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Accepted: 25 April 2024

DOI: 10.1111/ocr.12807

RESEARCH ARTICLE

Orthodontics & Craniofacial Research WILEY

Third molar agenesis in individuals with supernumerary teeth

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Abstract

Objectives: To explore the association between third molar agenesis and supernumerary tooth formation in a white-European population.

Materials and Methods: A record review in various orthodontic clinics identified 380 eligible white-European individuals, half of whom had non-syndromic permanent supernumerary teeth (122 males and 68 females, totalling 244 supernumerary teeth; median age: 13.1, iqr: 1.5 years), and the other half were age- and sex-matched controls with full dentition, excluding the third molars. Tooth sequences were identified in panoramic radiographs.

Results: In the supernumerary group, approximately 80% of the individuals had a single supernumerary tooth, followed by those having two additional teeth. In both groups, there was no sexual dimorphism in third molar agenesis severity. The prevalence of third molar agenesis in the supernumerary group was similar to that of the control group (28/190 = 14.7% in both groups; $p = 1.0$). In total, 53 third molars were missing in the supernumerary group (n = 190) compared to 67 in the control group (n = 190; $p = .862$). The ratio of bilateral to unilateral third molar agenesis was significantly lower in the supernumerary group than in the control group (1.0 vs. 3.7, respectively; $p = .026$).

Conclusion: The presence of supernumerary teeth did not significantly alter the likelihood of third molar agenesis or its severity. Bilateral third molar agenesis was considerably less prevalent in individuals with supernumerary teeth compared to controls. The present novel findings have important clinical and developmental implications.

KEYWORDS
non-syndromic, odontogenesis, permanent dentition, supernumerary tooth, third molars, tooth agenesis

1 | INTRODUCTION

Tooth agenesis is the congenital absence of one or more teeth and constitutes a common anomaly of the craniofacial area in humans.[1,2] In permanent dentition, the prevalence of missing teeth other than third molars is about 6.4%, with a similar occurrence in both jaws.[1] The third molars are the latest forming teeth and show high variability in the time and the event of formation.[1–3] In 22.6% of the human population, at least one third molar is missing, whereas in Asian populations this reaches 29.7%.[2] Females show about 30% higher

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prevalence of agenesis in teeth other than third molars[1] and are 14% more likely to have third molar agenesis, compared to males.[2] Third molar agenesis is mostly considered an evolutionary adaptation rather than a developmental disturbance.[3,4]

Genetic factors that are regarded as the primary cause of tooth agenesis are also involved in tooth shape and size discrepancies and in craniofacial bone morphogenesis.[5–7] The number of teeth in the permanent dentition is associated with facial size and shape, with agenesis related to smaller and differently shaped craniofacial configurations.[6,8] Similar findings have been reported in subjects with isolated third molar agenesis.[7,9] Data on sexual dimorphism and symmetry in third molar agenesis provide additional evidence of strong genetic control of the developmental process leading to third molar formation.[4,10] These findings suggest a coordinated regulation of dental and facial development that seems to follow the human evolutionary trend towards reduced molar number and facial size.[8,9]

Various studies have shown that third molar agenesis is positively correlated with the absence of formation of other teeth, despite considerable differences in effect sizes and sample characteristics.[4,11] Most previous studies investigated limited agenesis samples and Asian populations. A recent study on white-European subjects reported an increased prevalence of third molar agenesis in case of agenesis of other teeth (50.8% in the agenesis group vs. 20.5% in the control group) and a higher frequency of bilaterally missing third molars than unilaterally missing ones.[4]

