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Dental developmental disturbances in 50 individuals with the 22q11.2 deletion syndrome; relation to medical conditions?

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Abstract

Objective. The aims of the study were to examine tooth and enamel disturbances in individuals with 22q11.2 deletion syndrome and to analyze associations with medical conditions, birth characteristics and blood values of calcium and PTH. ***Materials and methods.*** Fifty individuals participated in the study (27 females, median age 10 years, range 1.5–44). Congenital absence of teeth was studied on orthopantomograms; 1148 teeth were examined, both clinically and radiologically, and enamel hypomineralizations and hypoplasias were recorded. Medical history and findings were recorded as part of a larger study on the manifestations of 22q11.2-deletion syndrome in Norway. ***Results.*** Tooth agenesis was observed in 15% of study participants. Sixty-six percent of the participants and 26.0% of teeth presented with enamel disturbances. Of these, 12 individuals (24.0%) and 215 teeth (18.7%) had hypomineralizations and four individuals (8.0%) and 86 teeth (7.5%) had hypoplasias. Seventeen participants (34.0%) presented with both types of disturbance, but rarely in the same tooth. Only two teeth (0.17%) had both types of disturbance. Hypomineralizations were twice as frequent in permanent as in primary teeth. No correlations were found to medical conditions, except that participants with congenital cardiac anomalies presented with fewer total enamel disturbances and hypomineralizations in permanent teeth than those without. ***Conclusions.*** Enamel disturbances were frequently seen. There were more hypomineralizations than hypoplasias. Hypoparathyroidism and/or hypocalcemia are not clear etiological factors for enamel disturbances and there were no major correlations between medical conditions and enamel disturbances.

Key Words: *22q11 deletion syndrome, amelogenesis, enamel hypoplasias, enamel hypomineralization*

Introduction

22q11.2 deletion syndrome (DS), also known as velocardiofacial syndrome (VCFS) or DiGeorge syndrome, is caused by a microdeletion on the long arm of chromosome number 22. More than 180 different clinical features, both physical and behavioral, have been described [1], although none of them occur in all cases [2]. The most frequent clinical findings are cardiac malformations, thymic hypoplasia, velopharyngeal insufficiency, feeding difficulties, hypoparathyroidism, immunodeficiency with recurrent infections and learning difficulties. Mildly affected individuals are difficult to diagnose. Increased awareness of the condition during recent years has led to a significant increase in diagnosis and the syndrome is now regarded as the most common microdeletion syndrome. The annual incidence in the Western Gotaland region of Sweden has been found to be one in 7000 live births [3]. However, an incidence as high as 1:4000 has been found in different populations [4], indicating that ~ 15 children with the deletion are born in Norway every year.

Despite plural clinical manifestations, the genotype is remarkably homogenous; 90% of affected individuals have a deleted region of three megabases

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including 30 genes, whereas 8% have a smaller deletion of 1.5 megabases containing 24 genes [5].

22q11.2 DS has been associated with developmental disturbances of dental enamel in addition to an increased prevalence of tooth agenesis [6,7]. Klingberg et al. [8] examined 53 individuals with the syndrome in the age group 3–43 years (median age of 8 years). They found enamel hypoplasia in 32% of the participants with primary teeth and 10% of participants with permanent teeth. Enamel hypomineralization was found in 39% and 41%, respectively. The enamel disturbances have traditionally been seen as secondary to conditions affecting other organ systems, particularly hypoparathyroidism [7,8], but also congenital cardiac anomalies (CCA) and premature birth [8]. Morphological examinations of exfoliated primary teeth from individuals with 22q11.2 DS have confirmed a high number of enamel aberrations and a relationship between a high number of medical events and enamel deviations has been demonstrated [9]. Recent studies in rodents have suggested that a direct genetic effect on enamel development may also play a role in the pathogenesis [10,11].

The main aim of the present study was to describe enamel disturbances in Norwegian individuals with genetically verified diagnosis of 22q11.2 DS and their possible links to medical conditions associated with the syndrome.

Material and methods

The study was approved by the Regional Committee for Research Ethics and The Norwegian Data Inspectorate and is part of a larger study of the clinical phenotype of 22q11.2 DS in Norway [12]. Individuals diagnosed using commercially available FISH probes between 1993 and 2006 were recruited for this study via Norway's genetic institutions. Invitation letters were sent to 86 individuals or their parents, following which 62 (71%) agreed to participate in the larger study. Two dropped out due to medical reasons before the study started and 56 agreed to participate in the present study. Written informed consent was obtained from either the study participant (age >18 years), the parents (person age <12 years) or both the study participant and parents (person age 12–18 years). After informed consent, the participants were assessed at the National Resource Centre for Oral Health in Rare Medical Conditions (TAKO-centre), Lovisenberg Diakonale Hospital, Oslo. Six individuals were excluded: one 55 year old person because all teeth had been extracted; two individuals, aged 3.5 and 3 years, due to extensive caries destruction which made it impossible to study enamel disturbances (they also had large amounts of dental plaque); and three individuals (aged 1.5, 5 and 29 years) due to lack of co-operation. One person was not excluded despite extremely high caries activity. This was because we had good clinical records and photographs of his dentition prior to the onset of dental disease, when he still lived with his parents.

