Third molar agenesis in modern humans with and without other tooth agenesis

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Research article

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Abstract

Background The number of teeth in the **human** dentition attracts special interest both from developmental and evolutionary aspects. The present case-control study focused on the formation of third molars in modern humans aiming to shed more light in this long lasting enigma. **Methods** For this reason, we investigated third molar formation in a sample of 303 individuals with tooth agenesis other than in third molars (agenesis group) and compared it to a sex and age matched control group of 303 individuals without tooth agenesis other than in third molars. **Results** The prevalence of third molar agenesis in the agenesis group was 50.8%, which is significantly higher than the 20.5% in the control group ($p < 0.001$). The chance of a missing third molar in the agenesis group was increased by 38.3% ($p < 0.001$), after controlling for the other tooth agenesis factor. When considering the percentages of the number of missing third molars per individual, a clear tendency towards more missing third molars was evident in the agenesis group compared to the control group. The frequency of bilaterally missing third molars in the agenesis group was 29% in the upper as well as in the lower jaw, which is about three times higher than the frequency of unilaterally missing third molars ($p < 0.001$). In the control group, bilaterally missing third molars occurred in 8.6% in the upper and 8.9% in the lower jaw. **Conclusion** The present results indicate that genetic factors involved in certain tooth agenesis also affect the entire dentition as a whole. Furthermore, the third molars are more vulnerable to factors involved in other tooth agenesis and they are more often affected as a total. These findings seem to be associated with the evolutionary trend in humans towards reduced molar number.

Background

Tooth agenesis is the congenital absence of one or more teeth. In the primary dentition the prevalence is ranging between 0.1% to 0.2%. However, in permanent dentition tooth agenesis is prevalent in 6.4% of the population, with similar occurrence in the two jaws [1, 2]. There is a large variation between different population groups and studies [2].

Tooth agenesis studies generally exclude third molars, due to the high frequency of their absence [2]. Agenesis of third molars is more or less considered a physiologic finding or an evolutionary adaptation of the dentition rather than a developmental disturbance ([3]. The third molar is the last tooth to develop in the dentition and is characterized by the variability in time of formation and by its diversity in presence or absence [4,5]. The worldwide average of third molar agenesis is 22.6%, with the Asian populations showing the highest rate of 29.7% [6].

A wide range of studies shows that the agenesis of third molars correlates with the number of the other teeth in the dentition. According to Garn et al. [7] the chance of another tooth to be missing is raised thirteen-fold if at least one third molar is missing. More recent studies point in the same direction, though with much reduced effect sizes [8-10]. Endo et al. [11] reported a significant association between missing third molars and bilateral agenesis of other teeth. Other researchers focused on the agenesis of specific teeth and third molar agenesis [12-14].

So far various studies have investigated the association between missing third molars and other missing teeth, but on limited tooth agenesis samples. Furthermore, most relevant studies tested Asian populations. Thus, we performed a study in a large sample of White subjects aiming to investigate third molar formation in individuals with and without agenesis of other teeth. To obtain a solid sample, we selected a large number of individuals with tooth agenesis

in teeth other than third molars and compared it to a matched group without tooth agenesis in teeth other than third molars.

Methods

We followed the STROBE guidelines for reporting observational studies [15].

Study sample

Consecutive orthodontic records of various time periods within the last 12 years (2006 - 2018, depending on the place of sample collection) were searched for eligible subjects at the following clinics: A) University of Bern, Switzerland b) University of Athens, Greece, c) two private practices in Athens and two in Thessaloniki, Greece, and d) one private practice in Biel, Switzerland. Sample collection was performed in the place of data generation by colleagues who were blinded to the aim of this study.

