Third molar agenesis in Down syndrome

Jens Fog Lomholt, Björn G. Russell, Kaj Stoltze and Inger Kjær

Departments of Orthodontics and Periodontology, School of Dentistry, Faculty of Health Sciences, University of Copenhagen, Denmark; Copenhagen County Hospital for Handicapped Children, Vangedehuse, Gentofte, Denmark

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The frequency, gender, and maxillary/mandibular occurrences of third molar agenesis have been studied in a Danish population of Down syndrome individuals (39 F and 51 M). The study was based on radiological examination and compared with 2 control groups of normal Caucasian populations. We found that the occurrence of third molar agenesis in Down syndrome individuals was around 4 times greater than in a normal population and higher than in corresponding previous studies. The agenesis occurred more often in the maxilla than in the mandible, and the frequency was not significantly higher in females than in males. The present study stresses the importance of focusing on the dental germs in the phenotypic discussion, as different genes are involved in tooth formation. The absence of teeth can contribute to an understanding of the interaction between genotype and phenotype. □ *Genetics; odontogenesis; tooth agenesis; trisomy*

Inger Kjær, Department of Orthodontics, School of Dentistry, Faculty of Health Sciences, University of Copenhagen, Nørre Allé 20, DK-2200 Copenhagen, Denmark. E-mail: ik@odont.ku.dk

In a normal population, the frequency of agenesis of third molars is reported to be higher than that of other teeth in the permanent dentition. The frequency of agenesis of third molars reported in the literature depends on the population studied. Thus, Peltola et al. (1) reported the frequency to be 17% in the Estonian population; Clayton (2) 20% in the Kansas population; Lavelle et al. (3) 20% in the British population; Garn et al. (4) 16.4% in the Ohio population; and Bredy et al. (5) 20.7% in the German population.

In the maxilla and mandible, different frequencies of agenesis of third molars have also been reported in normal populations. Scherngell (6) reported the frequency in the maxilla to be 29.6% compared to 26.3% in the mandible. This is in contrast to the findings of Bredy et al. (5), which did not show a significant difference. It has also been stated that the frequency of agenesis of third molars is highest in the mandible. Thus, Davies (7) found agenesis in the mandible to be 13.6% as against 11.0% in the maxilla.

In several studies, gender preference is reported indicating a higher frequency of third molar agenesis and a higher frequency of agenesis in general in the dentition among females (8–12).

The incidence of agenesis in dentitions, apart from agenesis of third molars, varies: Clayton (2) reported 6%, Brown (13) 4.2%, Gimnes (14) 4.5%, Davies (7) 5.9%, Hunstadbraaten (12) 10.1%, and Rølling (15) 7.8%. Furthermore, the frequency of agenesis is higher in subjects with agenesis of one or more third molars. Thus, Bredy et al. (5) reported the frequency to be 27.6% and Davies 45% (7). Agenesis has also been associated with a decrease in size and variation in shape (4). This suggests a common genetic basis for agenesis in the human dentition.

Agenesis is seen isolated, with variating inheritance, as demonstrated by Thomsen (16), Huskins (17), Alvesalo (18), or in connection with syndromes (19), especially craniofacial syndromes; for a complete review, see (20). This is the case in holoprocencephaly (21), ectodermal dysplasia (22), and Down syndrome (23). The dental agenesis seen in the above-mentioned phenotypes is the result of alterations in the genetic basis and of an unknown genotypic influence on development of the dentofacial region.

These findings indicate that different patterns in molecular signalling occur in different regions in the dentoalveolar region during development.

The frequency of agenesis is higher among individuals with Down syndrome than in a normal population. Russell & Kjær (23) demonstrated agenesis, excluding third molars, as occurring in 81% of the Down syndrome individuals examined. Shapira et al. (24) showed a frequency of 59% in the permanent dentition excluding third molars. Only Russell & Kjær (23) found a significant gender difference, with a higher frequency of agenesis among males than among females with Down syndrome.

