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# Prediction of agenesis of the mandibular second premolar using the developmental stages of the mandibular canine, first premolar, and second molar

Ji-Soo Song[a], Teo Jeon Shin[b], Young-Jae Kim[b], Jung-Wook Kim[b], Ki-Taeg Jang[b], Sang-Hoon Lee[b], Hong-Keun Hyun[b,*]

[a] Department of Pediatric Dentistry, Seoul National University Dental Hospital, 101, Daehakno, Jongno-gu, Seoul, Korea
[b] Department of Pediatric Dentistry, Dental Research Institute, School of Dentistry, Seoul National University, Seoul National University Dental Hospital, 101, Daehakno, Jongno-gu, Seoul, Korea

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ABSTRACT

*Objective:* The aim in this study was to suggest a standard for early diagnosis of agenesis of the mandibular second premolars (L5) by estimating the developmental stages of the mandibular canines (L3), first premolars (L4), and second molars (L7).

*Design:* Among all 5136 pediatric patients aged 5–11 years who received panoramic radiographs between June 2008 and December 2009 at Seoul National University Dental Hospital, 215 control patients and 74 agenesis patients who met inclusion criteria were analyzed. The developmental stages of all L3, L4, L5, and L7 of control and agenesis patients were estimated using the method proposed by Demirjian. To identify the tooth (L3, L4, L7) with the developmental pattern most similar to that of L5, Kendall rank correlation coefficients and Bootstrap method were used. To verify that patients with agenesis of L5 show delayed development, Wilcoxon rank sum test was used. To identify the stages in which to diagnose agenesis of L5, we performed survival analysis.

*Results:* There was a significant correlation between the developmental stages of L3, L4, L7 and L5. The developmental stages of those three teeth in the agenesis group were delayed compared with those in the control group at certain ages. If the developmental stages of at least two of those three teeth reach Demirjian stage D without the calcification of L5, agenesis of L5 can be confirmed.

*Conclusions:* Agenesis of L5 can be confirmed when two of the three teeth (L3, L4, L7) reach Demirjian stage D.

## 1. Introduction

Dental agenesis, the failure of one or more teeth to form, is one of the most frequent dental developmental variations. The prevalence of dental agenesis in permanent dentition varies by sex and race and is reported to be 2.8–13.3% (Nik-Hussein, 1989; Polder, Van't Hof, Van der Linden, & Kuijpers-Jagtman, 2004; Chung, Han, & Kim, 2008; Goya, Tanaka, Maeda, & Akimoto, 2008; Maatouk, Baaziz, Ghnima, Masmoudi, & Ghedira, 2008; Rolling & Poulsen, 2009; Khalaf, Miskelly, Voge, & Macfarlane, 2014; Al-Ani, Antoun, Thomson, Merriman, & Farella, 2017). Dental agenesis is more frequent in Asians and Native Americans (Goya et al., 2008; Khalaf et al., 2014; Al-Ani et al., 2017), and the most commonly affected teeth are the maxillary lateral incisors and mandibular second premolars (Chung et al., 2008; Goya et al., 2008).

Dental agenesis can induce functional and aesthetic problems, and early diagnosis in pediatric patients allows long-term treatment plans to be established. For example, if agenesis of the mandibular second premolar (L5) is diagnosed at early mixed dentition, it might help the clinician decide the generalized restorative and orthodontic treatment plans, such as timing and methods. Unlike the maxillary lateral incisors that develop relatively early, agenesis of L5 can only be confirmed clinically at age 9–10 because their development begins somewhat late (Bjerklin, Al-Najjar, Karestedt, & Andren, 2008). Also, patients with dental agenesis show delayed tooth development compared with those developing without agenesis (Al-Ani et al., 2017; Daugaard, Christensen, & Kjaer, 2010; Navarro, Cavaller, Luque, Tobella, & Rivera, 2014), so it is unreasonable to diagnose dental agenesis based

*Abbreviations:* L3, mandibular canines; L4, mandibular first premolars; L5, mandibular second premolars; L7, mandibular second molars

* Corresponding author at: Department of Pediatric Dentistry, School of Dentistry, Seoul National University, Seoul National University Dental Hospital, 101 Daehak-ro, Jongno-gu, Seoul ASI/KR/KS013/SEOUL, Korea.
*E-mail addresses:* hege1@snu.ac.kr, dds_hyun@daum.net (H.-K. Hyun).

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only on chronologic age.

Therefore, our aim in this study was to suggest a standard for early diagnosis of agenesis of L5 by estimating the developmental stages of the mandibular canines (L3), first premolars (L4), and second molars (L7), which all develop in a relatively similar period. The first objective is to confirm which of those three teeth (L3, L4, L7) has a developmental pattern most similar to that of L5. The second objective is to see whether patients with agenesis of L5 show delayed development of L3, L4, and L7 compared with those without agenesis. The final objective is to use the first two results to determine the stages that can confirm agenesis of L5.

## 2. Materials and methods

### 2.1. Subjects

This study was approved by the Institutional Review Board of Seoul National University (IRB No: S-D20160029) and performed through retrospective analysis of panoramic radiographs taken for dental treatment. Among all 5136 pediatric patients aged 5–11 years who took panoramic radiographs between June 2008 and December 2009 at Seoul National University Dental Hospital, 3754 patients who had no systemic disease, maxillofacial variations (cleft lip and palate, hemifacial macrosomia, Crouzon syndrome, and Apert syndrome), generalized dental development variations (amelogenesis imperfecta, dentinogenesis imperfecta, and regional odontodysplasia), pathologies of the mandible (fibrous dysplasia, tumor, and cyst), poor image quality, or abnormal angulation of the tooth germ were included in this study. Among those 3754 patients, control patients (those who showed no agenesis of any teeth) were defined as patients with at least two panoramic radiographs, in one of which L5 could not be observed and in another of which L5 could be observed. We defined agenesis patients (those with agenesis of one or both L5) as patients with at least two panoramic radiographs performed at different times and who had been diagnosed with agenesis of L5 using a panoramic radiograph taken after age 11. The control group contained 215 patients and 646 panoramic radiographs, and the agenesis group contained 74 patients (36 with unilateral agenesis and 38 with bilateral agenesis) and 283 panoramic radiographs.