The sample was collected based on the following inclusion criteria:

- Individuals older than 12.5 years
- Individuals with and without tooth agenesis other than third molars for the agenesis and the control group, respectively
- White racial background
- No syndromes, systemic diseases or other defects that affect the craniofacial complex development, as reported in the subjects' medical record
- Adequate quality panoramic radiographs for identification of missing teeth
- No individuals where the presence or absence of teeth could not be confirmed

The minimum age limit was determined according to previous studies that evaluated the correlation between chronological age and the degree of third molar mineralization [16-20]. They showed that in 95% of cases, Demirjian's stage A was observed at the age of 12.5 or younger, which means that the mineralization of third molar crowns has already started and is clearly visible on the panoramic radiographs.

Finally, the panoramic radiographs of 303 individuals with tooth agenesis in teeth other than third molars (agenesis group) were selected from a large orthodontic sample of approximately 10.000 individuals, based on availability. A control group of 303 individuals without tooth agenesis in teeth other than third molars, matched for age (within 6 months) and sex with the tooth agenesis group, was also formed from the same archives.

Data extraction

After reviewing the orthodontic files (medical and dental history, intraoral and extraoral photos, radiographs) at the place of sample collection, relevant data were recorded in an Excel sheet (Microsoft Excel, Microsoft Corporation, Redmond WA, USA) in a standardized manner. To identify tooth agenesis, panoramic radiographs were digitized and viewed on screen. A single researcher (M.S.) performed the data extraction procedure of the entire sample, in terms of missing teeth and repeated it for 40 randomly selected subjects (<https://www.random.org/>) following a 1-month washout period.

To record tooth agenesis patterns the TAC system was used [21]. This system assigns a binary value to each tooth providing a unique numeric value for each pattern. Each dental quadrant is analyzed separately, and thus, the combined values assigned to each of the quadrants (q1, q2, q3, and q4) represent a unique tooth agenesis pattern [21].

Statistical analysis

All statistical analyses were conducted with SPSS software (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp). Descriptive statistics were also calculated through the Tooth Agenesis Code Data Analysis Tool (<http://www.toothagenesiscode.com/>, last accessed 15 May 2019). Intra-rater agreement was evaluated through the percentage of different patterns identified in the two repeated assessments. The two-tailed Pearson's Chi square test was used to assess differences in the frequencies observed in the control and the agenesis samples. The Spearman's correlation coefficient was used to investigate the relation of the number of other teeth agenesis to the number of third molar agenesis as well as that of the agenesis in the same quadrant.

Results

Method error

Intra-rater agreement between repeated tooth agenesis pattern identification was 97.5%.

Agenesis group without considering third molars

In the 303 individuals (170 females, 133 males) of the agenesis sample, in total 799 teeth other than third molars were congenitally missing. In 38.6% of the sample one tooth, in 33.3% two and in 7.9% three teeth were missing (Appendix Table 1). The incidence for missing teeth in the upper jaw was 57.1%, compared to 68.6% in the lower jaw ($p = 0.079$). The most common missing tooth was the mandibular second premolar (29.3%), followed by the maxillary lateral incisor (21.0%) and the maxillary second premolar (14.0%) (Table 1).

Table 1. Distribution of missing teeth across quadrant and tooth number.

Tooth number	Upper right	Upper left	Lower right	Lower left	Total
1 - Agenesis	3	2	29	30	64
2 - Agenesis	85	83	15	18	201
3 - Agenesis	14	13	5	4	36
4 - Agenesis	20	21	15	15	71
5 - Agenesis	60	52	117	117	346
6 - Agenesis	5	4	9	7	25
7 - Agenesis	13	14	15	14	56
8 - Agenesis	101	105	104	108	418
Total Agenesis	301	294	309	313	1217
8 - Control	37	32	39	36	144

Regarding tooth symmetry, the teeth that were most often symmetrically missing in the maxilla were the lateral incisors (19.5%) followed by the second premolars (14.2%). In the mandible, the second premolars were missing bilaterally in 25.4%, followed by the central incisors in 7.9% (Table 2).

Table 2. Frequency tables that show single tooth agenesis and the prevalence of right sided, left sided or bilateral agenesis in the whole sample ($n = 606$).

