequency of third molar agenesis in Japanese population, however, considerably decreased along with the improvement of nutritional environment after the Second World War (Yamada et al., 2004). Therefore, it is difficult to explain the enlargement of remaining teeth in individuals with third molar agenesis by differences in the nutritional environment.

Microevolution: Microevolution seems to explain this phenomenon fairly well. This means that there are genetic findings corresponding to some extent to DTA and MTA, and some genes causing MTA seem to have had positive selection rates because of their pleiotropic phenotypes including dental traits.

Genetic findings corresponding to the two types of tooth agenesis

Although various factors are presumed to cause tooth agenesis, genetic factors have now been used to explain a significant part of tooth agenesis. To date, MSX1, PAX9, AXIN2, and EDAR genes have been identified as causes of familial tooth agenesis (Shahid et al., 2017), and some specific variants of PAX9 and EDAR genes have been identified as associated with third molar agenesis.

Abu-Hussein et al. (2015) reviewed genetic studies on tooth agenesis and concluded that mutations in MSX1, PAX9, and AXIN2 genes were associated with hypodontia and oligodontia, and mutations in AXIN2 were implicated only in rare, severer cases. Most of these cases seem to fall within the range of DTA. The average number of missing teeth for MSX1 mutations has been reported to be 8.4 to 16.4 (Lidral and Reising, 2002).

On the other hand, some common variants of PAX9 and EDAR genes seem to cause MTA where agenesis occurs specifically or mainly in third molars. Lee et al. (2012) found that several PAX9 variants, including A240P, were associated with both tooth enlargement and (single and double) shoveling of upper central incisors, and the tooth enlargement was correlated with number of missing third molars. Although they observed no correlation between PAX9 variants and third molar agenesis, Paixão-Côrtes et al. (2011a) reported an association of PAX9 A240P with third molar agenesis in European Brazilians.

The EDAR V370A allele is estimated to have arisen by mutation about 30000 years ago in central China and now is prevalent in East Asians and American natives at very high frequencies, while it is almost absent in European and African populations (Kamberov et al., 2013). EDAR V370A has been found to be associated with enlargement of teeth, shoveling of upper incisors, and third molar agenesis in Japanese populations (Kimura et al., 2009) and Han Chinese (Kamberov et al., 2013). The association of EDAR V370A with tooth enlargement and upper incisor shoveling were also reported for Koreans and Japanese by Park et al. (2012), although they did not examine tooth agenesis.

Therefore, it is likely that a significant part of MTA is caused by PAX9 variants in Europeans and by both PAX9 variants and EDAR V370A in East Asians, and a significant part of DTA is caused by mutations in MSX1 and PAX9 genes in both East Asians and Europeans (Vastardis et al., 1996).

Possibility of positive selection of MTA

For hunter-gatherers, the enlargement and stronger structure of teeth might be advantageous if they were not accompanied by dentoskeletal discrepancies and associated oral health problems. In addition, for human jaws under the evolutionary tendency of reduction, third molar agenesis itself, if not accompanied by serious agenesis of other teeth, might have some survival advantage. Therefore, the combination of these two characters must have positively contributed to the selection rate of their responsible allele. Pereira et al. (2006) suggested the possibility of positive selection of third molar agenesis caused by PAX9 A240P assuming that it is not associated with hypodontia or oligodontia. Paixão-Côrtes et al. (2011b) found that the pattern of frequencies of PAX9 alleles indicated positive selection of A240P. The EDAR V370A allele exhibits an exceptionally high selection
rate (Kamberov et al., 2013). Since the EDAR gene is highly pleiotropic, it is difficult to tell which aspects of the phenotype have contributed to the high positive selection rate of the V370A allele. The thicker hair, more numerous sweat glands, and mammary glands with increased branch density have been taken as the candidates (Kimura et al., 2009; Kamberov et al., 2013), and the possibilities of mating preferences for thicker hair and smaller breast fat pads have also been discussed (Kamberov et al., 2013).