The area of agenesis in the Down syndrome dentition is found to differ from that of the normal population, which is mandibular second premolar, maxillary second premolar, lateral incisor and mandibular central incisor (15). Thus, Russell & Kjær (23) reported the following order: mandibular central incisor, maxillary lateral incisor, maxillary second premolar and mandibular second premolar. The results of Shapira et al. (24) show the following, different order of frequency: maxillary lateral incisor, mandibular incisors, maxillary second premolar and mandibular second premolar.

Investigations on the agenesis of third molars among Down syndrome individuals are sparse. In one study (25),

Table 1. Frequency of third molar agenesis in the Down syndrome group and in the normal populations

Population	Investigated (No.)			Agenesis (No.)			Agenesis (%)		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
Down/present investigation	39	51	90	34	42	76	87.2	82.4	84.4
Normal/Thompson et al. (26)	237	284	521	54	62	116	22.8	21.8	22.3
Normal/Bredy et al. (7)	1,125	936	2,061	262	165	427	23.3	17.6	20.7

based on a population of 129 individuals ranging from 3 to 40 years of age, 48% of maxillary third molars and 46.3% of mandibular third molars were missing. In another Down syndrome study the frequency of third molar agenesis was 74% in a material of 28 subjects, and more third molars were missing in the maxilla than in the mandible, the ratio being 13:5. No significant gender difference was found by Shapira et al. (24).

One purpose of the present study was to elucidate the frequency of agenesis of third molars in a population of Danish-born Down syndrome individuals. A further purpose was to reveal a possible gender difference and intermaxillary difference in this population. A final purpose was to elucidate the connection between the clinical findings and the genetics behind tooth agenesis.

Subjects and methods

Ninety persons with Down syndrome, trisomy 21 (39 F and 51 M), institutionalized or home-bound in Copenhagen County, were included in this investigation. All received dental care at the County Hospital for Handicapped Children, Vangedehuse. They were all above the age of 11 years and were examined radiologically, including orthopantomographic and enoral radiographs or enoral radiographs alone. The study was approved by the Danish Central Scientific Ethics Committee.

To have the best obtainable estimate of a reference to a normal Caucasian population, the pooled samples from two studies (5, 26) were used. The largest study from Bredy et al. (5) consisted of 2,061 (1,125 F, 936 M) orthodontic patients between 12 and 36 years of age. The other was a Canadian study from Thompson et al. (26) on 521 children (237 F and 284 M) at the age of 16 years (Table 1). The reference sample for the present study thus added up to 2,582 individuals (1,362 F and 1,220 M).

Statistical methods

The differences in distribution of third molar agenesis between the Down and the normal population were analysed using the Fisher exact test or chi-square test, whenever the underlying assumptions were fulfilled (27). Level of significance 0.05.

Results

The Down population can be assumed to have the highest frequency of agenesis of third molars (Table 1). An absolute difference of 63.4% between the frequencies of agenesis was found when the Down and the reference group were compared (chi-square = 196.48, df = 1, $P < 0.00001$, Table 1).

In the Down population it was found that the frequency of agenesis of third molars was of the same magnitude in females and males ($P \sim 0.7469$; Table 1). This is in contrast to the reference group, where a significant higher frequency of agenesis of third molars could be demonstrated for females compared to males (chi-square = 8.18, df = 1, $P = 0.00424$; Table 1).

In the analysis of the intermaxillary difference of third molar agenesis, the Down population more often demonstrate agenesis in the maxilla compared to the mandible; however, agenesis in both jaws simultaneously was the most frequently observed (Table 2).

Discussion

The aetiology of dental agenesis is not yet fully understood. The pathogenesis behind comprises interaction of different tissues in the dentofacial region, variously controlled by genetic factors via signalling molecules, growth factors, etc. In our study, we found a higher frequency of third molar agenesis in a Down syndrome sample (84.4% among 90 individuals) than that found by Shapira et al. (24), who registered a frequency of 71.4% in a sample of 28 individuals. The higher frequency in our study might be explained by the age difference of those investigated in the 2 studies: in our group, the youngest individuals investigated were 11 years of age; in the Shapira et al. (24) study the investigations started at 14 years of age.

