Prevalence and patterns of permanent tooth agenesis in Down syndrome and their association with craniofacial morphology

Sunjay Suri[a]; Bryan D. Tompson[b]; Eshetu Atenafu[c]

ABSTRACT

Objective: To (1) document the prevalence and patterns of hypodontia (permanent tooth agenesis) in Down syndrome (DS) and (2) explore whether maxillary or mandibular hypodontia or simultaneous agenesis of all third molars was associated with differential alterations of the craniofacial morphology.

Materials and Methods: Longitudinal panoramic radiographs of 25 white patients with DS (12 male, 13 female; mean age, 15.1 years) treated at The Hospital for Sick Children, Toronto, Ontario, Canada, were evaluated to document hypodontia. Cephalometric measurements of subjects with maxillary or mandibular hypodontia or agenesis of all third molars were compared with those of subjects without hypodontia in these regions using analysis of covariance adjusted for age, gender, and proportion of other missing teeth in the total number of missing teeth.

Results: Hypodontia was seen in 92% of the sample when third molars were considered and in 56% when third molars were not considered. Hypodontia was more prevalent and severe in females. The most frequently agenetic teeth were maxillary and mandibular third molars > maxillary lateral incisors > mandibular second premolars > mandibular incisors > maxillary second premolars > maxillary second molars. Simultaneous agenesis of all third molars was seen in 52% of the sample. Maxillary hypodontia was not associated with significant regional craniofacial differences, while mandibular hypodontia was associated with decreased mandibular length and increased ramus:body ratio. Agenesis of all third molars was not associated with significant craniofacial differences.

Conclusions: Hypodontia is widely prevalent in DS. The effect of the syndrome appears to be stronger than that of regional hypodontia in differentially altering the craniofacial morphology. (*Angle Orthod.* 2011;81:260–269.)

KEY WORDS: Down syndrome; Hypodontia; Dental agenesis; Missing teeth; Craniofacial morphology; Cephalometrics

INTRODUCTION

Down syndrome (DS) is the most well known and common chromosomal disorder in humans.[1] Recent birth statistics in the United States show an increasing prevalence, currently observed at 11.8 per 10,000 births.[2] Cephalometric analyses of subjects with DS have described platybasia, reduced maxillary and mandibular alveolar heights, short teeth, reduced maxillary and mandibular dimensions, and forward rotation of the maxillary and mandibular planes, which collectively lead to overclosure and relative mandibular prognathism.[3–12] Hypodontia in DS is well known,[12–22] with prevalence documented at about 90%[12,19,20] if the third molars are considered and between 30%[13] and

[a] Assistant Professor, Discipline of Orthodontics, Faculty of Dentistry, University of Toronto, Ontario, Canada, and Staff Orthodontist, The Hospital for Sick Children, Toronto, Ontario, Canada.

[b] Associate Professor and Head, Discipline of Orthodontics, Faculty of Dentistry, University of Toronto, Ontario, Canada, and Head, Division of Orthodontics, The Hospital for Sick Children, Toronto, Ontario, Canada.

[c] Biostatistician, Child Health Evaluative Services, The Hospital for Sick Children, Toronto, Ontario, Canada.

Corresponding author: Dr Sunjay Suri, Discipline of Orthodontics, Faculty of Dentistry, University of Toronto, Rm 519B, 124 Edward St, Toronto, Ontario M5G 1G6 Canada (e-mail: sunjaysuri@hotmail.com)

Accepted: September 2010. Submitted: July 2010.

DOI: 10.2319/070910-391.1

60%[22] when the third molars are not considered in the analysis. A very high prevalence of total agenesis of all third molars has also been described.[19]

Numerous investigator groups around the world have explored associations between hypodontia and significant alterations in craniofacial morphology in nonsyndromic samples[23–31] and craniofacial anomalies such as ectodermal dysplasia[32,33] and Pierre Robin sequence.[34] Whether an association exists between the location of hypodontia and differential alterations in the regional craniofacial morphology in DS is unknown. This investigation aimed (1) to document the prevalence and patterns of hypodontia (permanent tooth agenesis) in DS, (2) to explore whether maxillary and mandibular hypodontia are associated with greater alteration of the regional craniofacial morphology within DS, and (3) to explore whether agenesis of all third molars is associated with greater alteration of craniofacial morphology within the syndrome.

MATERIALS AND METHODS

This retrospective investigation was conducted using longitudinal panoramic and pretreatment cephalometric radiographs of white patients with DS treated at The Hospital for Sick Children, Toronto, Ontario, Canada, whose pretreatment radiographic records had been acquired before July 2009. The hospital's Research Ethics Board (REB) approved the study.

Radiographic and clinical records of 25 white subjects with DS (12 males, 13 females; mean age, 15.1 years; range, 11.5–18.3 years) were available. Birth, gender, dentition, and treatment details were recorded. Hypodontia was defined and verified as the absence of one or more permanent teeth due to agenesis. The subjects' preorthodontic treatment cephalograms were traced by a single experienced digitizer and analyzed using Dentofacial Planner cephalometric software (Dentofacial Software, Toronto, Ontario, Canada). Other radiographs and clinical charts were reviewed longitudinally to confirm the occurrence and location of the permanent tooth agenesis. Cephalometric measurements specific to the craniofacial regions of interest were made according to the definitions in Tables 1 and 2 (Figure 1). An intraclass correlation coefficient (ICC) analysis of measurements from repeated tracings of one-third of the cephalograms revealed a high level of repeatability (the average ICC was .99).