The selective values of dental traits associated with EDAR V370A have not been fully examined. Although Kimura et al. (2009) referred to the possibility of a selective value of the stronger structure of teeth, they emphasized the possibility of the dental trait as a ‘by-product’ in selection of hair and exocrine glands. The concept of ‘by-product’ in evolution, however, seems to be questionable. We cannot test the selective values of different traits of a pleiotropic phenotype separately. The dental traits associated with MTA have their own evolutionary meaning to be discussed if they have any function. In particular, the pruning-like combination of the agenesis of a limited number of teeth and the enlargement of the remaining teeth would have contributed to raising the efficiencies of mastication and tool-like use of upper incisors without greatly increasing the risk of dentoskeletal discrepancies. In addition, if the upper incisors were used like a tool, the outstanding enlarged incisors may have served as a trait for sexual selection, more effectively than a female trait such as the small breast size caused by EDAR V370A. According to Bateman’s Principle, it is the males who are mainly subject to sexual selection (Bateman, 1948). Although cautions have been made about naïve application of the principle based on studies of fruit flies to human reproductive strategy (Brown et al., 2009), there has been no evidence for its opposite tendency in human prehistory.

Examples that may be better understood in relation to MTA

The enlargement of the remaining teeth associated with tooth agenesis or reduction has been interpreted as a compensatory or competitive interaction in dental development but seems to be often better understood in relation to MTA. As we already discussed, if we accept the logic and formula of the IC model, the association of enlargement of a tooth with agenesis or size reduction of its posterior later developing tooth cannot be explained by the inhibitory effect in dental development, and its only possible interpretation would be pleiotropic expression of a single cause or closely linked causes.

As already mentioned, Sofaer et al. (1971b) reported enlargement of UI1 associated with agenesis of UI2 in high school students in Hawai‘i. They observed that UI1 of the affected side was significantly larger than UI1 of the opposite side. A similar phenomenon was observed in our sample, where 15 out of 16 cases of unilateral UI2 agenesis provided the data. The mean measurement of UI1 was 9.07 for the affected side and 8.89 for the opposite side, and the difference was statistically significant by a paired t-test (t = 2.533, P = 0.024) and a paired Wilcoxon signed-rank test (z = 2.121, P = 0.034). In addition, both these means were considerably greater than that of the other 202 individuals with non-UI2 tooth agenesis (8.72) which was greater than that of reference group (8.56) with statistical significance (t = 2.165, P = 0.031). Although Sofaer et al. (1971b) attributed this enlargement of UI1 to its reduced competition with UI2, a more reasonable interpretation would be that they both were aspects of a pleiotropic phenotype of MTA whose probability and extent of expression vary among individuals and somewhat between sides.

Sofaer et al. (1971b) also observed that the enlargement of UI1 was greater in unilateral agenesis than in bilateral agenesis of UI2, and interpreted this contradiction as the unilateral UI2 agenesis (observed in 72% of cases) indicating a better environment. However, Stamatou and Symons (1991) observed unilateral UI2 agenesis in only 30% of UI2 agenesis in European Australians. The higher rate of unilateral agenesis in Sofaer et al. (1971b) seems to reflect the existence of East Asian ancestry in their sample. Although they did not report the composition of ancestries, their materials must have been collected mainly from East Asian and European descendants living in Hawai‘i. In our sample, 16 out of 18 cases of UI2 agenesis were unilateral. Harada et al. (1986) observed unilateral UI2 agenesis in 15 out of 21 cases of Japanese students. The higher rate of asymmetric UI2 agenesis in Hawai‘i and Japanese samples suggests a significant contribution of environmental factors to expression of MTA. Lidral and Reising (2002) reported four cases of UI2 agenesis due to an MX1 mutation, which were all bilateral. The description of Garn and Lewis (1970) also suggests that most cases of UI2 agenesis in their sample were bilateral, although they did not explicitly write this.

Sofaer et al. (1971b) reported a size reduction of UI1 associated with peg-shaped UI2. They thought that the peg-shape indicated a poor environment. It is more likely, however, that this condition reflected DTA, perhaps mainly from European descendants because an opposite phenomenon has been reported for the Japanese as below.

Kondo et al. (2014) reported the enlargement of UI1 associated with reduced UI2 in their study of twins and interpreted it as the enlargement of UI1 causing the reduction of UI2 through increased inhibition by the larger UI1. This observation would be better interpreted as pleiotropic expressions of a single cause because for the reasons already discussed. In addition, its cause seems to be the same as of MTA because we also observed the enlargement of UI1 and a (not statistically significant) tendency of reduction in the size of UI2 in pooled agenesis although no information is available about third molar agenesis in their materials, which were collected from juvenile twins without X-ray examination (Kondo et al., 2010).