The condition opposite to tooth agenesis is known as hyperdontia or supernumerary tooth and is defined as the formation of an extra tooth or odontogenic structure in addition to the regular dentition. Supernumerary teeth can occur unilaterally or bilaterally and can either erupt or remain unerupted.[12,13] Only in 4.6% of the cases more than three supernumerary teeth are formed.[14,15] In the permanent dentition, the prevalence of supernumerary teeth varies between 1.2% and 6.0%,[15–17] with males having 1.37 times higher risk than females.[18] The prevalence also differs depending on racial background, with a higher occurrence reported in Asian populations than in white populations.[19,20] Supernumerary teeth can occur as isolated findings or can be associated with several syndromes, such as Down syndrome, cleidocranial dysplasia, familial adenomatous polyposis, or Gardner's syndrome.[12,21] The most common theory regarding the aetiology of supernumerary teeth attributes their occurrence to the dichotomy of a tooth bud or to a hyperactive dental lamina. Various environmental, epigenetic, and genetic factors have been involved,[12,15,22–24] but the molecular mechanisms of supernumerary tooth formation still remain unclear.[24,25]

Supernumerary teeth are often misdiagnosed or unidentified unless they lead to complications such as impaction, delayed eruption of the adjacent teeth, crowding, ectopic tooth eruption or cyst formation.[18,22] The individual treatment need and type depend on several factors such as the age of the patient, the type and the position of the supernumerary tooth.[26] Typically, multidisciplinary treatment approaches and long-term follow-ups are required. The presence of a supernumerary tooth can considerably impact a patient's oral health-related quality of life, as it often results in clinical complications.[27,28]

To our knowledge, investigations exploring supernumerary tooth patterns in large patient populations have been limited, and these studies did not include comprehensive data on racial backgrounds.[14,29–32] Moreover, they did not explore the association between third molars and supernumerary tooth formation, apart from one study that included only four patients with supernumerary teeth.[33] This information could facilitate treatment planning by predicting third molar development in young patients with supernumerary teeth and enable a better understanding of the condition, with developmental and evolutionary implications. Therefore, the aim of the present study was to investigate the patterns of third molar agenesis in individuals with supernumerary teeth compared to control individuals with full permanent dentition, excluding third molars.

2 | MATERIALS AND METHODS

Certain methodological details of a similar sample have been documented in earlier publications.[34] Necessary information will be repeated here to ensure reader comprehension. Ethical approval for the present retrospective study was obtained by the Research Ethics Committees of the antons of Bern, Neuchatel, Basel, and Jura, Switzerland (Protocol Nr: 2022-00399, Date of Approval: 20.06.2022) and the Institutional Ethics and Research Committees of the Dental Schools of the National and Kapodistrian University of Athens (Protocol Nr: 518/05.09.2022, Date of Approval: 13.10.2022) and the Aristotle University of Thessaloniki, Greece (Protocol Nr: 182/10.02.2023, Date of Approval: 16.03.2023). The methods were carried out in accordance with the relevant guidelines and regulations. An informed consent form was signed by all participants before their data were used in the study.

2.1 | Study Sample

The patient archives of the Department of Orthodontics at the University of Bern, the University of Basel, two private practices in Switzerland, as well as the National and Kapodistrian University of Athens and the Aristotle University of Thessaloniki were searched to identify individuals with supernumerary teeth. Archives were consecutively searched for different periods of time, depending on the site of sample collection, in reverse chronological order. All included patients visited the respective clinics between 2002 and 2023. For individuals who met the eligibility criteria, full medical and dental histories, dental models, intraoral and extraoral photos, and radiographs were examined at the place of sample collection. Afterwards, the data were anonymized for further assessment. Pre-treatment panoramic and cephalometric radiographs, along with any other radiographs (e.g. periapical or cone beam computed tomography),

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were retrieved. These pre-treatment panoramic and cephalometric radiographs, dental models, and intraoral and extraoral photos constituted the standard records available for regular patients undergoing orthodontic treatment in the aforementioned clinics.

In total, 190 individuals meeting the inclusion criteria were identified. The tooth sequences were documented through coded panoramic radiographs and recorded in an Excel spreadsheet (Microsoft Excel, Microsoft Corporation, Redmond WA, USA), along with the patients' age and sex.