According to a study on normal individuals the third molars are visible as an eruptional follicle on radiographs, the first of 9 developmental stages according to Garn et al. (28), at a mean age of 8.6 years for females and 8.7 years

Table 2. Distribution of third molar agenesis in the present study

Agenesis	Maxilla	Mandible	Bimaxillary	No agenesis
Individuals	15	3	58	14

for males, with an 85 percentile of 10.2 years for males and females (28). This might not apply to Down syndrome individuals, as they show a general retardation in growth, development and maturation (29). Therefore the mean age for the presence of follicle stage concerning Down individuals can be expected to be higher than 8.7 years.

In this connection, one might suspect more false-positive results in our study than in the study by Shapira et al. (24), resulting in a higher frequency of agenesis. For the same reason, the study on third molar agenesis in Down syndrome by Jensen et al. (25) was not used as a standard of reference, because their sample ranged from 3 to 40 years of age.

Compared with the reference group, we found an almost 4 times higher frequency of third molar agenesis in Down individuals. This was expected, and agenesis is accordingly classified as a characteristic phenotypical feature in Down syndrome. A higher frequency of agenesis is also seen in the Down permanent dention when third molars are excluded (23).

The present study on Down syndrome shows a higher proportion of third molar agenesis in the maxilla than in the mandible, in contrast to the situation in normal populations, where agenesis is most pronounced in the mandible (7, 26, 30), but in accordance with the situation in the Down population studied by Shapira et al. (24).

Down syndrome individuals have a shorter palate than that seen in a normal population (24, 31). This could indicate a general lack of growth and retarded maturation in the maxillary complex, which might also affect the dentition, including the third molars. This is a possible explanation of the higher frequency of agenesis of the maxillary third molars.

There are many local factors in the dentofacial region that are relevant to dental agenesis, among which the oral mucosa, the supporting tissues and the nerve tissue have been elucidated by Kjær et al. (32). A malfunction in any of these tissues compromises odontogenesis, ultimately resulting in agenesis. Concerning the genetic and molecular basis controlling odontogenesis, experimental studies have revealed subtle interactions of transcription factors and growth factors over time (for review, see 33).

In relation to agenesis of the permanent molars, a mutation in the homeobox gene MSX-1, causing haploinsufficiency in the MSX1 transcription factor, was found in family members affected by dental agenesis, especially of premolars and third molars (34). In a kindred study showing varying agenesis of mainly permanent molars, no mutation in MSX1 was found (35), but instead a mutation in PAX9 (36). This was approved in a similar kindred study expressing molar agenesis, but with a different mutation in PAX9 (37).

One might express the genetic control of odontogenesis as a multi-hit function, i.e. that different genes are involved. Mutations in different genes interfere at separate stages in odontogenesis in particular and influence penetrance and expressivity in general, causing differences in dental phenotypes.

In Down syndrome, the genotype is known to differ. Thus, meiotic non-disjunction of the 21st chromosome pair is seen in 95% of cases. In 4%, a Robertsonian translation of chromosome 21q and usually the long arm of chromosome 14 or 22 are seen. Finally, 21q21 translocation, Mosaic Down syndrome and partial trisomy 21 are seen in the remainder of cases (38).

The frequency of agenesis in Down syndrome individuals is presumably related to their deviant genotype. It has been shown by Delabar et al. (39) that specific regions in chromosome 21 contribute to the phenotypic feature of Down syndrome. Down syndrome chromosome region (DCR), located on q22.2 covering 0.4–3 Mb, is associated with such features as short stature, hypotonia, and mental retardation. D21S55-MX1 on q22.2 and part of q22.3 spanning 6Mb, including DCR, is involved in facial and dermatoglypic anomalies. These tissues share a common embryological origin with those involved in odontogenesis, i.e. neuronal, mesenchymal, and ectodermal origin. One might therefore suspect that these same regions/loci are crucial in the aetiology of agenesis, but further research is needed to elucidate this subject.

The present study calls attention to the importance of implementation of the dental germs as a phenotypical characteristic in future studies to contribute to a deeper understanding of the mutual interaction between the genotype and phenotype of syndromes.

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