### 2.2. Methods

The developmental stages of all L3, L4, L5, and L7 were estimated using the method proposed by Demirjian et al. (Demirjian, Goldstein, & Tanner, 1973). To minimize measurements errors by several investigators and to meet the requirements of the Institutional Review Board, one pediatric dentist analyzed the developmental stages of all teeth and repeated the analysis 2 weeks later using 100 randomly selected panoramic radiographs to assess reliability. To assess intra-examiner reliability, the intra-class correlation coefficient (ICC) was used.

#### 2.2.1. Statistical analysis

To test the first objective, which was to identify the tooth (L3, L4, or L7) with the developmental pattern most similar to that of L5, Kendall rank correlation coefficients, commonly referred to as Kendall's tau, were used, and the differences between each pair of correlation coefficients by the bootstrap method and significance tests were performed. We applied Bonferroni's corrections to confirm the confidence intervals between the correlation coefficients. Calculations were repeated 1000 times using the bootstrap method to test the significance and assess the reliability of the estimated scores.

To test the second objective, which was to verify that patients with agenesis of L5 show delayed development of L3, L4, and L7 compared with those without agenesis, the Demirjian stages of L3, L4, L5, and L7 were evaluated in the 647 panoramic radiographs of the control group and the 279 panoramic radiographs of the agenesis group, and differences between two the groups were analyzed using the Wilcoxon rank sum test.

To test the final objective, which was to identify the stages in which to diagnose agenesis of L5, we performed survival analysis as follows.

In the first step, a model for univariate variables was established considering only one tooth (L3, L4, or L7). Xt is defined as the developmental stage of one of the three teeth at age t, and Yt is defined as the developmental stage of L5 at age t. X and Y have the following properties: $t \le t'$, $Xt \le Xt'$ and $Yt \le Yt'$.

$$Z: = \max Xt \; t\epsilon\{t:Yt = 0\}$$

Z represents the most developed stages of L3, L4, and L7 when L5 was not observed. In the control group, it represents the developmental stages of the three teeth just before the initiation of calcification of L5, and in the agenesis group, it represents the final developmental stages of the three teeth. Thus, observing (X,Y) = (x,0) means $Z \ge x$. Defining M = 1 as agenesis and M = 0 as without-agenesis, the purpose of this analysis is to determine $P(M = 1 \mid Z \ge x)$. Using Bayes' theorem, it can be expressed as follows:

$$P(M=1 \mid Z \ge x) = \frac{P(Z \ge x \mid M=1)P(M=1)}{P(Z \ge x \mid M=1)P(M=1) + P(Z \ge x \mid M=0)P(M=0)}$$

The purpose is to determine $P(Z \ge x \mid M = 1)$ and $P(Z \ge x \mid M = 0)$, which is a mathematical problem estimating a survival function. P(M = 1) and P(M = 0) were adopted from the study reported by Chung et al. conducted on Korean pediatric patients (Chung et al., 2008). In that study, the prevalence of dental agenesis in 1622 patients was 11.2%. From the total of 329 missing teeth, agenesis of the mandibular second premolars accounted for 67 missing teeth. Considering the possibility of bilateral agenesis of the mandibular second premolars, P(M=1) was calculated to be at most 4.13%.

Because all three teeth, L3, L4, and L7, should be included in the analysis, there are actually three variables to deal with.

$$Z: = (Z1;Z2;Z3);\; x: = (x1;\; x2;\; x3)$$

For the three variables, multivariate estimation was performed as follows. First, we estimated $P(M = 1 \mid Zi \ge x)$ for each tooth as a univariate variable. If the value was larger than threshold i, we diagnosed agenesis of L5. If not, we considered it to be without agenesis of L5. This estimation using univariate variables was repeated three times for the three kinds of teeth, and the final decision was made by the majority of results. For example, if the result based on the developmental stages of L3 and L4 was agenesis of L5, and the result based on that of L7 was not agenesis, the conclusion was agenesis. To estimate the survival function, the data from all the patients in the control and agenesis groups were used as training data, and we checked the predictive power with LOOCV (leave-one-out-cross-validation) results.

## 3. Results

The ICC value for intra-reliability was as high as 0.957 ($p < .001$), indicating excellent reliability.

Kendall's tau for the first objective is shown in Table 1. Because the correlation coefficients in all cases are around 0.8, it can be concluded that L3, L4, and L7 all grow similarly to L5. Our tests show that the correlation coefficients are statistically significant ($p < .001$), and all the confidence intervals for the correlation coefficients calculated by Bonferroni's correction were less than 0.02.

The correlation coefficient with L5 was greatest for L4 and smallest for L3. Bootstrap samples were used to confirm the probability that this sequence was maintained, and the probabilities of corr(L4,L5) > corr(L7,L5) > corr(L3,L5) were 1 in left and right sides.

The results for the second objective, which compared the developmental stages of L3, L4, and L7 between the control and agenesis groups, are shown in Table 2.