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The Epidemiology of Third Molar Agenesis and Its Relationship with Craniofacial Growth in Spanish and Peruvian Populations: A Cross-Sectional Study

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Abstract

Congenital third molar (3M) agenesis is a common dental anomaly associated with genetic, epigenetic, and craniofacial growth factors. Evidence regarding its prevalence across populations and its relationship with sagittal and vertical growth patterns remains limited. This study aimed to compare the prevalence of 3M agenesis in Spanish and Peruvian samples and analyze its association with craniofacial growth patterns. A multicenter cross-sectional study was conducted in 1191 patients aged 10–14 years (348 Spanish, 843 Peruvian). 3M agenesis was assessed on digital panoramic radiographs. Sagittal and vertical growth patterns were evaluated using Steiner's cephalometric analysis (ANB and GoGn–SN angles). Overall, 3M agenesis prevalence was 25.1%, with no difference between the Spanish (25.0%) and Peruvian (25.15%) groups. A non-significant trend toward higher prevalence was observed in Spanish females. 3M agenesis was more frequent in maxillary than mandibular 3M (16.8% vs. 10.2%; $p < 0.001$). Growth patterns differed between populations, with Class I and normodivergent patterns predominating in Spanish subjects, and Class II and hyperdivergent patterns in Peruvians ($p < 0.001$). No significant associations were found between 3M agenesis and sagittal or vertical growth patterns ($p > 0.05$), although Class II patients exhibited a higher prevalence of mandibular 3M agenesis (14.8% vs. 10.8%; $p = 0.04$). 3M agenesis showed similar prevalence in both populations and was not associated with craniofacial growth patterns, except for mandibular 3M agenesis in Class II patients, suggesting a multifactorial etiology driven by genetic and developmental factors rather than demographic or skeletal variables. It should be noted, however, that the cross-sectional nature of the study, the recruitment of patients from university dental clinics, and the absence of multivariate regression analysis limit both the generalizability and the causal interpretation of the findings.

Keywords: craniofacial growth; dental agenesis; epidemiology; third molar

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1. Introduction

Third molars (3Ms) erupt between 18 and 25 years of age, making them the last teeth to develop and erupt in humans [1,2]. This fact increases the risk of various pathologies and complications. Among these complications are those related to the position and eruptive process of third molars, their structural and morphological alterations [3,4], and agenesis [2,5].

The congenital absence of teeth, known as dental agenesis, constitutes the most common developmental anomaly affecting the human dentition and may present in isolation or in association with complex syndromes [6,7]. In the permanent dentition, when agenesis does not involve 3Ms, its frequency is estimated at approximately 6.4%, with a preferential distribution in the maxillary lateral incisors and mandibular second premolars, and a higher prevalence in females [8–11].

In contrast, the congenital absence of 3Ms occurs at a notably higher frequency, affecting approximately one-fifth to one-quarter of the population, which has led to its recognition as a common developmental variant of the permanent dentition [11,12]. However, the accumulated evidence indicates that agenesis of other permanent teeth is significantly associated with the absence of 3Ms, increasing their likelihood of occurrence by approximately 40%, which suggests a shared etiological background [13–15].

Various alterations related to the position and development of 3Ms have been associated with the presence of dento-maxillary discrepancies in the permanent dentition [16,17]. In parallel, epidemiological studies have documented a progressive increase in the frequency of 3M agenesis over time [18]. To explain this trend, various evolutionary hypotheses have been proposed, suggesting an adaptation characterized by the gradual reduction in jaw size, accompanied by a higher prevalence of congenital tooth absence [19,20]. In this context, both dental agenesis and dental morphological variations appear to be modulated by common genetic mechanisms, which highlights the complex and tightly regulated nature of dental development.

The scientific literature has identified various genes involved in the regulation of craniofacial and dental development that participate jointly in the occurrence of dental and skeletal alterations, highlighting their essential role in the early stages of morphogenesis and in the organization of the dental pattern. Among the most relevant are MSX1, PAX9, RUNX2, DLX1, DLX2, AXIN2, and EDA, all of which are related to key processes of odontogenesis.

These genes form part of finely controlled signaling pathways that regulate epithelial–mesenchymal interactions, dental germ initiation, and the processes of morphogenesis and cell differentiation. Alterations in their expression, whether in the form of pathogenic variants, mutations, or genetic polymorphisms, can interfere with the molecular networks required for adequate dental development. As a consequence, anomalies may arise in the number, size, shape, or eruption pattern of the teeth, contributing to the emergence of common phenotypic traits across the various presentations of agenesis and dental morphological alterations described [21,22].