As this sample partially overlaps with that of a study testing supernumerary tooth patterns,[34] similar inclusion criteria were applied:

- Individuals aged 10.5 to 50.0 years when the pre-treatment panoramic radiograph was obtained.
- European ancestry (white subjects). This was the major racial group represented in the searched archives. Other racial backgrounds were quite variable and largely underrepresented to form reasonable group sizes.
- Individuals with supernumerary teeth.
- No syndromes, systemic diseases or any other defects that affect craniofacial morphology as reported in the subjects' medical records.
- No extensive dental restorations that may affect craniofacial morphology.
- High-quality panoramic radiographs or cone-beam computed tomographies for identification of supernumerary teeth.
- No intervention that could influence craniofacial morphology, such as orthodontic treatment, prior to image acquisition.
- No other severe dental anomaly in tooth size or form in any tooth apart from third molars.
- No cases where the reason for missing teeth was unknown.

A matched for age (within 6 months) and sex control group of another 190 individuals with full dentition, without considering the third molars, was also formed with all other conditions and criteria similar to the supernumerary group.

The sample size was based on availability, and according to empirical evidence, it was considered satisfactory for the study purpose.[32] Post-hoc power analysis for the differences in third molar agenesis prevalence between the supernumerary and the control groups revealed adequate power (power: 83%, critical x^2: 3.84, $\alpha = 0.05$, total sample size: 380, df: 1) for small effect size (Cohen's w) of 0.15 (G*power, version 3.1.9.6).

2.2 | Data collection

Further evaluation of the anonymized radiographs was performed by the first two authors (senior orthodontic residents) to verify data extraction. All panoramic radiographs were viewed on screen to identify tooth patterns. Both researchers re-assessed the data extraction procedure of the entire sample 1 month after the first assessment and any disagreements were resolved by consensus and consultation with the last author (experienced orthodontist). If needed, additional radiographs, dental models, intraoral or extraoral photos, as well as medical and dental histories, were re-examined to enhance the diagnostic ability. All data were recorded in an Excel spreadsheet. A numerical coding system analogous to the TAC system[35] that was used previously to study tooth agenesis[36] was implemented to investigate the patterns of supernumerary teeth and of third molars. Through this, a unique numeric value was generated for each tooth pattern through Microsoft Excel.

2.3 | Statistical analysis

The study data were recorded in Microsoft Excel, where basic descriptive measures were generated. Further statistical analysis was performed using the IBM SPSS statistics for Windows (Version 29.0, Armonk, NY: IBM Corp). Pearson's Chi-square tests were used to check for associations between categorical or ordinal variables when all expected frequencies were at least 5. Otherwise, the Likelihood Ratio test was used instead. Cramér's V statistic was used to measure the strength of associations between categorical or ordinal variables, where applicable. An ordinal logistic regression model was also applied to test the predictive value of sex (fixed factor) and number of supernumerary teeth (covariate) on the number of missing third molars (dependent variable). Age was not incorporated into the model since exploratory testing indicated no effects. In all cases, the alpha level for the tests was defined at 0.05.

3 | RESULTS

3.1 | Method error

Two primary investigators assessed all data independently to define third molar agenesis patterns and the intra-rater agreement was 100%. The error rate in supernumerary tooth identification has been previously reported and was minimal.[34]

3.2 | Supernumerary tooth patterns

In the 190 individuals (68 females, 122 males; median age: 13.1, interquartile range: 1.5 years) with supernumerary tooth formation, 244 supernumerary teeth were present (164 teeth for the males and 80 for the females). Most individuals (76.2% of males and 82.4% of females) had a single supernumerary tooth, followed by two teeth per individual (16.4% of males and 17.6% of females). Only a few male individuals had more than two supernumerary teeth (Table 1). Males showed more often supernumerary teeth (male/female ratio: 1.8, Chi-square test: $p = .006$) and higher numbers of supernumerary teeth compared to females ($p = .042$, Table 1). The effect of sex on the number of supernumerary teeth

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TABLE 1 Number of supernumerary teeth per individual in males ($n = 122$) and females ($n = 68$).