The null hypotheses framed were that maxillary and mandibular hypodontia were not associated with significant differences in the cephalometric measurements of these regions and that agenesis of all third molars in DS was not associated with significant differences in craniofacial measurements. To test these null hypotheses, the sample was first categorized into maxillary hypodontia and mandibular hypodontia subgroups based on the location of permanent tooth agenesis. Between-group comparisons of measurements representative of the region of interest (maxilla or mandible) were analyzed by a two-way analysis of covariance (ANCOVA) or Friedman's nonparametric ANCOVA, adjusted for age and gender. Similarly, measurements of subjects exhibiting absence of all third molars were compared with those without this presentation. Since dental agenesis is frequently observed in both jaws in DS,[12–22] ANCOVA tests were additionally adjusted for the proportion of other missing teeth (vs in the regions of interest) in the total number of missing teeth. Statistical tests were conducted using SAS (version 9.1; SAS Institute Inc, Cary, NC). Differences were considered significant when $P < .05$.

RESULTS

Hypodontia was prevalent in 92% of our sample with DS when third molars were considered (Table 3). Almost all patients were missing one or more permanent teeth (Figure 2). The average number of missing permanent teeth per affected subject was 4.74. Two subjects did not show hypodontia (Figure 3). Hypodontia was more prevalent among females (100%) than males (83.3%), and the severity in females was also greater. The average number of missing teeth was 5.38 in affected females and 4.10 in males. Among females, 23.1% were missing all quadrant analogues of at least two tooth types. This severe pattern was seen less often in males (16.7%). Among subjects affected by hypodontia, bilateral absence of the same tooth type was also generally more prevalent in females (Table 4).

Mandibular hypodontia was slightly more prevalent (80%) than maxillary hypodontia (76%) and was much more frequent than maxillary hypodontia in males, whereas the opposite was seen in females (Table 3). In subjects with hypodontia, the average number of missing teeth in the mandible was 2.39 and 2.35 in the maxilla. Although slightly greater numbers of missing teeth were recorded on the right (52.3%) than on the left (47.7%), maxillary and mandibular hypodontia for specific tooth types, when unilateral, was relatively more frequent on the left (72.7%).

When frequencies of hypodontia of individual teeth were examined, the most frequently agenetic teeth were (in decreasing order) maxillary and mandibular third molars > maxillary lateral incisors > mandibular second premolars > mandibular incisors > maxillary second premolars > maxillary second molars. Maxillary lateral incisors and mandibular incisors were missing much more frequently in females (Table 3).

Table 1. Landmarks and Definitions Used in Cephalometric Analysis

Landmark	Definition
Conventional landmarks	
Ba	Basion
Na	Nasion
S	Sella
Po	Porion
Or	Orbitale
ANS	Anterior nasal spine
PNS	posterior nasal spine
Sn	Subnasale
A	Subspinale (A point)
Pr	Prosthion
Co	Condylion
Go	Gonion
Me	Menton
Gn	Gnathion
Pg	Pogonion
B	Supramentale (B point)
Id	Infradentale
Idl	Lingual point infradentale
Ptm	Pterygomaxillary fissure
Specific landmarks used in this study	
Prl	Lingual prosthion
Al	Lingual A point
pamaxj (palate-anterior maxillary junction)	Most superoanterior point on palatal contour of basal anterior maxilla
mamax (midpoint of anterior maxillary base)	Midpoint of line drawn from paramax to Sn
amaxaj (anterior maxilla-alveolar junction)	Midpoint of a line drawn from Al to A
Malvmx (midpoint of anterior alveolus, maxillary)	Midpoint of line drawn from Prl to Pr
pAPmd (posterior alveolar point, mandibular)	Most posteroinferior mid planed point on the anterior border of the ascending ramus
Inf Go (inferior gonion)	Midplaned point on the lower border of the mandible where the convexity at gonion merges with the concavity of the antegonial notch
RBS (ramus body syncline)	Point of intersection of a line drawn from Inf Go to PAPmd with the cortical outline of the midplaned mandibular nerve
Bl (lingual point B)	Point of intersection of a line drawn from RBS to B with the lingual contour of the symphysis
saj (symphysis-alveolar junction)	Midpoint of a line drawn from Bl to B
Pgl (lingual point pogonion)	Most prominent point on the lingual contour of the symphysis, as located by the greatest perpendicular distance from a line drawn from saj to Me
malvmd (midpoint of anterior alveolus, mandibular)	Midpoint of line drawn from Id(l) to Id

When agenesis of permanent teeth other than third molars was considered, a prevalence of 56% was noted, with greater prevalence in the maxilla (40%) than in the mandible (32%). The average number of teeth missing per affected subject was 2.78 (maxillary, 1.36; mandibular, 1.43). Bilateral absence of a tooth type other than the third molars was seen to be associated with concurrent absence of all third molars in 90% of instances. Simultaneous agenesis of all third molars was seen in 52% of the sample, with greater prevalence in females (61.5%) than males (41.7%).

All subjects with maxillary hypodontia exhibited agenesis of at least one maxillary third molar, and 84.2% were missing both maxillary third molars. Comparison of the maxillary measurements of subjects having maxillary hypodontia with those without maxillary hypodontia revealed no significant differences in any of the measurements, both with and without the additional adjusting for the proportion of other (ie, mandibular) missing teeth in the total number of missing teeth (Table 5).

On the other hand, all subjects with mandibular hypodontia were missing at least one mandibular third molar, and 80% had agenesis of both mandibular third molars. Comparison of mandibular cephalometric measurements of subjects having mandibular hypodontia with those without mandibular hypodontia (Table 6) revealed a significantly smaller body length (by 4.8 mm; $P = .015$) and a greater ramus:body ratio (by 15%; $P = .017$). These differences remained significant even when additional adjusting was applied for the proportion of other (ie, maxillary) missing teeth in the total number of missing teeth. Other cephalometric measurements were not significantly different.