The genetic variants responsible for the absence of 3M can simultaneously influence odontogenesis and the craniofacial growth pattern, favoring the emergence of specific skeletal discrepancies, such as hypodivergent growth, Class II or Class III malocclusion, and a reduction in maxillary and mandibular length [10,23–25]. In this context, 3M agenesis may be considered a phenotypic marker of alterations in craniofacial development, reflecting the coordinated action of genes that regulate both dental formation and facial bone morphology [26–28].

Craniofacial growth and 3M development are mediated not only by genetic factors, but also by epigenetic influences, such as biomechanical forces during mastication and the interaction between the dental lamina and the ectomesenchyme [28–30]. In this con-

text, some studies have associated the congenital absence of the 3M with hypodivergent growth, skeletal Class II malocclusion and reductions in maxillary size [23,24,31–33], suggesting that a decrease in jaw dimensions may impact the initiation and progression of odontogenesis, highlighting its clinical relevance as a marker of alterations in craniofacial development [34–36].

On the other hand, the last few decades reported a prevalence range of 3M agenesis between 12.7% and 51.1%. Carter and Worthington attribute the wide variability of these data mainly to the fact that the study samples belonged to different populations, establishing demographic factors as a possible predictor of 3M agenesis [12].

Despite the clinical and anthropological relevance of 3M agenesis, there remains a substantial lack of evidence regarding its prevalence. Furthermore, no multicenter studies have compared this condition in cohorts from distinct continents while simultaneously examining its potential implications for craniofacial growth patterns. In this context, the present study aimed to evaluate and compare the prevalence of 3M agenesis in patients exhibiting various sagittal and vertical craniofacial growth patterns from Spanish and Peruvian samples. This study hypothesized that the prevalence of 3M agenesis may vary according to craniofacial growth pattern and patients' geographic origin, given that dental developmental factors and population-level differences may simultaneously influence both 3M formation and facial skeletal morphology.

2. Materials and Methods

2.1. Study Design

The present multicenter, analytical, cross-sectional observational study received ethical approval from the Research Ethics Committees of the Hospital Clínico San Carlos (CI 19/477-E, Madrid, Spain) and the Faculty of Human Medicine at the Universidad Nacional Mayor de San Marcos (19-0099, Lima, Perú). All procedures were carried out in full compliance with the STROBE statement guidelines. Data collection was conducted over the period spanning 2019 to 2020.

2.2. Sample Size and Participants

Patients aged 10 to 14 years who attended the Dental Schools of the Universidad Complutense de Madrid (Madrid, Spain) and Universidad Nacional Mayor de San Marcos (Lima, Peru) were included as participants during the period 2014–2019. Radiographic analysis was conducted between 2019 and 2020.

The inclusion criteria were non-syndromic patients without major pathologies affecting the 3M region (e.g., cysts or tumors). Patients with orthodontic appliances and those without extraoral digital radiographs or with insufficient resolution were excluded. The procedures used in this study adhere to the guidelines of the Declaration of Helsinki.

Sample size estimation was performed using the global prevalence of 3M agenesis established by Carter et al. (22.63%) [12] as a reference value, with a 95% confidence interval and an accepted margin of error of $\pm$5%. These parameters yielded a minimum required sample of 270 participants per group.

As the study included two independent cohorts—one Spanish and one Peruvian—this target was sought for each population, with adjustments made for potential exclusions or inadequate digital radiographs to ensure reliable prevalence estimates.

2.3. Radiographic Assessment

3M agenesis was evaluated by a single blind operator using the Planmeca Romexis Viewer (Helsinki, Finland) version 4.6.2 software. 3M agenesis was defined as the absence of crown mineralization in the initial and subsequent orthopantomographs (OPGs), if

available, ruling out a clinical history of previous extraction. When uncertainty arose, more than one OPG from the same patient was evaluated to confirm the diagnosis. Patient age was considered in relation to the expected initial 3M formation observable on the OPG [37].

To minimize the risk of false negatives in early-aged patients (10–11 years), subsequent orthopantomographs were reviewed when available; cases lacking radiographic follow-up were excluded from the analysis.

Examiner calibration was performed using 30 radiographs drawn from both populations combined. Intra-examiner agreement was assessed using the kappa statistic, yielding values exceeding 0.85, which indicates excellent intra-examiner reliability.

2.4. Cephalometric Analysis

Sagittal and vertical craniofacial growth patterns and 3M agenesis were analyzed on lateral cephalometric radiographs using the measuring 'straight', 'angle', 'contrast', and 'brightness' tools of the aforementioned software.