Nr. of supernumerary teeth	Males	Females	*p*-value*
1	93 (76.2%)	56 (82.4%)	$p = .042$
2	20 (16.4%)	12 (17.6%)	
3	5 (4.1%)	0	
4	4 (3.3%)	0	

*Likelihood Ratio test between males and females.

was considered small (Cramer's V: 0.166, $p = .072$). On average, 1.28 ± 0.62 supernumerary teeth were identified per individual (males: 1.34 ± 0.71, 95% CI: 1.22, 1.47; females: 1.18 ± 0.38, 95% CI: 1.08, 1.27).

Table 2 presents the number of supernumerary teeth per tooth type and the prevalence according to the total number of supernumerary teeth in the sample. The most common supernumerary tooth was the maxillary central incisor (33.6%), followed by the maxillary lateral incisor (18.5%), and the mandibular first premolar (13.1%) (Table 2).

3.3 | Third molar agenesis patterns in the supernumerary and the control groups

There was no sexual dimorphism in third molar agenesis severity in both the supernumerary and the control groups ($p > .05$, Table 3). Therefore, no sexual subgroups were considered for further analysis and the data were joined. The age and sex distribution of the supernumerary sample, which is similar to that of the control sample, is shown in Figure 1.

The prevalence of third molar agenesis in the supernumerary group was similar to that of the control group (28/190 = 14.7%; $p = 1.0$). In total, 53 third molars were missing in the supernumerary group ($n = 190$) compared to 67 third molars in the control group (n = 190, Mann Whitney U-test: $p = .862$). There was no correlation between the number of missing third molars and the number of supernumerary teeth (n = 380, rho = −0.03, $p = .603$) and no significant difference between the distributions of the number of missing third molars in the supernumerary and the control group (Likelihood Ratio test: $p = .097$, Figure 2). Within the supernumerary tooth group, there was a very weak negative correlation between the number of supernumerary teeth with the number of missing third molars, which also did not reach the level of significance (rho = −0.09, $p = .199$).

An ordinal logistic regression model was also applied to the data, confirming than neither sex (parameter estimate for female sex with male as reference = −0.51, $p = .114$, 95% CI: −1.14, 0.12) nor the number of supernumerary teeth (parameter estimate = −0.14, $p = .481$, 95% CI: −0.52, 0.24) could predict the number of missing third molars (model fitting: −2 Log-likelihood

TABLE 2 Number of supernumerary teeth per tooth type and prevalence (%) according to the total number of supernumerary teeth in the sample.

Maxilla																									
Teeth	**18**	**17**	**16**	**15**	**14**	**13**	**12**	**11**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**									
Total ($n = 169$)	15 6.1%	1 0.4%	2 0.8%	-	4 1.6%	1 0.4%	27 11.1%	35 14.3%	47 19.3%	18 7.4%	3 1.2%	4 1.6%	3 1.2%	1 0.4%	-	8 3.3%									
Mandible																									
Teeth	**48**	**47**	**46**	**45**	**44**	**43**	**42**	**41**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**									
Total ($n = 75$)	4 1.6%	-	-	8 3.3%	15 6.1%	2 0.8%	3 1.2%	2 0.8%	5 2.0%	2 0.8%	3 1.2%	17 7.0%	10 4.1%	1 0.4%	-	3 1.2%									

Abbreviation: n, number of teeth.

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TABLE 3 Number of missing third molars per individual in the supernumerary and the control group, in males and females.

Nr. of missing third molars	Supernumerary group			Control group		
	Males ($n=122$)	Females ($n=68$)	p-value*	Males ($n=122$)	Females ($n=68$)	p-value*
0	99 (81.1%)	63 (92.6%)	$p=.066$	104 (85.2%)	58 (85.3%)	$p=.743$
1	10 (8.2%)	4 (5.9%)		3 (2.5%)	2 (2.9%)	
2	6 (4.9%)	1 (1.5%)		9 (7.4%)	5 (7.4%)	
3	3 (2.5%)	0		2 (1.6%)	3 (4.4%)	
4	4 (3.3%)	0		4 (3.3%)	0	

*Likelihood Ratio test between males and females.