Cephalometric comparison of subjects having agenesis of all third molars and those without this severe presentation (Table 7) showed reduced divergence between the maxillary plane and S-N (1.85°; $P =$

Table 2. Linear and Angular Measurements Made in Cephalometric Analysis

Measurement	Description
Anterior cranial base length	Length of the line drawn from S to N
Posterior cranial base length	Length of the line drawn from Ba to S
Pituitary fossa diameter	Greatest sagittal dimension of pituitary fossa
ST elevation to FHP	Perpendicular distance from S to FHP (Frankfort Horizontal Plane)
ST to Ptm	Perpendicular distance from S to Ptm
Posterior maxillary height	Perpendicular distance from S to PNS
Cranial base angle	Internal angle Ba-S-Na
Maxillary length	Length of the line drawn from PNS to ANS
Maxillary anterior basal width	Length of the line drawn from Snl to Sn
Maxillary anterior apical width	Length of the line drawn from Al to A
Anterior maxillary height	Length of perpendicular dropped from amaxaj to PNS-ANS
Maxillary anterior alveolar height	Length of line drawn from amaxaj to malvmx
Palatal/anterior maxillary deflection	Internal angle between the palatal plane (ANS-PNS) and line drawn from amaxaj to mamax
Mandibular length	Length of the line drawn from Co to Gn
External ramal length	Length of the line drawn from Co to Go
Internal ramal length	Length of the line drawn from Co to RBS
External body length	Length of the line drawn from Go to Gn
Internal body length	Length of the line drawn from RBS to Gn
Gonial angle	Angle Co-Go-Gn
Internal mandibular deflection	Angle Co-RBS-Gn
Mandibular posterior alveolar height	Length of the perpendicular dropped from PAPmd to RBS-B
Mandibular posterior body height	Length of the perpendicular dropped from Inf Go to RBS-B
Mandibular anterior alveolar height	Length of the line drawn from malvmd to saj
Symphyseal height	Length of the line drawn from the saj to Me
Symphyseal thickness	Sum of the lengths of perpendiculars dropped from Pg and Pgl to a line drawn from saj to Me
Mandibular/symphyseal deflection	Internal angle between Go-Gn and the line drawn from saj to Me
Ramal width	Length of the line drawn from the midplaned deepest points on the posterior and anterior borders of the ramus
Mandibular anterior apical base width	Length of the line drawn from Bl to B
U1_ maxillary plane	Perpendicular distance of U1 crown tip to ANS-PNS
U6_ maxillary plane	Perpendicular distance of U6 crown tip to ANS-PNS
L1_mandibular plane	Perpendicular distance of L1 crown tip to Go-Me
L6_mandibular plane	Perpendicular distance of L6 crown tip to Go-Me

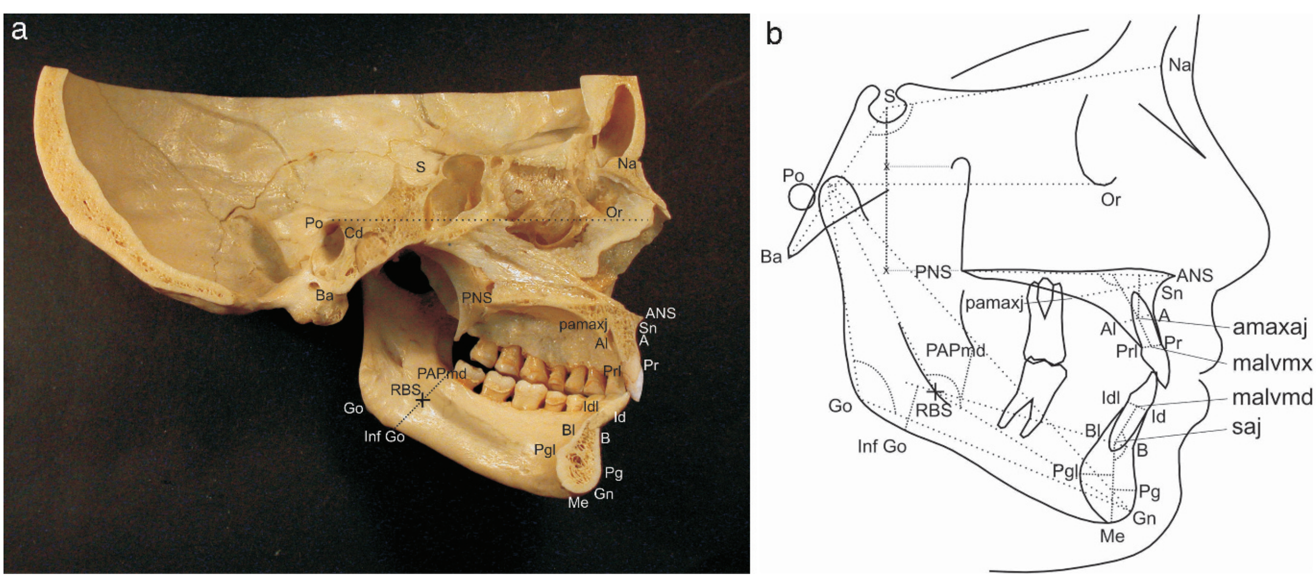

Figure 1. Cephalometric (a) landmarks and (b) measurements.

Table 3. Prevalence and Patterns of Permanent Tooth Agenesis Observed

Permanent Tooth Agenesis Pattern	Prevalence in Total Sample (n = 25)	Prevalence in Males (n = 12)	Prevalence in Females (n = 13)
Hypodontia (including third molar hypodontia)	92% (n = 23)	83.3% (n = 10)	100% (n = 13)
Hypodontia (excluding third molar hypodontia)	56% (n = 14)	41.7% (n = 5)	69.2% (n = 9)
Maxillary hypodontia (including third molar hypodontia)	76% (n = 19)	58.3% (n = 7)	92.3% (n = 12)
Maxillary hypodontia (excluding third molar hypodontia)	40% (n = 10)	25% (n = 3)	53.8% (n = 7)
Mandibular hypodontia (including third molar hypodontia)	80% (n = 20)	75% (n = 9)	84.6% (n = 11)
Mandibular hypodontia (excluding third molar hypodontia)	40% (n = 10)	33.3% (n = 4)	46.2% (n = 6)
Maxillary third molar hypodontia	76% (n = 19)	58.3% (n = 7)	92.3% (n = 12)
Mandibular third molar hypodontia	76% (n = 19)	66.7% (n = 8)	84.6% (n = 11)
Maxillary lateral incisor hypodontia	28% (n = 7)	8.3% (n = 1)	46.2% (n = 6)
Mandibular incisor hypodontia	20% (n = 5)	8.3% (n = 1)	30.8% (n = 4)
Mandibular second premolar hypodontia	24% (n = 6)	25% (n = 3)	23.1% (n = 3)
Maxillary second premolar hypodontia	12% (n = 3)	16.6% (n = 2)	7.7% (n = 1)
Maxillary second molar hypodontia	4% (n = 1)	0 (n = 0)	7.7% (n = 1)
Simultaneous agenesis of all third molars	52% (n = 13)	41.7% (n = 5)	61.5% (n = 8)