ANB and GoGn-SN angles according to Steiner's cephalometric analysis [38] were measured to identify sagittal and vertical growth, respectively. These angles were chosen because they are widely accepted cephalometric parameters: ANB evaluates the sagittal relationship between the maxilla and mandible, while GoGn–SN reflects vertical skeletal divergence. Both show good reproducibility and allow for comparison with previous studies on craniofacial morphology and dentofacial development. Based on these measurements, patients were classified into craniofacial growth patterns. For sagittal growth, 0–4°, >4°, and <0° angles indicated class I, II, and III, respectively, whereas for vertical growth, <28°, 28–36°, and >36° angles indicated hypodivergent, normodivergent, and hyperdivergent patterns [39].

Before data collection, the only evaluator was trained and calibrated with an oral radiologist, obtaining a concordance level of 0.929 (3M agenesis) and intraclass correlation indices of 0.933 (ANB angle) and 0.943 (GoGn-SN angle).

2.5. Statistical Analysis

The data were processed and analyzed using the statistical program SPSS version 25.0 for Windows (IBM, Armonk, NY, USA). Population clusters were studied independently and pooled. Descriptive statistics were calculated for all measured variables. For the age variable, measures of central tendency were calculated, and for the qualitative variables, frequencies and percentages. Student's T-test was used to compare age distribution by origin group, and Fisher's Exact Test for gender and the prevalence of differences in 3M agenesis within origin, sex, and anatomical location.

The association between sagittal and vertical growth patterns was assessed using odds ratios (ORs) with 95% confidence intervals (CIs 95%). The Chi-Square Test was used for intragroup comparisons of growth patterns and of the distribution of 3M agenesis within craniofacial growth patterns in both population groups.

3. Results

3.1. Sample and Demographics

A total of 1738 patients met the inclusion criteria, including 507 of Spanish origin and 1231 of Peruvian origin. Of these, 547 were excluded due to poor-quality radiographs, with exclusions distributed similarly across both origin groups, representing 31.4% of the Spanish sample and 31.6% of the Peruvian sample.

The mean age of the total sample was 12.30 ± 1.45 years, and 57.26% were female. Samples were homogeneous with respect to age and sex (Student's t test and Fisher's exact test, respectively; $p > 0.05$) (Table 1).

Table 1. Demographic characteristics of the sample.

Origin	Sample Size (Patients)	Mean Age	Sex				*p* *	*p* **
			Male		Female			
			n	%	n	%		
Spain	348	12.2 ± 1.5	147	42.2	201	57.8	0.321	0.847
Peru	843	12.3 ± 1.5	362	42.9	481	57.1		
Total sample	1191	12.3 ± 1.5	509	42.7	682	57.1	-	

* Student's *t*-Test for comparison of ages between both groups. ** Fisher's Exact Test for gender distribution according to origin.

3.2. Prevalence of 3M Agenesis by Origin and Sex

Overall, 25.10% of patients had agenesis of at least one 3M, with a mean of 0.53 ± 1.07 missing 3Ms per patient.

Prevalence did not differ between the Spanish and Peruvian groups ($p = 1.000$) (Table 2). When analyzed by sex, the prevalence was also similar, both in the overall sample and in the Peruvian population. However, although no statistically significant differences were observed, a trend was identified in the Spanish population, where 3M agenesis was found in 28.90% of female cases, compared with 19.70% in men ($p = 0.06$) (Table 2).

Table 2. 3M agenesis according to demographic characteristics of the sample.

Origin	Sex	3M Agenesis				Total		*p* *	*p* **
		Yes		No					
		n	%	n	%	n	%		
Spain	Male	29	19.7	118	80.3	147	42.2	0.060	1.000
	Female	58	28.9	143	71.1	201	57.8		
	Total	87	25.0	261	75.0	348	100.0		
Peru	Male	93	25.7	269	74.3	362	42.9	0.810	
	Female	119	24.7	362	75.3	481	57.1		
	Total	212	25.2	631	74.9	843	100.0		
Total sample	Male	122	24.0	387	76.0	509	42.7	0.458	-
	Female	177	26.0	505	74.0	682	57.3		
	Total	299	25.1	892	74.9	1191	100.0		

* Fisher's Exact Test for prevalence of 3M agenesis according to sex. ** Fisher's Exact Test for prevalence of 3M agenesis according to origin.