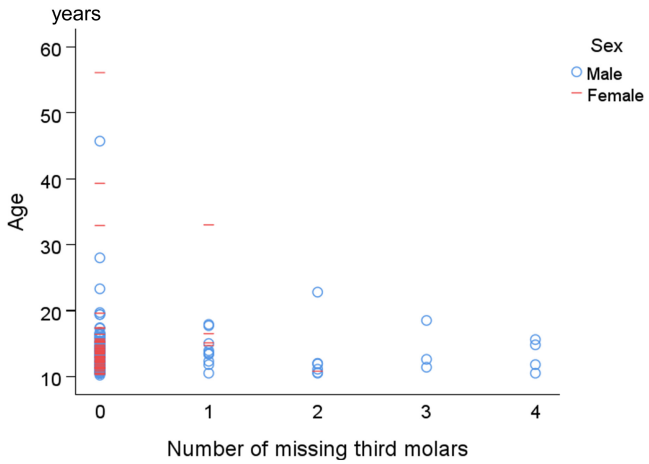

FIGURE 1 Age and sex distribution of the supernumerary group per number of missing third molars.

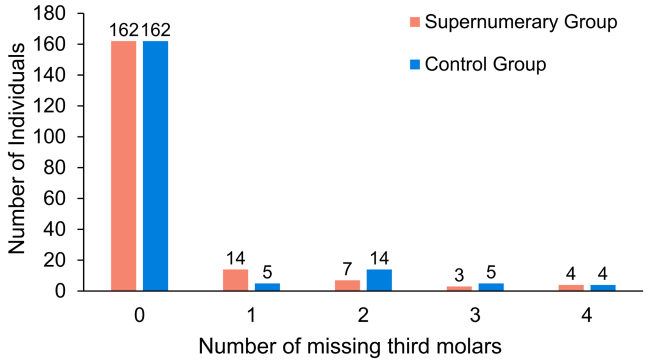

FIGURE 2 Number of missing third molars per individual in the supernumerary and the control group.

$p=.216$; goodness-of-fit: Pearson's chi-square $p=.042$; Pseudo R-Square: McFadden = 0.007).

Within the supernumerary tooth group, 14 individuals had bilaterally missing third molars, and 14 showed unilateral occurrence. In the control group, 22 individuals had bilaterally missing third molars, and 6 showed unilateral occurrence. The ratio of bilateral to unilateral third molar agenesis was significantly lower in the supernumerary group compared to the control group (1.0 vs. 3.7, respectively, Chi-square $p=.026$, Cramer's V: 0.298, $p=.026$). The most common patterns of third molar agenesis in each group aligned with this trend (Table 4).

TABLE 4 The five most common third molar agenesis patterns in individuals with and without supernumerary teeth.

Most Common Patterns	Frequency (%)	Third Molar Agenesis Patterns	
		Bilateral[a]	Unilateral[a]
Supernumerary group			
1	6/190 (3.2%)	-	18
2	5/190 (2.6%)	-	38
3–4	4/190 (2.1%) each	18, 28 18, 28, 38, 48	-
5	3/190 (1.6%)	38, 48	-
Control group[b]			
1	8/190 (4.2%)	38, 48	-
2	7/190 (3.7%)	18, 28, 38, 48	-
3	5/190 (2.6%)	18, 28	-
4	2/190 (1.1%)	-	48

[a]Within cells, each row represents a single pattern.
[b]There was no other pattern occurring more than once in this group.

4 | DISCUSSION

The present study explored the third molar agenesis patterns in a well-documented white-European population with supernumerary teeth and compared them to control individuals without supernumerary teeth. The presence of supernumerary teeth did not alter the likelihood of third molar agenesis or the number of missing third molars. However, in individuals with supernumerary teeth, bilateral third molar agenesis occurred as frequently as unilateral agenesis, contrasting with controls where bilateral agenesis was predominant. These findings appear to be unique in the literature.