Upper Jaw					
Tooth number	Present bilaterally (%)	Missing right side (q1) (%)	Missing left side (q2) (%)	Missing unilaterally (%)	Missing bilaterally (%)
1 - Agenesis	300 (99.0)	1 (0.3)	0 (0.0)	1 (0.3)	2 (0.7)
2 - Agenesis	194 (64.0)	26 (8.6)	24 (7.9)	50 (16.5)	59 (19.5)
3 - Agenesis	286 (94.4)	4 (1.5)	3 (1.0)	7 (2.5)	10 (3.3)
4 - Agenesis	277 (91.4)	5 (1.7)	6 (2.0)	11 (3.7)	15 (5.0)
5 - Agenesis	234 (77.2)	17 (5.6)	9 (3.0)	26 (8.6)	43 (14.2)
6 - Agenesis	297 (98.0)	2 (0.7)	1 (0.3)	3 (1.0)	3 (1.0)
7 - Agenesis	287 (94.7)	2 (0.7)	3 (1.0)	5 (1.7)	11 (3.6)
8 - Agenesis	185 (61.1)	13 (4.3)	17 (5.6)	30 (9.9)	88 (29.0)
8 - Control	260 (85.8)	11 (3.6)	6 (2.0)	17 (5.6)	26 (8.6)
Lower jaw					
Tooth number	Present bilaterally (%)	Missing right side (q4) (%)	Missing left side (q3) (%)	Missing unilaterally (%)	Missing bilaterally (%)
1 - Agenesis	268 (88.4)	5 (1.7)	6 (2.0)	11 (3.7)	24 (7.9)
2 - Agenesis	281 (92.7)	4 (1.3)	7 (2.3)	11 (3.6)	11 (3.6)
3 - Agenesis	297 (98.0)	2 (0.7)	1 (0.3)	3 (1.0)	3 (1.0)
4 - Agenesis	284 (93.7)	4 (1.3)	4 (1.3)	8 (2.6)	11 (3.6)
5 - Agenesis	146 (48.2)	40 (13.2)	40 (13.2)	80 (26.4)	77 (25.4)
6 - Agenesis	292 (96.4)	4 (1.3)	2 (0.7)	6 (2.0)	5 (1.7)
7 - Agenesis	283 (93.4)	6 (2.0)	5 (1.7)	11 (3.7)	9 (3.0)
8 - Agenesis	179 (59.1)	16 (5.3)	20 (6.6)	36 (11.9)	88 (29.0)
8 - Control	255 (84.2)	12 (4.0)	9 (3.0)	21 (7.0)	27 (8.9)

The most common agenesis patterns in the upper jaw were bilaterally missing lateral incisors (23.1%) followed by bilaterally missing second premolars (12.7%). In the lower jaw, the most common pattern was bilateral agenesis of second premolars in 27.9%, followed by unilateral agenesis of the right second premolar (17.3%). In the whole dentition, bilateral agenesis of maxillary lateral incisors occurred most often (11.2%), followed by bilateral agenesis of mandibular second premolars (10.2%; Table 3).

Table 3. Most common tooth agenesis patterns in individuals that have at least one agenesis in the maxilla, the mandible, and the whole dentition (agenesis group without third molars).

Index	Frequency (%)	Missing teeth	Index	Frequency (%)	Missing teeth
Upper jaw			Lower jaw		
1	40/173 (23.1)	12, 22	1	58/208 (27.9)	35, 45
2	22/173 (12.7)	15, 25	2	36/208 (17.3)	45
3	21/173 (12.1)	12	3	34/208 (16.3)	35
4	20/173 (11.6)	22	4	10/208 (4.8)	31, 41
5	11/173 (6.4)	15	5	5/208 (2.4)	34, 35, 44, 45 32, 42
Overall	114/173 (65.9)		Overall	143/208 (68.8)	
Whole dentition					
1	34/303 (11.2)	12, 22	6	17/303 (5.6)	12
2	31/303 (10.2)	35, 45	7	11/303 (3.6)	15, 25, 35, 45
3	29/303 (9.6)	45	8	8/303 (2.6)	31, 41
4	27/303 (9.0)	35	9	7/303 (2.3)	15, 25
5	18/303 (6.0)	22	10	4/303 (1.3)	15 41 31
Overall		186/303 (61.4)			