Patients presenting with a single missing 3M were the most frequent (35.8%), followed by those with 2, 4, and 3 missing 3Ms (34.1%, 18.4%, and 11.7%, respectively). No statistically significant association was found between sex and the number of missing 3M ($p = 0.517$), indicating a similar distribution of agenesis patterns in males and females (Table 3). Similarly, no statistically significant association was observed between geographic origin (Peruvian vs. Spanish) and the number of missing 3Ms ($p = 0.381$) (Table 3).

Table 3. Number of missing 3Ms according to sex and origin.

		Number of Missing 3Ms				*p* *
		1 n (%)	2 n (%)	3 n (%)	4 n (%)	
Sex	Male	63 (35.6%)	56 (31.6%)	21 (11.9%)	37 (20.9%)	0.517
	Female	44 (36.1%)	46 (37.7%)	14 (11.5%)	18 (14.8%)	
	Total	107 (35.8%)	102 (34.1%)	35 (11.7%)	55 (18.4%)	

Table 3. *Cont.*

		Number of Missing 3Ms				
		1 n (%)	2 n (%)	3 n (%)	4 n (%)	*p* *
Origin	Spanish	32 (36.8%)	24 (27.6%)	11 (12.6%)	20 (23.0%)	0.381
	Peruvian	75 (35.4%)	78 (36.8%)	24 (11.3%)	35 (16.5%)	
	Total	107 (35.8%)	102 (34.1%)	35 (11.7%)	55 (18.4%)	

* Chi-Square Test.

3.3. 3M Agenesis According to Location

Of the 4764 3Ms assessed, 641 were congenitally absent (13.50%). Maxillary 3Ms showed a higher prevalence of agenesis than mandibular 3Ms (16.80% vs. 10.20%), with statistically significant differences in the total sample and within both origins (Spain: $p = 0.003$; Peru: $p < 0.001$) (Table 4).

Table 4. 3M agenesis according to maxillary or mandibular location.

Origin	Location	3M Agenesis				*p* *
		Yes		No		
		n	%	n	%	
Spain	Maxilla	116	16.7	580	83.3	**0.003**
	Mandibular	77	11.1	619	88.9	
	Total	193	13.9	1199	86.1	
Peru	Maxilla	283	16.8	1403	83.2	**<0.001**
	Mandibular	165	9.8	1521	90.2	
	Total	448	13.3	2924	86.7	
Total sample	Maxilla	399	16.8	1983	83.2	**<0.001**
	Mandibular	242	10.2	2140	89.8	
	Total	641	13.5	4123	86.5	

* Fisher's Exact Test for prevalence of 3M agenesis according to location. Bold values indicate statistically significant differences ($p < 0.05$).

3.4. Craniofacial Sagittal and Vertical Growth

The mean ANB angle in the total sample was 4.13 ± 2.68°. ANB was higher in the Peruvian group (4.41 ± 2.73°) than in the Spanish group (3.43 ± 2.40°; $p < 0.001$). The most frequent sagittal pattern in the total sample and in the Peruvian group was Class II, followed by Class I and Class III; by contrast, the Spanish group most frequently exhibited Class I, followed by Class II and Class III ($p < 0.001$) (Table 5). The mean GoGn–SN angle was 35.33 ± 5.33°, higher in the Peruvian group (35.93 ± 5.25°) than in the Spanish group (33.90 ± 5.24°; $p < 0.001$). Vertically, the total and Spanish samples were predominantly normodivergent, followed by hyperdivergent and hypodivergent. In the Peruvian group, the hyperdivergent pattern was most frequent, followed by normodivergent and hypodivergent ($p < 0.001$) (Table 5).

Table 5. Distribution of craniofacial sagittal and vertical growth according to origin.

Variables		Origin				*p* *	Total Sample	
		Spain		Peru				
		n	%	n	%		n	%
Sagittal growth pattern	Class I	176	50.6	331	39.3	**<0.001**	507	42.6
	Class II	128	36.8	432	51.3		560	47.0
	Class III	44	12.6	80	9.5		124	10.4

Table 5. *Cont.*

Variables		Origin				p *	Total Sample	
		Spain		Peru				
		n	%	n	%		n	%
Vertical growth pattern	Normodivergent	205	58.9	391	46.4	**<0.001**	596	50.0
	Hypodivergent	38	10.9	52	6.2		90	7.6
	Hyperdivergent	105	30.2	400	47.5		505	42.4
Total		348	29.2	843	70.1	-	1191	100.0

* Chi-Square Test for intragroup comparisons of growth patterns. Bold values indicate statistically significant differences ($p < 0.05$).