.035), and their ramus:body ratio was larger (by 9%; $P = .010$). However, when the comparison was additionally adjusted for the proportion of other missing teeth in the total number of missing teeth, these differences were not significant. No other cephalometric differences were statistically significant.

DISCUSSION

The prevalence of hypodontia varies in different ethnic groups and regions of the world.[35] While the third molars are the teeth most frequently affected by agenesis, when third molars are not considered, the

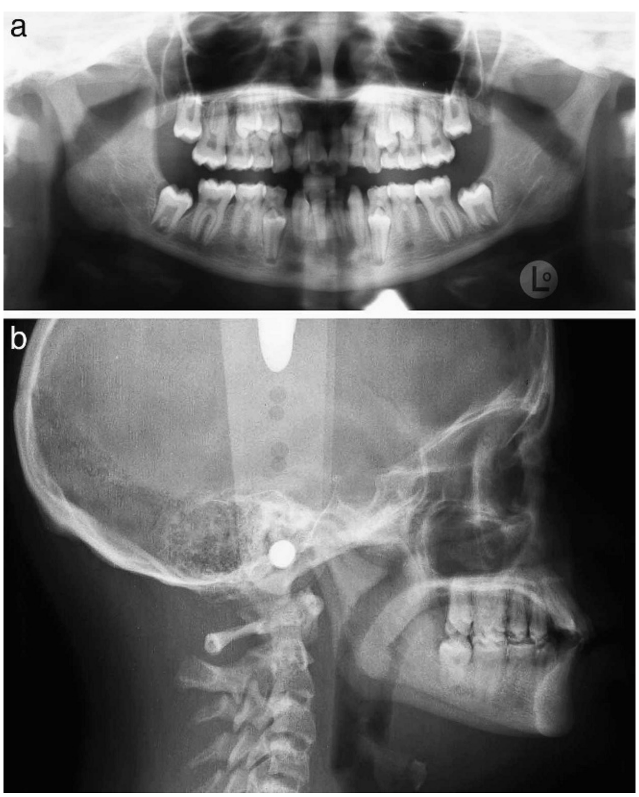

Figure 2. Radiographs of a subject with Down syndrome with a large number of missing permanent teeth.

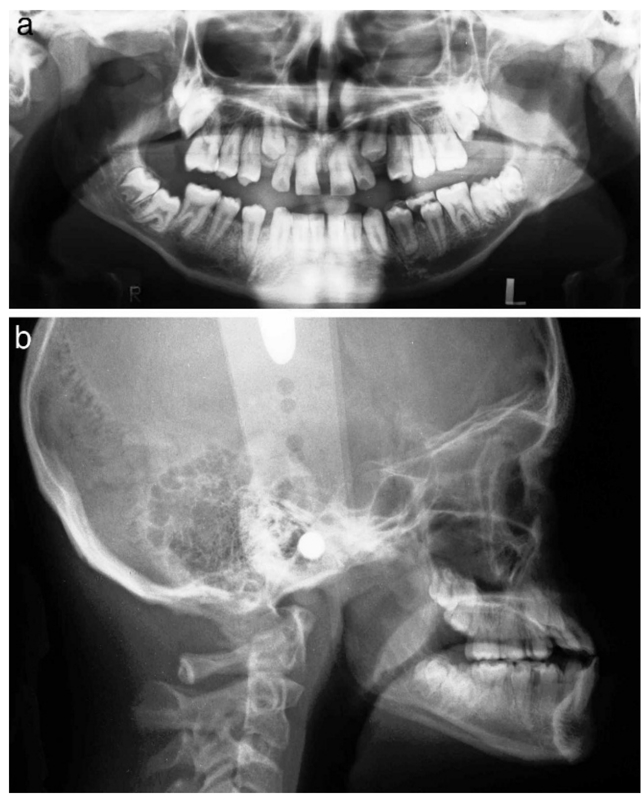

Figure 3. Radiographs of a subject with Down syndrome without any permanent tooth agenesis.

Table 4. Prevalence of Bilateral Permanent Tooth Agenesis Observed Within Subjects Having Specific Types of Permanent Tooth Agenesis

Bilateral Occurrence of Permanent Tooth Agenesis	Prevalence of Bilateral Occurrence in Affected Subjects	Prevalence of Bilateral Occurrence in Affected Males	Prevalence of Bilateral Occurrence in Affected Females
Hypodontia	87% (20 of 23)	80% (8 of 10)	92.3% (12 of 13)
Maxillary hypodontia	94.7% (18 of 19)	85.7% (6 of 7)	100% (12 of 12)
Mandibular hypodontia	90% (18 of 20)	88.9% (8 of 9)	90.9% (10 of 11)
Maxillary third molar hypodontia	84.2% (16 of 19)	71.4% (5 of 7)	91.6% (11 of 12)
Mandibular third molar hypodontia	84.2% (16 of 19)	87.5% (7 of 8)	81.8% (9 of 11)
Maxillary lateral incisor hypodontia	71.4% (5 of 7)	100% (1 of 1)	66.6% (4 of 6)
Mandibular incisor hypodontia	80% (4 of 5)	100% (1 of 1)	75% (3 of 4)
Mandibular second premolar hypodontia	83.3% (5 of 6)	100% (3 of 3)	66.6% (2 of 3)
Maxillary second premolar hypodontia	100% (3 of 3)	100% (2 of 2)	100% (1 of 1)
Maxillary second molar hypodontia	100% (1 of 1)	0	100% (1 of 1)

prevalence of hypodontia reported from North America ranges from 3.5%[36] to 7.4%,[37] with slightly greater prevalence in females. Most studies report that mandibular second premolars, maxillary lateral incisors, maxillary second premolars, and mandibular central incisors are the teeth most often affected (in decreasing order).[35] In DS, the prevalence of hypodontia is much greater and more severe[12–22] and is recognized as a characteristic phenotypical feature of the syndrome.