If the association of UI1 enlargement and UI2 reduction was caused by EDAR V370A, it would be difficult to prove it by the twin data because of the high gene frequency and rather low penetrance rate. In such a circumstance, the correlation between twins will reflect mostly the similarity in the individual’s probability of gene expression (PGE), which is individual-specific penetrance, between them. The similarity in PGE between monozygotic twins will be higher than in dizygotic twins, and of the level of similarity between sides if the PGE is determined by the surrounding tissue influenced by other genes. These speculations are in
accordance with the results of Kondo et al. (2010), which indicate a significant contribution of both genetic and environmental factors to the PGE.

In dentitions with M1 agenesis observed by Yamada (2010), the aberrant M2 was larger than normal M1 with statistical significance in females. This excessive enlargement has been left unexplained. These cases are classified as a rare subtype of MTA by definition, whence the excessive enlargement of aberrant M2 can be interpreted as tooth enlargement characteristic to MTA in addition to the removal of inhibition that allowed the aberrant M2 to grow to the size of normal M1. Although further investigations are required about the appropriateness of this interpretation, the frequent coincidence of M3 agenesis with M1 agenesis (7 cases of M3 agenesis out of 11 cases of M1 agenesis) suggests existence of a common genetic factor responsible for both agenoses. Abe et al. (2010) also suggested the existence of a common genetic factor for both agenoses by the same reason. They observed M3 agenesis in 22 out of 32 cases of M1 agenesis although their materials were collected regardless of existence of the aberrant M2.

**PV of remaining teeth**

In our results, in the dentition excluding third molars, the most variable tooth was U12. It exhibited the greatest PV in every agenesis group as well as in the reference group (Table 4, Table 5). The U12 is situated at the distal end of the incisive bone and the UM3 at the posterior end of the maxillary bone. Those locations are in accordance with the observation by Dahlberg (1945) and Sofaer et al. (1971b) about the greater variability of the last developing tooth in a field.

The PV of remaining teeth in agenesis groups, especially in *multiple agenesis*, tended to be greater than in the reference group (Table 4, Figure 3). Statistically significant increases were exhibited by UC and LC in *multiple agenesis* and *pooled agenesis*, and nearly significant increases were observed in UM1 and LM1 in *pooled agenesis*. The *third molar agenesis* group also showed the same pattern of increase in PVs, although this was not statistically significant. Among four types of *third molar agenesis*, type 2 and type 4 exhibited the same pattern of increase in PVs as of *third molar agenesis*, but type 3 showed a somewhat different pattern (Table 5, Figure 4).

Dempsey and Townsend (2001) showed that the additive genetic factors were the major source of tooth size variation. If this is also true for individuals with tooth agenesis, the increase of PV associated with tooth agenesis should reflect an increased variability in genetic factors responsible for tooth size. However, the variability of the effect of additive genetic size factors is not likely to be increased by selection of individuals with agenesis. When the probability of agenesis is given by a logistic regression function of a normally distributed size variable, its variability decreases in individuals with tooth agenesis unless the probability is constant (hence the variability remains unchanged). A concave probability curve (with higher probability of tooth agenesis on both ends of the size variable) can increase the variability of tooth size in individuals with tooth agenesis, although we have no evidence for the existence of such a phenomenon. Another explanation, perhaps more likely, is that a higher probability of agenesis of an individual (or PGE), probably by its nature, allows the surrounding tissue and other environmental factors such as the size of jaws to more affect the dental development. This interpretation is in accordance with the significant contribution of environmental factors in the reduction of upper lateral incisor observed by Kondo et al. (2014) and the decreased frequency of third molar agenesis in the Japanese after the Second World War observed by Yamada et al. (2004).

The increased variability of tooth size in dental development (including tooth agenesis as its extreme expression) would be advantageous for human jaws with the evolutionary tendency of reduction if the tooth size or agenesis is controlled to some extent in accordance with the size of jaws or the extent of tooth migration compensating the attritional reduction noted by Kaifu et al. (2003). For example, increased nutritional effects may help later developing teeth grow in accordance with the size of jaws. The stability of PV of TTS, contradictory to the significant increase of PV in respective teeth observed in our results, suggests the existence of such a mechanism, and the compensatory growth of third molar observed by Mizoguchi (1983) also seems to indicate this possibility.