3.5. 3M Agenesis by Sagittal Growth Pattern

The mean ANB value recorded in patients presenting with 3M agenesis was $3.99 \pm 2.69^{\circ}$, compared to $4.17 \pm 2.67^{\circ}$ in those without agenesis; however, these differences failed to reach statistical significance in any of the origin groups ($p > 0.05$). Regarding skeletal classification across the total sample, the prevalence of 3M agenesis was 24.3% among Class I patients, 25.0% among Class II patients, and 29.0% among Class III patients. In the Peruvian cohort, corresponding prevalences were 23.9%, 25.0%, and 31.3% ($p = 0.391$). In the Spanish cohort, prevalence was 25.0% across all sagittal classes; no significant differences were identified in either origin group ($p = 1.000$) (Table 6).

Table 6. Distribution of 3M agenesis by sagittal growth pattern and origin.

		Agenesis				p *	Total	
		Yes		No				
		n	%	n	%		n	%
Spain	Class I	44	25.0	132	75.0	1.000	176	50.6
	Class II	32	25.0	96	75.0		128	36.8
	Class III	11	25.0	33	75.0		44	12.6
	Total	87	25.0	261	75.0	-	348	100.0
Peru	Class I	79	23.9	252	76.1	0.391	331	39.3
	Class II	108	25.0	324	75.0		432	51.2
	Class III	25	31.3	55	68.7		80	9.5
	Total	212	25.1	631	74.9	-	843	100.0
Total sample	Class I	123	24.3	384	75.7	0.545	507	42.6
	Class II	140	25.0	420	75.0		560	47.0
	Class III	36	29.0	88	71.0		124	10.4
	Total	299	25.1	892	74.9	-	1191	100.0

* Chi-Square Test for 3M agenesis according to sagittal growth pattern.

No statistically significant association was found between sagittal skeletal pattern and the number of missing 3Ms ($p = 0.182$). Although Class II subjects tended to exhibit a higher proportion of four missing 3Ms, and Class III subjects more frequently presented with two missing 3Ms, these differences did not reach statistical significance (Table 7).

The prevalence of maxillary and mandibular 3M agenesis was analyzed according to sagittal skeletal pattern. No statistically significant association was found between maxillary 3M agenesis and the sagittal pattern ($p = 0.651$). Although the association between mandibular 3M agenesis and sagittal pattern did not reach statistical significance ($p = 0.061$), a trend toward higher prevalence was observed in Class II individuals (Table 8).

Table 7. Number of missing 3Ms according to growth patterns.

		Number of Missing 3Ms				
		1 **n (%)**	**2** **n (%)**	**3** **n (%)**	**4** **n (%)**	***p* ***
Sagittal growth pattern	Class I	49 (39.8%)	43 (35.0%)	15 (12.2%)	16 (13.0%)	0.182
	Class II	48 (34.3%)	42 (30.0%)	16 (11.4%)	34 (24.3%)	
	Class III	10 (27.8%)	17 (47.2%)	4 (11.1%)	5 (13.9%)	
Vertical growth pattern	Hypodivergent	8 (42.1%)	7 (36.8%)	0 (0.0%)	4 (21.1%)	0.638
	Normodivergent	47 (32.0%)	53 (36.1%)	19 (12.9%)	28 (19.0%)	
	Hyperdivergent	52 (39.1%)	42 (31.6%)	16 (12.0%)	23 (17.3%)	

* Chi-Square Test for 3M agenesis according to the number of missing 3Ms.

When Class II individuals were compared with the remaining sagittal patterns combined (Classes I and III), mandibular 3M agenesis was significantly more prevalent in the Class II group (14.8% vs. 10.8%), with this association reaching statistical significance ($p = 0.045$; OR = 1.44, 95% CI: 1.02–2.03) (Table 8).

Table 8. 3M agenesis according to sagittal growth pattern and location.

		n	**Maxillary 3M Agenesis n (%)**	***p* ***	**Mandibular 3M Agenesis n (%)**	***p***
Sagittal growth pattern	Class I	507	107 (21.1%)	0.651	51 (10.1%)	0.061 *
	Class II	560	111 (19.8%)		83 (14.8%)	
	Class III	124	29 (23.4%)		17 (13.7%)	
	Class I + III	631	136 (21.6%)	-	68 (10.8%)	**0.045** †

* Chi-Square Test for intragroup comparisons of growth pattern according to agenesis location. † Chi-Square Test (comparing mandibular 3M agenesis in Class II patients vs. the remaining sagittal skeletal patterns. Bold values indicate statistically significant differences ($p < 0.05$).