In the nonsyndromic population, hypodontia may have multiple causes.[38] In DS, it has been hypothesized that altered peripheral nervous system growth and abnormal development of localized chondral elements[16] may contribute as potential mechanisms responsible for the greater occurrence of dental agenesis. A recent report described that trigeminal nerve fiber growth and patterning are integrated with tooth morphogenesis, and the report hypothesized that mesenchymal dental follicles fail to form as a result of inadequate local epithelial-mesenchymal interactions due to thyroid deficiency, causing delayed proliferation of nerve cells and decreased rate of neuron production in DS.[21] Another reason described earlier implicates poor terminal vascularization of developing tooth buds, causing complete or partial odontoblast degeneration.[18]

Prevalence rates of agenesis of one or more third molar in the nonsyndromic population have been reported to be between 9%[39] and 30.8%[40] in North America, while the prevalence of simultaneous agenesis of all third molars is much lower, ranging from 0.50%[39] to 2.3%.[40] The reported prevalence of third molar agenesis in DS is much higher. It was noted in

Table 5. Comparison of Regional Cephalometric Measurements of Subjects With Down Syndrome Having Maxillary Hypodontia With Those Not Having Maxillary Hypodontia[a]

Measurement	Mx Hypodontia (±Md Hypodontia) (n = 19)		Complete Mx Dentition (±Md Hypodontia) (n = 6)		ANCOVA (Adjusted for Age and Gender), *P* Value	ANCOVA (Adjusted for Age, Gender, and Proportion of Other Missing Teeth in Total Missing Teeth), *P* Value
	LS Mean	SE	LS Mean	SE		
Cranial base angle, °	140.01	0.90	141.26	1.70	.538	.993
Pituitary fossa diameter, mm	10.70	0.53	10.84	0.99	.911	.461
ST elevation, mm	15.97	0.78	15.67	1.48	.864	.442
S-PNS, mm	38.35	0.52	36.92	0.97	.227	.500
S-Ptm, mm	11.40	0.59	9.83	1.11	.242	.815
Maxillary length, mm	47.87	0.70	47.56	1.32	.842	.858
Maxillary anterior apical width, mm	11.83	0.71	11.93	1.33	.949	.948
Maxillary anterior basal width, mm	18.19	0.85	18.46	1.60	.755[b]	.712[b]
Anterior maxillary height, mm	7.90	0.26	7.40	0.50	.402	.551
Maxillary anterior alveolar height, mm	9.29	0.38	9.31	0.71	.978	.186
Palatal anterior maxillary deflection, °	52.82	2.77	54.18	5.21	.825	.229
U1_maxillary plane, mm	24.22	0.73	23.50	1.38	.664	.911
U6_maxillary plane, mm	21.78	0.57	22.31	1.07	.676	.103
N-ANS:ANS-Me, %	76.38	1.69	80.13	3.18	.327	.870
S-Go:N-Me, %	65.90	1.24	62.60	2.34	.243	.834
FHP/Go-Gn, °	19.97	1.55	21.42	2.91	.887[b]	.890[b]

[a] Least squared (LS) means displayed in this table have been adjusted for age and gender.

[b] Indicates that Friedman's nonparametric analysis of covariance (ANCOVA) was used due to nonnormal data distribution for this variable.

Table 6. Comparison of Regional Cephalometric Measurements of Subjects With Down Syndrome Having Mandibular Hypodontia With Those Not Having Mandibular Hypodontia[a]

Measurement	Md Hypodontia (±Mx Hypodontia) (n = 20)		Complete Md Dentition (±Mx Hypodontia) (n = 5)		ANCOVA (Adjusted for Age and Gender), *P* Value	ANCOVA (Adjusted for Age, Gender, and Proportion of Other Missing Teeth in Total Missing Teeth), *P* Value
	LS Mean	SE	LS Mean	SE		
Mandibular length, mm	112.80	1.55	113.36	3.12	.874	.539
Internal ramal length, mm	60.54	0.97	56.73	1.95	.096	.207
Internal body length, mm	56.43	0.91	61.23	1.83	.015*[,b]	.011*[,b]
Internal ramus:body ratio	1.08	0.02	0.93	0.04	.017*[,b]	.003**[,b]
Ramal width, mm	33.00	0.88	32.37	1.76	.753	.687
Symphyseal thickness, mm	13.62	0.34	12.57	0.68	.185	.574
Symphyseal height, mm	20.64	0.58	20.21	1.17	.874b	.957[b]
Mandibular anterior apical width, mm	8.94	0.27	8.22	0.55	.253	.607
Mandibular posterior body height, mm	11.89	0.55	10.24	1.10	.195	.572
Mandibular posterior alveolar height, mm	10.17	0.45	11.80	0.91	.125	.145
Mandibular anterior alveolar height, mm	8.36	0.51	9.14	1.03	.509	.334
Internal mandibular deflection, degree	149.97	1.52	148.82	3.06	.742	.660
Gonial angle, °	121.47	1.51	122.51	3.04	.764	.948
Mandibular plane symphyseal deflection, °	76.36	1.63	74.22	3.27	.566	.766
L1_mandibular plane, mm	39.03	0.78	39.79	1.58	.504[b]	.791[b]
L6_mandibular plane, mm	29.65	0.69	29.37	1.39	.841[b]	.770[b]
N-ANS:ANS-Me, %	77.94	1.61	74.65	3.23	.373	.875
S-Go:N-Me, %	65.72	1.18	62.63	2.37	.257	.346
FHP/Go-Gn, °	20.17	1.47	20.90	2.96	.826	.815

[a] Least squared (LS) means displayed in this table have been adjusted for age and gender.
[b] Indicates that Friedman's nonparametric analysis of covariance (ANCOVA) was used due to nonnormal data distribution for this variable.
* $P < .05$; ** $P < .01$.