Third molar agenesis in the agenesis and the control group

The prevalence of third molar agenesis in the agenesis group was 50.8% and it was significantly larger than the 20.5% in the control group ($p < 0.001$). 418 third molars were congenitally missing in the agenesis group ($n = 303$) compared to 144 in the control group ($n = 303$). If the probability of third molar agenesis in the agenesis group was equal to other tooth agenesis, this would increase the value of 144 missing third molars observed in the control group by 114. Consequently, 258 missing third molars would have been expected in the agenesis group, after controlling for the other tooth agenesis factor. This value is significantly lower than the actual value observed (418; $p < 0.001$). Thus, the chance of a missing third molar in the agenesis group is increased by 38.3% compared to controls.

In the agenesis group, there was a significant but weak correlation of the total number of other missing teeth to the total number of missing third molars ($\rho = 0.31$, $p < 0.001$). Similarly, very weak correlations were identified when third molar agenesis was correlated to the number of other tooth agenesis within quadrants (Q1: $\rho = 0.16$, $p = 0.006$; Q2: $\rho = 0.14$, $p = 0.015$; Q3: $\rho = 0.20$, $p = 0.001$; Q4: $\rho = 0.29$, $p = 0.001$).

The frequency of bilaterally missing third molars in the agenesis group was 29% in the upper as well as in the lower jaw, which is about three times higher than the frequency of unilaterally missing third molars (maxilla: 9.9%, $p < 0.001$, mandible: 11.9%, $p < 0.001$) (Table 2). The ratio of bilateral to unilateral third molar agenesis was significantly higher in the agenesis group compared to the control group (Maxilla: 2.93 vs. 1.53, respectively, $p < 0.001$; Mandible: 2.44 vs. 1.29, respectively, $p < 0.001$) (Table 2).

In the tooth agenesis group, symmetrical third molar agenesis occurred in a similar manner within jaws (29% within each jaw), between jaws (right side: 24%, left side: 24%), or crossed quadrant (q1 vs. q3: 22.1%; q2 vs q4: 24.4%) ($p > 0.05$; Table 4). The same was true for the control groups ($p > 0.05$; Table 4), though the prevalence of all respective symmetrical patterns was much lower (range: 6.6 - 8.9%, $p < 0.001$).

Table 4. Symmetry of tooth agenesis patterns.

Pattern symmetry	Comparison		Symmetry I (%)	Symmetry II (%)
Upper jaw	Right vs. left side	No 3 rd - Agenesis	26.7	46.8
		3 rd - Agenesis	29.0	74.6
		3 rd - Control	8.6	60.5
Lower jaw	Right vs. left side	No 3 rd - Agenesis	30.0	43.8
		3 rd - Agenesis	29.0	71.0
		3 rd - Control	8.9	56.3
Left side	Upper left vs. lower left	No 3 rd - Agenesis	6.9	8.8
		3 rd - Agenesis	24.1	52.1
		3 rd - Control	6.6	41.7
Right side	Upper right vs. lower right	No 3 rd - Agenesis	7.9	9.8
		3 rd - Agenesis	24.4	56.5
		3 rd - Control	8.6	52.0
Crossed q1 vs q3	Upper right vs. lower left	No 3 rd - Agenesis	6.9	8.71
		3 rd - Agenesis	22.1	47.2
		3 rd - Control	6.6	37.7
Crossed q2 vs q4	Upper left vs. lower right	No 3 rd - Agenesis	7.6	9.5
		3 rd - Agenesis	24.4	54.8
		3 rd - Control	6.6	39.2

Symmetry I: percentage relative to the whole sample (n = 303) without considering the patterns of no missing teeth as symmetrical. **Symmetry II:** percentage relative to subsample of subjects with missing teeth in the respective area (i.e. upper jaw, lower jaw etc.).