3.6. 3M Agenesis by Vertical Growth Pattern

Patients with 3M agenesis had a GoGn–SN of 35.45 ± 5.00°, versus 35.29 ± 5.43° in those without agenesis; differences were not statistically significant ($p > 0.05$). In the total sample, 3M agenesis prevalence was 24.7% in normodivergent, 21.1% in hypodivergent, and 26.3% in hyperdivergent subjects. Distributions were similar across origins without significant differences ($p > 0.05$) (Table 9).

Table 9. Distribution of 3M agenesis by vertical growth pattern and origin.

		Agenesis				***p* ***	**Total**	
		Yes		**No**				
		n	**%**	**n**	**%**		**n**	**%**
Spain	Normodivergent	48	23.4	157	76.6	0.420	205	58.9
	Hypodivergent	8	21.1	30	78.9		38	10.9
	Hyperdivergent	31	29.5	74	70.5		105	30.2
	Total	87	25.0	261	75.0	-	348	100.0
Peru	Normodivergent	99	25.3	292	74.7	0.789	391	46.4
	Hypodivergent	11	21.2	41	78.8		52	6.2
	Hyperdivergent	102	25.5	298	74.5		400	47.4
	Total	212	25.1	631	74.9	-	843	100.0
Total sample	Normodivergent	147	24.7	449	75.3	0.540	596	50.0
	Hypodivergent	19	21.1	71	78.9		90	7.6
	Hyperdivergent	133	26.3	372	73.7		505	42.4
	Total	299	25.1	892	74.9	-	1191	100.0

* Chi-Square Test for 3M agenesis according to vertical growth pattern.

No statistically significant association was found between vertical skeletal pattern and the number of missing 3M ($p = 0.21$). Although normodivergent and hyperdivergent individuals tended to present a higher proportion of three or more missing 3M compared with hypodivergent subjects, these differences were not statistically significant. Similarly, no statistically significant associations were observed between maxillary or mandibular agenesis and vertical growth pattern ($p = 0.581$ and $p = 0.529$, respectively) (Table 10).

Table 10. 3M agenesis according to vertical growth pattern and location.

		n	Maxillary 3M Agenesis n (%)	p *	Mandibular 3M Agenesis n (%)	p *
Vertical growth pattern	Hypodivergent	596	120 (20.1%)	0.581	78 (13.1%)	0.529
	Normodivergent	90	16 (17.8%)		8 (8.9%)	
	Hyperdivergent	505	111 (22.0%)		65 (12.9%)	

* Chi-Square Test for intragroup comparisons of growth pattern according to agenesis location.

4. Discussion

This multicenter study aimed to analyze whether demographic factors are determining elements in the congenital absence of 3Ms and if it is related to skeletal growth. The sample was selected considering both the average age of 3M initial mineralization radiographic evidence and when these teeth are typically extracted, thereby maximizing diagnostic accuracy [40–43], and both patient groups were shown to be homogeneous in terms of age and sex.

Spanish and Peruvian populations exhibited similar prevalences of 3M agenesis, 25% and 25.15%, respectively. These findings are consistent with those reported by Gómez de Diego et al. [31], Hattab et al. [44], John et al. [20], Kilinç et al. [45], Sandhu et al. [46], and Huang et al. [32], who described comparable 3M agenesis prevalence results, affecting approximately one-quarter of the populations analyzed. Overall, these findings suggest that demographic factors may not be a primary determinant of congenital 3M absence, contrary to previous assumptions. However, Carter and Worthington, in their systematic review, reported a lower prevalence of 3M agenesis among African populations (5.74%), whereas Asian populations exhibited the highest prevalence (29.71%) [12]. Angelakopoulos et al. [47] conducted a study in Black and White South African populations, reporting that the prevalence of 3M agenesis was significantly higher in White South Africans (28.42%) compared with Black South Africans (6.81%). Notably, Hirakata et al. [48] reported an even higher prevalence of 41.7% in a Japanese orthodontic population. In the same systematic review, South American (18.19%) and European (21.60%) populations demonstrated lower prevalences than those observed in the present study [12]. In this regard, Kanavakis et al. [49] demonstrated that 3M agenesis occurs at relatively comparable rates across various European and South American populations, supporting the notion that ethnic origin alone does not constitute a determining factor in the congenital absence of 3M. Variations in dental agenesis frequency across demographic groups may reflect a substantial role of phenotypic characteristics within specific populations [11,12,49].