88% of our sample, similar to the 84.4% reported by Lomholt et al.[20] from Denmark but greater than the 74% reported by Shapira et al.[19] from Israel. Agenesis of all third molars was seen in 52% of our sample, similar to the 55% reported by Shapira et al.[19]

Because of the frequent agenesis of all third molars in our sample, we explored whether this occurrence was associated with any specific craniofacial features. Russel and Kjaer[41] hypothesized that an association in DS between the sella turcica structure and the innervations determined occurrence of tooth agenesis due to the proximity of sella to the trigeminal ganglion. In our cephalometric analysis, specific measurements (pituitary fossa diameter, sella turcica elevation from FHP, posterior maxillary vertical height, and the vertical distance of sella from the pterygomaxillary fissure) were included to explore whether the sella and vertical growth of the infrasellar region were differentially affected in individuals with DS having maxillary hypodontia and agenesis of all third molars, respectively.

In the regional cephalometric comparison of subjects having maxillary hypodontia with those without maxillary hypodontia, none of the measurement differences, including those specific for the vertical growth of the sella region, were statistically significant (Table 5). The null hypothesis could not be rejected. On the other hand, in the comparison of regional measurements of subjects having mandibular hypodontia with those without mandibular hypodontia, a significant decrease in body length, with a consequent increase in the ramus:body ratio, was found (Table 6). A decrease in body length can teleologically be argued to result from the shorter dental lamina (all subjects with mandibular hypodontia had unilateral mandibular third molar agenesis, and 80% had bilateral agenesis). However, this argument was not supported by results of tests for maxillary hypodontia or agenesis of all third molars. The differences in most of the measurements, including mandibular plane angle, face:height ratio, and Jarabak's ratio, were not significant. These results did not allow for fully rejecting the null hypothesis for the mandibular hypodontia analysis.

Finally, subjects with agenesis of all third molars, when compared with those having at least one third molar, were seen to have relatively less divergence between the anterior cranial base and the palatal plane and an increase in the ramus:body ratio, but none of the other differences, nor those specific to the sella region, were statistically significant (Table 7). Even these two differences were not statistically significant when the analysis was additionally adjusted for the proportion of other missing teeth. The paucity of significant differences did not allow rejecting the null hypothesis for agenesis of all third molars.

Table 7. Comparison of Cephalometric Measurements of Subjects With Down Syndrome Having Agenesis of All Third Molars With Those Having at Least One Third Molar Present[a]

	Agenesis of All Third Molars (±Hypodontia of Other Teeth) (n = 13)		At Least One Third Molar Present (±Hypodontia of Other Teeth) (n = 12)		ANCOVA (Adjusted for Age and Gender), *P* Value	ANCOVA (Adjusted for Age, Gender, and Proportion of Other Missing Teeth in Total Missing Teeth), *P* Value
Measurement	LS Mean	SE	LS Mean	SE		
S-N, mm	65.16	0.88	64.76	0.92	.761	.897
Ba-S, mm	44.61	0.71	44.29	0.74	.763	.186
Total cranial base length, mm	109.77	1.21	109.05	1.26	.955[b]	.427[b]
Cranial base angle, °	140.21	1.08	140.42	1.13	.896	.110
Pituitary fossa diameter, mm	10.76	0.63	10.72	0.65	.966	.522
ST elevation, mm	16.47	0.92	15.29	0.96	.390	.213
S-PNS, mm	38.17	0.73	37.32	0.76	.438	.894
S-Ptm, mm	11.37	0.74	10.81	0.77	.613	.717
Maxillary length, mm	48.35	0.82	47.20	0.85	.348	.686
S-N/maxillary plane, °	7.64	0.61	9.49	0.63	.035*[,b]	.663[b]
Ba-N/maxillary plane, °	23.66	0.66	25.41	0.68	.329[b]	.648
Maxillary anterior apical width, mm	11.08	0.81	12.69	0.84	.189	.588
Maxillary anterior basal width, mm	17.25	0.97	19.34	1.01	.155	.391
Anterior maxillary height, mm	7.85	0.32	7.70	0.33	.529[b]	.069[b]
Maxillary anterior alveolar height, mm	8.92	0.43	9.69	0.45	.242	.098
Palatal anterior maxillary deflection, °	55.48	3.22	50.61	3.36	.314	.905
U1_maxillary plane, mm	24.55	0.86	23.50	0.90	.417	.122
U6_maxillary plane, mm	21.54	0.67	22.30	0.70	.446	.106
Mandibular length, mm	113.66	1.94	112.09	2.02	.585	.542
Internal ramal length, mm	61.37	1.21	58.06	1.26	.095[b]	.646[b]
Internal body length, mm	56.16	1.22	58.72	1.28	.168	.245
Internal ramus:body ratio	1.09	0.02	1.00	0.03	.010*[,b]	.100[b]
Ramal width, mm	33.96	1.05	31.70	1.10	.354[b]	.518[b]
Symphyseal thickness, mm	13.36	0.45	13.47	0.46	.864	.140
Symphyseal height, mm	20.37	0.73	20.76	0.76	.449[b]	.429
Mandibular anterior apical width, mm	8.69	0.35	8.91	0.37	.669	.422
Mandibular posterior body height, mm	11.73	0.72	11.37	0.75	.734	.403
Mandibular posterior alveolar height, mm	9.91	0.57	11.14	0.60	.161	.445
Mandibular anterior alveolar height, mm	8.58	0.65	8.45	0.68	.891	.971
Internal mandibular deflection, °	151.38	1.85	147.96	1.93	.281[b]	.902[b]
Gonial angle, °	122.89	1.88	120.37	1.95	.369	.599
Mandibular plane symphyseal deflection, °	75.89	2.06	75.97	2.15	.981	.439
L1_mandibular plane, mm	39.25	0.99	39.11	1.03	.920	.758
L6_mandibular plane, mm	29.92	0.86	29.23	0.90	.591	.771
N-ANS:ANS-Me, %	76.33	2.04	78.31	2.12	.515	.334
N-Me, mm	106.89	2.24	105.52	2.33	.680	.171
S-Go, mm	71.14	1.67	69.50	1.74	.509	.237
S-Go:N-Me, %	66.08	1.50	64.04	1.56	.364	.944
FHP/Go-Gn, °	20.13	1.85	20.52	1.93	.900[b]	.434[b]
Ba-N/Co-Gn, °	68.51	1.22	70.23	1.27	.346	.593