In both groups, there was no statistically significant difference between the number of missing third molars in the different quadrants (Chi square test, $p > 0.05$; Table 1). The agenesis group differed significantly from the control group in the distribution of the number of missing third molars ($p < 0.001$). There is a clear tendency towards more missing third molars in the agenesis group compared to the controls. The agenesis group has 1.55, 2.14, 3.80, and 3.48 times higher possibility of having one, two, three, or four missing third molars respectively, when compared to the control group (Figure 1).

Appendix Table 2 shows the most common patterns of tooth agenesis in the agenesis group including third molars. These were in the upper jaw the missing lateral incisors in 14.1%, followed by bilaterally missing third molars in 13.6% and in the lower jaw, the bilaterally missing second premolars in 12.8%, followed by unilateral second premolar agenesis.

Appendix Table 3 shows the most common patterns of third molar agenesis in control subjects where agenesis was observed. In the maxilla as well as in the mandible bilateral third molar agenesis was the most common pattern (60.5% and 56.3%, respectively). In the entire dentition the most common pattern was four missing third molars (17.4%), followed by bilateral third molar agenesis in the mandible in 14.5%. Appendix Table 4 shows the most

common patterns of third molar agenesis in agenesis subjects where third molar agenesis was observed. In this group also bilateral third molar agenesis was the most common pattern within jaws (74.6% and 71.0%, in the maxilla and the mandible, respectively). Furthermore, in the entire dentition the most common pattern was also in this group the four missing third molars (38.3%) followed by bilateral third molar agenesis in the mandible in 12.3%.

Discussion

The purpose of this study was to explore the patterns of third molar agenesis in a large sample of modern white subjects with and without other tooth agenesis. The prevalence of third molar agenesis in the agenesis group was 50.8%, which is about 2.5 times higher than in the control group. There was weak correlation of the number of other tooth agenesis with the number of third molar agenesis within individuals, as well as very weak correlations of third molar agenesis to the number of other tooth agenesis within quadrants. When considering the percentages of the number of missing third molars per subject in the control and the agenesis group, there is a tendency towards more missing third molars in the agenesis group. The frequency for bilaterally missing third molars in the agenesis group is about three times higher than the frequency of unilaterally missing third molars. The ratio of bilateral to unilateral third molar agenesis was also significantly higher in the agenesis group.

Our methodology differs from all previous studies in terms that we investigated the patterns of third molar agenesis in a large sample with other tooth agenesis. To our knowledge, all the existing studies divided their groups according to third molar agenesis. Through this approach, only a small percentage of the subsequent subsamples had agenesis in teeth other than third molars, and thus these groups did not have adequate or comparable size to the control groups. Our study tested a large agenesis sample of 303 agenesis individuals, as well as 303 controls, selected out of a total of around 10000 records. Furthermore, the groups were matched for sex and age, accounting for any confounding effect of these factors. This allowed for findings that are presented for first time in the literature, such as those related to symmetry or to occurrences within quadrants.

The age range that we considered was limited from 12.5 to 40 years old. The minimum limit was defined according to various longitudinal studies that showed the correlation between chronological age and the degree of third molar mineralization using Demirjian's developmental stages. This classification is widely used and tested to facilitate age estimation. Therefore, the choice of this age limit is **considered safe** [16-20]. The upper age limit of 40 years was chosen to avoid false positive results due to extraction or tooth loss for other reasons that could have been registered as agenesis.

Without considering the third molars, the present tooth agenesis findings are in agreement with other studies [2, 22]. This indicates that our agenesis sample was comparable to other samples presented in the literature, confirming the generalizability of our findings.

We found a prevalence of 50.8% for third molar agenesis in the agenesis group compared to 20.5% in the control. According to a recent meta-analysis [6] the worldwide average of third molar agenesis is 22.6% (21.6% for Europeans), confirming the appropriateness of our control group. Our results clearly demonstrated that in individuals with other tooth agenesis, the prevalence of third molar agenesis is higher. This points in the same direction with previous studies that showed an increased prevalence of other tooth agenesis in individuals with third molar agenesis [8-10].