In the cohort examined here, Spanish female subjects exhibited a trend toward greater prevalence of 3M agenesis compared to their male counterparts, although this difference did not reach statistical significance ($p = 0.060$). This pattern is consistent with observations reported across Caucasian, Asian, and Black populations, where a predominance of dental agenesis among females over males has been documented [10,18,20,50–53]. While certain investigations have excluded 3M from their analyses, studies incorporating 3M

have yielded analogous results, confirming a higher rate of 3M agenesis among female individuals [51].

Carter and Worthington [12] attribute these results to reduced mandibular size in women; however, this hypothesis does not fully account for sex-related differences in dentition, and other factors may also play a relevant role, like the age-related differences in development [12,20]. In females, the growth of maxillary and mandibular lengths decelerates after 12 and 14 years of age, respectively, while in males, significant growth continues until the age of 16 years [53]. Additionally, the formation of the M3 crypt initiates considerably later after birth, particularly among female individuals [20].

With respect to anatomical location, agenesis was observed more frequently in the upper 3M in both population groups (Spain, $p < 0.003$; Peru, $p < 0.001$). These results are in agreement with those reported by Goyal et al. [54], John et al. [20], and Singh et al. [50], all of whom documented a greater prevalence of 3M agenesis in the maxilla relative to the mandible. This finding may be explained by the earlier completion of maxillary growth during adolescence, which represents approximately half the anteroposterior growth magnitude observed in the mandible over the same developmental period [20,54].

In the literature, it has been identified that limited dimensions of jaws and tooth agenesis are produced by genetic factors, such as MSX1 mutations [21,55]. However, further investigation on the genes related to agenesis is needed, especially if this phenomenon occurs in a non-syndromic form [7]. Also, epigenetic factors, such as lower mastication forces [28] and the lack of an adequate interaction between dental lamina and ectomesenchyme [29,30], also play a crucial role. In this sense, recent studies have reported that 3M agenesis is significantly related to hypodivergent growth [23,24,31,32] and class II skeletal malocclusion [33]. Nonetheless, it remains unclear whether a causal relationship exists, in which direction it operates, or whether both conditions arise from the same underlying factors [28,56]. Furthermore, according to the concept of the dental anomaly pattern proposed by Brook, variations in tooth number may reflect multifactorial developmental alterations rather than direct morphological constraints of the jaws [57].

Analysis of the ANB angle revealed significantly lower values in the Spanish cohort compared to the Peruvian cohort, with the Spanish group predominantly displaying a Class I skeletal pattern and the Peruvian group a Class II pattern; these intergroup differences attained statistical significance. Likewise, the Spanish group showed a significantly lower GoGn–SN angle compared with the Peruvian group, predominantly displaying a normodivergent pattern, whereas the Peruvian group was mainly hyperdivergent.

However, no statistically significant differences were found when relating 3M agenesis to sagittal skeletal classification in either population group, in agreement with the results reported by Cocos et al. [24], Fernandez et al. [25], and Sánchez et al. [58]. In contrast, Huang et al. [32], Alam et al. [34] and Moghadam et al. [35] established that the ANB angle was significantly lower in patients with lower 3M agenesis. Differences could stem from some of the studies being carried out in Asian [34] and African [35] populations.

No association was found with the number of missing 3Ms either, although Class II patients more frequently presented with four missing 3Ms and Class III patients with three. However, a significant association was identified between mandibular 3M agenesis and Class II skeletal pattern. These findings are consistent with those of Alam et al. [34] and Ota et al. [33], who observed that Class II subjects of Chinese and Japanese origin, respectively, exhibited a significantly higher prevalence of 3M agenesis than Class I and Class III patients. This association has been attributed to reduced mandibular length or alterations in craniofacial development, factors that may interfere with the formation of the mandibular 3M germ [59,60].

In contrast, Huang et al. [32] reported a significantly lower prevalence of 3M agenesis in Class II patients. These discrepancies may be attributable to the fact that Ota et al. [33] exclusively evaluated Class II division 2 patients, unlike the present study, which included all three sagittal patterns, and, once again, to the higher prevalence of 3M agenesis reported in Asian populations [12].

However, the evidence is not uniform [32], as factors such as the specific Class II division assessed, intra-Asian genetic variability, and differences in vertical growth patterns may all influence outcomes. Taken together, this suggests that the observed association reflects shared underlying factors rather than a direct causal relationship, and that future studies with larger sample sizes and stratification by Class II subtypes are warranted to clarify this finding.