[a] Least squared (LS) means displayed in this table have been adjusted for age and gender.
[b] Indicates that Friedman's nonparametric analysis of covariance (ANCOVA) was used due to nonnormal data distribution for this variable.
* $P < .05$.

The strengths and limitations of this study should be considered. Confirming hypodontia from longitudinal radiographs ensured that hypodontia patterns were accurately recorded without false-positives. Only pre-orthodontic treatment cephalograms were analyzed to avoid patient reinclusions and confounding cephalometric data by treatment effects. Only white subjects were included to avoid confounding effects of ethnicity on hypodontia patterns and cephalometric measurements. These considerations, however, limited the number of subjects included. Because of the large prevalence (92%) of hypodontia in the sample, the number of subjects without any hypodontia was too small to allow cephalometric comparison of the regional hypodontia subgroups with a subgroup having DS but without any missing permanent teeth.

Except for the association of mandibular hypodontia with significant differences in body length and ramus:body ratio, when the statistical analyses were additionally adjusted for the relative proportion of other missing teeth (vs those in the region of cephalometric interest) removed from statistical significance the few other measurements that were significantly different fell out of the range of statistical significance. This indicated that the high overall frequency of missing teeth possibly compounded any differential effect of regional hypodontia on the craniofacial morphology. Keeping these considerations in perspective, and recognizing the known severe craniofacial features of DS, it can be cautiously interpreted that widely prevalent hypodontia in the sample may have contributed to altered craniofacial morphology, but the effect of the syndrome and its characteristic short, under erupted teeth on craniofacial and dentoalveolar dimensions appeared to be stronger than any differential effect regional hypodontia may have had on altering regional craniofacial morphology. Similarly, agenesis of third molars was not associated with further differential alterations in their craniofacial characteristics or with diminished vertical growth proximal to the sella.

CONCLUSIONS

- The prevalence of hypodontia noted in the sample with DS was 92%, with the average number of missing teeth per affected subject being 4.74 when third molars were considered, and when third molars were not considered, the prevalence was 56%, with the average number of missing teeth per affected subject being 2.78.
- Hypodontia was more prevalent and severe in females.
- The most frequently agenetic teeth were (in decreasing order) maxillary and mandibular third molars > maxillary lateral incisors > mandibular second premolars > mandibular incisors > maxillary second premolars > maxillary second molars.
- Maxillary hypodontia was not associated with significant differences in maxillary morphology.
- Mandibular hypodontia was associated with smaller body length and increased ramus:body ratio, but other dimensions were not significantly different.
- Agenesis of all third molars was associated with a small decrease in maxillary plane to cranial base divergence and increase in ramus:body ratio, but these differences were not significant when the analysis was additionally adjusted for the proportion of other missing teeth in the total number of missing teeth.

ACKNOWLEDGMENT

The authors would like to acknowledge the contribution of Lynn Cornfoot in tracing and digitizing the cephalograms.