Previous studies have analysed patterns of supernumerary teeth[14,29–32,37] or third molar agenesis,[1,2] but none have investigated the co-existence of these two conditions in a substantial sample. Most available studies had limited sample sizes or did not report on the racial backgrounds of the tested samples, which could confound the outcomes.[14,29–33,37] We employed a

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well-defined sample of substantial size, comprising orthodontic patients who have been thoroughly documented and closely monitored by specialists for a specified period. This approach minimizes the risk of misdiagnosis.

From a clinical pespective, understanding the patterns of supernumerary teeth and third molar agenesis aids in proper diagnosis and treatment planning, particularly in young individuals with complex problems. Moreover, it assists researchers in designing future studies. From an anthropological point of view, these studies enable a better understanding of the development of dentition, with potential biological and evolutionary implications.[6,7]

In our study, most individuals exhibited one or, less frequently, two supernumerary teeth, with only a few males showing three or four supernumerary teeth. The maxillary central incisor was the most common supernumerary tooth, followed by the maxillary lateral incisor and the mandibular first premolar. This is in accordance with previous studies indicating a higher prevalence of supernumerary teeth in the maxilla compared to the mandible.[14,23,25,26,31,37]

In line with previous studies, males showed more often supernumerary teeth than females.[18] On the contrary, studies on tooth agenesis showed a higher prevalence in females.[1] In the present sample, no sexual dimorphism was found in the severity of third molar agenesis in individuals with supernumerary teeth, as evident in controls, as well as in individuals with agenesis of teeth other than third molars.[10] The prevalence of third molar agenesis was not affected by the presence of supernumerary teeth. On the contrary, a previous study revealed that the chance of missing third molars was increased by 38% in subjects with agenesis of teeth other than third molars.[4] Therefore, an upregulating effect, opposite to the downregulating effect in third molar formation by decreased number of teeth in a dentition, was not evident for supernumerary teeth. However, bilateral third molar agenesis occurred significantly less often than in controls, as opposed to the increased occurrence in the presence of agenesis of teeth other than third molars. In accordance with previous studies on tooth agenesis,[4,9,10,36] these findings indicate a strict genetic control on the development of the dentition in terms of number of teeth, with more global, non-sex-specific effects, when this process is disrupted. The lack of impact on the prevalence of third molar agenesis in the presence of supernumerary teeth, as opposed to tooth agenesis, adds to the cumulating evidence that these patterns may stem from an evolutionary mechanism leading to less number of teeth and smaller faces in modern humans.[6,7,9,10,36,38]

There was no significant difference in the distribution of the number of missing third molars between the supernumerary and the control group and no correlation between the total number of supernumerary teeth to the total number of missing third molars. In contrast, previous studies demonstrated a correlation between the number of third molar agenesis and the agenesis of other teeth in the dentition.[4,11,33] Moreover, individuals with supernumerary teeth exhibited a lower ratio of bilateral to unilateral third molar agenesis compared to the control group. This is in contrast to studies of third molar agenesis in the absence of supernumerary teeth, which have shown a clear tendency towards a higher prevalence of bilaterally missing third molars.[4] These findings suggest a stricter genetic control towards tooth agenesis compared to supernumerary tooth formation. This may also be related to the biological mechanism of tooth number reduction observed during human evolution, which may still be active in modern humans.[4,9,10,36]

5 | LIMITATIONS

A limitation of our study relates to the inclusion of orthodontic patients, which may vary in incidence or severity of supernumerary tooth or third molar agenesis compared to the general population. There might also be a slight underestimation of the reported male/female ratio, as typically, a slightly higher number of females pursue orthodontic treatment.[39] On the other hand, several findings are in line with those of previous studies on different populations, adding validity to the outcomes. This, along with the endemic occurrence of malocclusion and the widespread offer of orthodontic services in modern societies,[39] might justify the extrapolation of the present findings to the general population.