No differences were found in 3M agenesis in relation to the GoGn–SN angle, consistent with Fernández et al. [25] and with the findings of Celikoglu et al. [18], who, using the SN–GoMe angle in a manner analogous to the methodology applied in the present study, did not identify a characteristic craniofacial growth pattern associated with 3M agenesis. In contrast, Gómez de Diego et al. [31] observed that facial height was significantly reduced in patients with 3M agenesis. Similarly, the results of the present study differ from those reported by Huang et al. [32], who found that the GoGn–SN angle was significantly smaller in patients with 3M agenesis.

Likewise, the prevalence of 3M agenesis was comparable across the three vertical craniofacial growth patterns, with no differences identified in either the location or number of missing 3Ms. These findings are consistent with those reported by Alam et al. [34], Cocos et al. [24], and Fernández et al. [25]. However, the results of the present study diverge from those of Gómez de Diego et al. [31], Huang et al. [32], Moghadam et al. [35], Ramiro-Verdugo et al. [23], and Sánchez et al. [58], who observed that hypodivergent individuals exhibited a significantly higher prevalence of 3M agenesis compared with hyperdivergent patients.

The results of this study provide valuable information for general dentists and orthodontists in the planning, monitoring, diagnosis, and treatment of young patients. Knowledge of the prevalence and distribution of 3M agenesis across different populations enables more targeted radiographic assessment during critical developmental windows (10–14 years), thereby avoiding delayed diagnoses or unnecessary interventions. Furthermore, the findings reinforce the importance of a comprehensive approach that considers family history and the individual characteristics of each patient, beyond demographic origin or craniofacial morphology, ultimately contributing to more personalized protocols in preventive and orthodontic dentistry.

Nevertheless, certain limitations inherent to the present study should be acknowledged when interpreting the findings. Primarily, the diagnosis of 3M agenesis relied solely on radiographic assessment combined with the review of clinical records. Although participants were selected within an age range deemed optimal for maximizing diagnostic accuracy, the possibility of delayed 3M mineralization cannot be entirely excluded.

Second, the study population consisted of patients treated at university dental clinics, most of whom had orthodontic needs. Since craniofacial growth alterations are more frequent in orthodontic populations, this may have introduced selection bias and limited the generalizability of the results to the general population. Additionally, socioeconomic factors that may influence both 3M agenesis and craniofacial development were not accounted for. The cross-sectional design of the study and the absence of multivariate analyses limit the ability to establish causal relationships and to control for potential confounding factors.

Third, the Peruvian population exhibits high genetic heterogeneity because of historical processes of admixture and regional diversity. This variability may have influenced the

results and masked potential associations between ancestry, craniofacial growth patterns, and 3M agenesis, as no genetic analyses were performed. Therefore, although the results do not support a direct relationship between craniofacial growth patterns and 3M agenesis, future studies incorporating genetic and epigenetic markers are warranted to better elucidate the underlying mechanisms involved.

Consequently, while the present findings contribute relevant information regarding the prevalence and distribution of 3M agenesis, future research should consider expanding the sample size, incorporating general population samples, accounting for socioeconomic factors, and conducting genetic and epigenetic analyses to better elucidate the underlying mechanisms and enhance the generalizability of the findings.

5. Conclusions

The prevalence of 3M agenesis was similar in patients of Spanish and Peruvian ancestry. These findings suggest that demographic factors may not be primary determinants of congenital 3M absences. Despite the craniofacial growth pattern differences identified between the Spanish and Peruvian cohorts, such variations did not translate into significant differences in the prevalence of 3M agenesis, with the exception of Class II patients, who exhibited a higher prevalence of mandibular 3M agenesis.

A tendency toward elevated 3M agenesis prevalence was noted among female subjects, most prominently within the Spanish cohort, a finding that corroborates prior evidence and points to a potential role of developmental factors and sexual dimorphism in the etiology of 3M agenesis. Additionally, maxillary location was identified as a relevant factor in the occurrence of 3M agenesis.

These findings should nonetheless be interpreted with caution, given the cross-sectional design of the study, the recruitment of patients from university dental clinics, and the absence of multivariate regression analysis, all of which limit the generalizability of the results and the assessment of causal relationships.

Overall, the results support the hypothesis that 3M agenesis is a multifactorial condition, likely influenced by complex interactions among genetic, epigenetic, and developmental factors, rather than by demographic origin or craniofacial growth patterns in isolation.

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Abbreviations

The following abbreviations are used in this manuscript:

3M	Third Molars
OPG	Orthopantomograph
ANB	A point (A), Nasion (N), B point (B)
GoGn-SN	Gonion (Go), Gnathion (Gn), Sella (S), Nasion (N)

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