In our control group, the sequence of the number of missing third molars was similar to that of Carter and Worthington [6] that showed the highest prevalence for one missing third molar, followed by two and four missing third molars. However, the most common number of missing third molars in the agenesis group was four, followed by two and one molar. This inconsistency is attributed to the different sample composition in each case. The aforementioned meta-analysis tested third molar agenesis in the general population, meaning that individuals with other tooth agenesis would be limited. The above findings clearly show that the presence of

agenesis in teeth other than third molars has a considerable effect on third molar agenesis patterns, rising the probability to have four missing third molars. This suggests that the third molars might be more vulnerable to genetic factors involved in tooth agenesis, as compared to other tooth types. Indeed, this is also supported by the increased number of missing third molars in the agenesis sample compared to that expected by chance. This concept is in line with the evolutionary trend in humans towards less number of teeth, and more specifically, less molars [23].

In the agenesis group, the prevalence for bilaterally missing third molars was more than three times higher than in the control group, in the upper as well as in the lower jaw. The ratio of bilateral to unilateral third molar agenesis was significantly higher in the agenesis group compared to control. The same was true for all types of symmetry. Furthermore, in both agenesis and control groups, the most common third molar agenesis pattern in the entire dentition was the four missing third molars, followed by bilateral third molar agenesis in the mandible. This is in line with our previous statement that third molars are more susceptible to genetic or epigenetic factors that cause tooth agenesis and might more possibly be affected as a total. The above claim is also supported by the increasing possibility for more missing third molars in the other tooth agenesis group than in the controls. Furthermore, very weak correlations were identified between other missing teeth and third molar agenesis within quadrants, suggesting that there are no significant genetic effects limited within quadrants.

A limitation of the study could be that the sample was selected from orthodontic practices, meaning that it may not be representative of the general population. However, when considering that malocclusion is endemic in recent years it is not expected that our sample would highly differ from the general population. Indeed, this was confirmed by comparisons to other studies. In any case, with the present approach to the study question this is not considered a limitation. Another limitation could be that the results are based only on subjects of white racial background and have to be confirmed on other races. However, the study sample originated from places where the white background is highly represented. Thus, we decided to include only white subjects to avoid confounding.

Conclusions

The present study showed that individuals with non-syndromic tooth agenesis in teeth other than third molars show a higher prevalence of third molar agenesis compared to matched control individuals, with no other tooth agenesis. There was also a clear tendency towards more missing third molars in the agenesis group. Furthermore, in the agenesis group, the prevalence for bilaterally missing third molars was more than three times higher than in the control. The ratio of bilateral to unilateral third molar agenesis was also significantly higher. The above findings indicate that the third molars might be more vulnerable to genetic or epigenetic factors involved in other tooth agenesis and they are often affected as a total. These findings seem to be associated with the evolutionary trend in humans towards reduced number of teeth.

Declarations

Ethics approval and consent to participate

The ethical approval was provided by the Ethics Commission of the Canton of Bern, Switzerland (Project-ID: 2018-01340) and the Research Committee of the School of Dentistry, National and Kapodistrian University of Athens, Greece (Project-ID: 281, 2/9/2016). The need for informed consent was waived for part of the sample and was obtained for the rest.

Consent for publication

Not applicable.

Availability of data and materials

All data is available in the main text or the supplementary material. The datasets generated and/or analyzed are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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No funding was received for this study.

Authors' contributions

M. Scheiwiller, contributed to design, data acquisition, analysis, and interpretation, drafted and critically revised the manuscript; E.S. Oeschger, contributed to data acquisition, drafted and critically revised the manuscript; N. Gkantidis contributed to conception and design, data acquisition, analysis, and interpretation, drafted and critically revised the manuscript. All authors read and approved the final manuscript.

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Figures

Figure 1

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