The age range that we considered was defined from 10.5 to 50 years old for availability reasons. In the youngest individuals, as supernumerary teeth or third molars may have developed at a later age, there was a possibility of underestimation of supernumerary tooth formation or overestimation of third molar agenesis. To overcome this limitation, available records from later developmental stages were also examined to confirm diagnosis. In older ages, there was a risk that an extracted third molar could have been considered not formed. This information was reported in the patients' history, and the fact that the vast majority of included individuals were below 20 years old minimizes the risk of misinformation. There was also no indication that the number of missing third molars increased with age (rho = −0.03, $p = .517$; Figure 1). Furthermore, it should be noted that any potential confounding factors are expected to have a similar effect on both the supernumerary and control groups. Therefore, the validity of the comparisons is not considered compromised.

Supernumerary tooth formation can vary in severity and pattern depending on geographic area or ancestry.[19,20] To minimize confounding, only white European subjects were included in the study, as they were overrepresented in the searched archives. However, the present findings might not be generalizable to other populations.

Finally, we employed a well-defined sample of substantial size, comprising orthodontic patients who have been thoroughly documented and closely monitored by specialists over a specified period. This approach minimized the risk of misdiagnosis and led to a satisfactory sample for the study purpose, selected from over 12 000 patient files.[32] However, the relatively limited number of individuals with third molar agenesis might have reduced the statistical power to detect less prevalent traits in the samples. Based on the present data, future studies can take this into account during the sample size calculation process and adjust their design accordingly.

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6 | CONCLUSION

The prevalence of third molar agenesis among individuals with supernumerary teeth was comparable to that of control individuals, with no sexual dimorphism. Nevertheless, the ratio of bilateral to unilateral third molar agenesis was significantly lower in the supernumerary group.

This knowledge is clinically valuable for predicting third molar formation, which aids in diagnosis and treatment planning, particularly in young individuals with complex clinical problems. From a developmental standpoint, the stricter genetic control over tooth agenesis, in contrast to supernumerary tooth formation, may be linked to the evolutionary mechanism of tooth number reduction in humans.

AUTHOR CONTRIBUTIONS

Conceptualization, N.G.; methodology, N.G., L.F. and E.H.; validation, L.F. and E.H.; formal analysis, N.G., L.F. and E.H.; investigation, L.F., E.H., M.A.M., V.F.Z., M.A.P., G.K. and N.G.; resources, L.F., E.H., M.A.M., V.F.Z., M.A.P., G.K. and N.G.; data curation, L.F., E.H., M.A.M., V.F.Z. and G.K.; writing—original draft preparation, N.G., L.F. and E.H.; writing—review and editing, L.F., E.H., M.A.M., V.F.Z., M.A.P., G.K. and N.G.; visualization, N.G., L.F. and E.H.; supervision, N.G.; project administration, N.G. All the authors have read and agreed to the published version of the manuscript.

ACKNOWLEDGEMENTS

We would like to thank all our colleagues who contributed to the selection of this demanding sample. Open access funding provided by Universitat Bern.

FUNDING INFORMATION

There is no funding received for this study.

CONFLICT OF INTEREST STATEMENT

None of the authors have a conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICAL INFORMATION

Ethical approval for the present retrospective study was obtained by the Research Ethics Committees of the cantons of Bern, Neuchatel, Basel and Jura, Switzerland (Protocol Nr: 2022–00399, Date of Approval: 20 June 2022) and the Institutional Ethics and Research Committees of the Dental Schools of the National and Kapodistrian University of Athens (Protocol Nr: 518/05.09.2022, Date of Approval: 13 October 2022) and the Aristotle University of Thessaloniki, Greece (Protocol Nr: 182/10 February 2023, Date of Approval: 16 March 2023). The methods were carried out in accordance with the relevant guidelines and regulations. An informed consent form was signed by all participants before their data were used in the study.

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How to cite this article: Friedli L, Henninger E, Makrygiannakis MA, et al. Third molar agenesis in individuals with supernumerary teeth. *Orthod Craniofac Res*. 2024;00:1-8. doi:10.1111/ocr.12807

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