REFERENCES

1. Hannekam RCM, Krantz ID, Allanson JE. *Gorlin's Syndromes of the Head and Neck*. 5th ed. New York, NY: Oxford University Press; 2010.
2. Shin M, Besser LM, Kucik JE, Lu C, Siffel C, Correa A, et al. Prevalence of Down syndrome among children and adolescents in 10 regions of the United States. *Pediatrics*. 2009; 124:1565–1571.
3. Kisling E. *Cranial Morphology in Down's Syndrome: A Comparative Roentgencephalometric Study in Adult Males*. Copenhagen, Denmark: Munksgaard; 1966.
4. Baer PN, Coccaro PJ, Baer MJ, Kilham L. Craniofacial manifestation of virus-induced Mongolism in the hamster and Down's syndrome in man. *Am J Orthod*. 1971;60: 221–234.
5. Frostad WA, Clea UJF, Melosky LC. Craniofacial complex in the Trisomy 21 syndrome (Down's syndrome). *Arch Oral Biol*. 1971;16:707–722.
6. Fink GB, Madaus WK, Walker GF. A quantitative study of the face in Down's syndrome. *Am J Orthod*. 1975;67: 540–553.
7. Fischer-Brandies H, Schmid RG, Fischer-Brandies E. Craniofacial development in patients with Down's syndrome from birth to 14 years of age. *Eur J Orthod*. 1986;8:35–42.
8. Fischer-Brandies H. Cephalometric comparison between children with and without Down's syndrome. *Eur J Orthod*. 1988;10:255–263.
9. Quintanilla JS, Biedma BM, Rodriguez MQ, Mora MT, Cunqueiro MM, Pazos MA. Cephalometrics in children with Down's syndrome. *Pediatr Radiol*. 2002;32:635–643.
10. Gosman SD, Vineland NJ. Facial development in mongolism. *Am J Orthod*. 1951;37:332–349.
11. Alio JJ, Lorenzo J, Iglesias C. Cranial base growth in patients with Down syndrome: a longitudinal study. *Am J Orthod Dentofacial Orthop*. 2008;133:729–737.
12. Suri S, Tompson B, Cornfoot L. Cranial base, maxillary, and mandibular morphology in Down syndrome. *Angle Orthod*. 2010;80:861–869.
13. Cohen MM, Blitzer FJ, Arvystas MG, Bonneau RH. Abnormalities of the permanent dentition in trisomy G. *J Dent Res*. 1970;49(6 suppl):1386–1393.
14. Orner G. Congenitally absent permanent teeth among mongols and their sibs. *J Ment Defic Res*. 1971;15:292–302.
15. Jensen GM, Cleall JF, Yip AS. Dentoalveolar morphology and developmental changes in Down's syndrome (trisomy 21). *Am J Orthod*. 1973;64:607–618.
16. Russell BG, Kjaer I. Tooth agenesis in Down syndrome. *Am J Med Genet*. 1995;55:466–471.
17. Kumasaka S, Miyagi A, Sakai N, Shindo J, Kashima I. Oligodontia: a radiographic comparison of subjects with Down syndrome and normal subjects. *Spec Care Dent*. 1997;17:137–141.
18. Mestrovic SR, Rajic Z, Papic JS. Hypodontia in patients with Down's syndrome. *Coll Antropol*. 1998;22(suppl):69–72.
19. Shapira J, Chaushu S, Becker A. Prevalence of tooth transposition, third molar agenesis, and maxillary canine impaction in individuals with Down syndrome. *Angle Orthod*. 2000;70:290–296.
20. Lomholt JF, Russell BG, Stoltze K, Kjær I. Third molar agenesis in Down syndrome. *Acta Odontol Scand*. 2002;60: 151–154.
21. Reuland-Bosma W, Reuland MC, Bronkhorst E, Phoa KH. Patterns of tooth agenesis in patients with Down syndrome in relation to hypothyroidism and congenital heart disease:

an aid for treatment planning. *Am J Orthod Dentofacial Orthop*. 2010;137:584.e1–584.e9.
22. Acerbi AG, de Freitas C, de Magalhães MH. Prevalence of numeric anomalies in the permanent dentition of patients with Down syndrome. *Spec Care Dent*. 2001;21:75–78.
23. Wisth PJ, Thunold K, Boe OE. The craniofacial morphology of individuals with hypodontia. *Acta Odontol Scand*. 1974; 32:281–290.
24. Nodal M, Kjaer I, Solow B. Craniofacial morphology in patients with multiple congenitally missing permanent teeth. *Eur J Orthod*. 1994;16:104–109.
25. Ogaard B, Krogstad O. Craniofacial structure and soft tissue profile in patients with severe hypodontia. *Am J Orthod Dentofacial Orthop*. 1995;108:472–477.
26. Yuksel S, Ucem T. The effect of tooth agenesis on dentofacial structures. *Eur J Orthod*. 1997;19:71–78.
27. Endo T, Ozoe R, Yoshino S, Shimooka S. Hypodontia patterns and variations in craniofacial morphology in Japanese orthodontic patients. *Angle Orthod*. 2006;76:996–1003.
28. Bauer N, Heckmann K, Sand A, Lisson JA. Craniofacial growth patterns in patients with congenitally missing permanent teeth. *J Orofac Orthop*. 2009;70:139–151.
29. Ben-Bassat Y, Brin I. Skeletal and dental patterns in patients with severe congenital absence of teeth. *Am J Orthod Dentofacial Orthop*. 2009;135:349–356.
30. Sanchez MJ, Vincente A, Bravo LA. Third molar agenesis and craniofacial morphology. *Angle Orthod*. 2009;79:473–478.
31. Acharya PN, Jones SP, Moles D, Gill D, Hunt NP. A cephalometric study to investigate the skeletal relationships in patients with increasing severity of hypodontia. *Angle Orthod*. 2010;80:511–518.
32. Bondarets N, McDonald F. Analysis of vertical facial form in patients with severe hypodontia. *Am J Phys Anthropol*. 2000;111:177–184.
33. Johnson EL, Roberts MW, Guckes AD, Bailey LJ, Phillips CL, Wright JT. Analysis of craniofacial development in children with hypohidrotic ectodermal dysplasia. *Am J Med Genet*. 2002;112:327–334.
34. Suri S, Ross RB, Tompson B. Mandibular morphology and growth with and without hypodontia in Pierre Robin sequence. *Am J Orthod Dentofacial Orthop*. 2006;130: 37–46.
35. Polder BJ, Van't Hof MA, Van der Linden FP, Kuijpers-Jagtman AM. A meta-analysis of the prevalence of dental agenesis of permanent teeth. *Community Dent Oral Epidemiol*. 2004;32:217–226.
36. Glenn FB. Incidence of congenital missing permanent teeth in a private pedodontic practice. *J Dent Child*. 1961;28: 317–320.
37. Thompson GW, Popovich F. Probability of congenitally missing teeth: results in 1191 children in the Burlington Growth Centre in Toronto. *Community Dent Oral Epidemiol*. 1974;2:26–32.
38. Vastardis H. The genetics of human tooth agenesis: new discoveries for understanding dental anomalies. *Am J Orthod Dentofacial Orthop*. 2000;117:650–656.
39. Nanda RS. Agenesis of third molar in man. *Am J Orthod*. 1954;40:698–706.
40. Hellman M. Our third molar teeth, their eruption, presence and absence. *Dental Cosmos*. 1936;78:750–762.
41. Russell BG, Kjaer I. Postnatal structure of the sella turcica in Down syndrome. *Am J Med Genet*. 1999;87:183–188.