**Stability of canines and first molars in their size and PV**

The field effect would diminish with increased distance from the most stable tooth within each morphological field (Dahlberg, 1945; Moorrees and Reed, 1954; Keene, 1965). Mizoguchi (1977, 1980) suggested the lowest variation in heritability as a criterion to determine the most stable tooth in its morphological field. Although canines and first molars are considered to be the most stable teeth in their respective developmental fields, researchers have noted a considerable increase of variability in their size with incidence of tooth agenesis in the dentition (Garn et al., 1963a, b; Lavelle et al., 1970; Baum and Cohen, 1971a, b; Yamada et al., 2005).

In the present study too, canines and first molars exhibited fairly large increases in PV in tooth agenesis groups. In particular, the upper and lower canines exhibited statistically significant increases in their magnitude of PV in both the *multiple agenesis* and *pooled agenesis* groups. This appears to contradict to the hypothesis of lower genetic variability in these teeth. Moreover, these results cannot be explained by the previous hypotheses of lower odontometric variabilities in canines and first molars (Dahlberg, 1945; Osborne et al., 1958).

A possible explanation for this is to assume that some special factors affecting the size of all the remaining teeth to a similar extent emerge with tooth agenesis, and hence the proportion of variation due to these factors is greater in the ‘stable teeth’ than in other teeth. (Such special factors can be genetic or environmental as already discussed.) This explanation is in accordance with our observation that the PV’s in canines and first molars remained smaller than or at the same level in other teeth despite of their considerable increase compared to those of reference group.

**Problem of multiple comparisons**

In both analyses of tooth size and its PV, we automatically regarded comparisons between the agenesis groups
and the reference group as a set of multiple comparisons, and applied the BH method based on the familywise hypothesis. However, whether a case should be regarded as a part of multiple comparisons or as an independent comparison depends on the purpose of the study or interest of the reader. In addition, although we adopted \( q < 0.05 \) for statistical significance, a greater FDR such as \( q < 0.1 \) or \( q < 0.2 \) would be more beneficial for exploratory purposes. Therefore, the statistical non-significance of difference in multiple comparisons in this study should be regarded not as indicating acceptability of the null hypothesis but only as recommending reservation of diagnosis about the difference.

On the other hand, we did not adopt the familywise hypothesis across variables. Although we are sceptical about the appropriateness of adopting an across-variable familywise hypothesis for a standard set of variables, the major results of tooth size will remain the same under a familywise hypothesis because the number of eigenvalues over 1.0 was only three for the correlation matrix of our data of 14 variables.

### Conclusion

The relationship between mesiodistal crown diameters and tooth agenesis was examined in 276 Japanese males. The results were as follows.

1. The remaining teeth were generally larger with statistical significance in hypodontia, followed by multiple agenesis and third molar agenesis in descending order when compared with the reference group. Among the four types of third molar agenesis, the greatest difference was exhibited by type 4, followed by type 2. No significant differences were observed in type 1 and type 3.
2. The direction of change of tooth size observed with tooth agenesis in Japanese (enlargement) was opposite to the direction of change in European descendants (reduction).
3. The findings suggest the existence of two types of tooth agenesis differing in nature, where remaining teeth tend to enlarge in ‘moderate type’ and reduce in ‘degenerative type’.
4. The discordance of findings with the inhibitory cascade model indicates the possibility that the same factor is responsible for both the tooth agenesis and its associated tooth enlargement.
5. The EDAR V370A seems to be responsible for both the tooth agenesis and the associated enlargement of tooth size in a significant proportion of cases in East Asians.
6. The enlargement of remaining teeth associated with tooth agenesis may often be better understood as an aspect of pleiotropic expression of ‘moderate type’ than by the conventional explanations based on dental development such as a compensatory interaction and a better nutritional condition.
7. Further studies are required to identify the factors determining the individual-specific penetrance of the genes responsible for ‘moderate type’ tooth agenesis.
8. Canines and first molars tended to exhibit a greater increase of PV associated with tooth agenesis than the other remaining teeth. This can be explained by the genetic stability of these teeth and the existence of common factors across all teeth that affect dental development of individuals with tooth agenesis.

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