An interview and oral examination were performed by one of two specialists in pediatric dentistry (HN or NS). The interview focused on previous dental treatment including tooth extractions, tooth development and dental traumas before the age of 3 years. Intraoral photographs were taken of all participants. Orthopantomograms and bite-wing radiographs were taken when possible, but never in children younger than 5 years of age. Orthopantomograms were used to record congenital absence of one or more permanent teeth, third molars excluded. Enamel developmental disturbances were recorded clinically by one dentist. The photographs were studied by both dentists together to verify and agree on diagnoses. Developmental disturbances of enamel were defined as follows [8]:

(1) *Enamel hypoplasia*: A quantitative, macroscopic defect of the enamel with reduced enamel thickness. The borders of the defect should be round and smooth.
(2) *Enamel hypomineralization*: A defect of the enamel seen as a change in the color and translucency of the enamel while the surface remains smooth.

A physical examination and an additional semi-structured interview were performed by one of the authors (KL) at the Outpatient Clinic of the Division of Pediatrics at Oslo University Hospital. The specific genotype was examined by multiplex ligation probe amplification (MLPA) in 49 of 50 patients. Variables obtained in the interview included the presence or absence of congenital cardiac anomaly (CCA), autoimmune diseases, velopharyngeal insufficiency (VPI), a history of frequent infections during childhood (more than three pneumonias a year and/or recurrent otitis media treated with antibiotics) and hypoparathyroidism. Information regarding length of pregnancy and birth weight was also included. All information was confirmed by reading medical records. Blood tests included concentrations of ionized and total calcium and parathyroid hormone (PTH).

Statistical methods

Hypoplasias and hypomineralizations in enamel were registered as present or absent in each individual (individual level) as well as on each tooth (tooth level). As the number of teeth present varied between individuals, the percentage (frequency) of affected total, primary and permanent teeth in each participant was calculated and used for further analyses. To evaluate any differences in frequency of hypoplasias and/or

hypomineralizations between primary and permanent teeth on the tooth level, chi square tests were performed. Enamel development in primary and permanent teeth within a single individual is affected by multiple factors, many of which may affect both dentitions. The potential differences in the prevalence of enamel disturbances between primary and permanent teeth were explored by analyzing the group with mixed dentition using a McNemar test.

To evaluate if a history of CCA, VPI, autoimmune diseases, frequent infections in childhood, hypoparathyroidism before the age of 12 years or gestational birth weight under the 5th percentile were associated with the presence of hypoplasias and hypomineralizations in total, Mann-Whitney tests were used. Possible correlations between the frequency of enamel disturbances and blood calcium and PTH levels up to 12 years of age, duration of pregnancy and birth weight were analyzed using Spearman's rank tests.

The tests outlined above were also used to analyze possible associations between medical conditions, blood calcium and PTH levels and enamel disturbances in primary and permanent teeth separately. However, for these analyses, the participants were sorted into three groups: (a) individuals with primary teeth only, (b) participants with a mixed dentition and (c) participants with permanent teeth only. This prevented individuals with a mixed dentition from being included twice. The level of significance was set at 5%.

Results

Oral findings

The number of teeth present varied between six and 28. Orthopantomograms were taken of 40 participants. Six of these (15.0%), aged 6–33 years, demonstrated agenesis of permanent teeth; three of them were missing one tooth and three were missing two teeth. No history of extractions or other tooth loss was identified in these participants. Two of the patients registered as having tooth agenesis were under the age of 9 years. One of these lacked the lower second premolars, which may, in some cases, mineralize at a later age. The other one was a 6-year old lacking the upper canines, teeth which are usually visible on X-rays from the age of 1–2 years.

The distribution of participants with primary, mixed and permanent teeth, as well as the age distribution and number of patients with enamel disturbances can be found in Table I.

None of the participants/parents reported trauma to the upper front teeth before the age of 3 years. Hypomineralizations alone were observed in 12 participants (24.0%). Permanent teeth were affected in eight of these, primary teeth in three and both dentitions were affected in one participant. Hypoplasias alone were observed in four patients (8.0%). Permanent teeth were affected in two of these participants, whilst primary teeth were affected in the other two. Seventeen participants (34.0%) demonstrated both hypomineralizations and hypoplasias. In 10 of these, both types of enamel disturbance were observed within the same dentition. The severity of enamel disturbances varied from mild (not requiring treatment) to severe (requiring operative dental treatment for functional and/or aesthetic reasons) (Figure 1).

In all but three participants the enamel disturbances on two or more different teeth were located in enamel formed at the same time (chronological distribution). However, in 18 of these, enamel formed at other periods in time was also affected. One example is hypomineralizations observed in the occlusal enamel of all first and second molars in a single patient, the former mineralizing several years before the latter.

In the whole group a total of 1148 teeth were present, 518 primary teeth and 630 permanent teeth. The frequencies of teeth with and without hypomineralizations and hypoplasias are shown in Table II. Analysis of the 22 individuals with a mixed dentition found that more participants had hypomineralizations in permanent ($n = 13$) than in primary ($n = 5$) teeth ($p = 0.04$), whilst no statistical difference could be demonstrated for hypoplasias.

Figure 2 shows the distribution of participants according to severity, defined as percentage of teeth affected. Note that with regard to enamel disturbances many individuals have no or very few teeth affected. One exception is hypomineralizations and total enamel disturbances in the group with permanent teeth, where up to 52.0% had more than 25.0% of the teeth affected.

Only two teeth were registered with both hypoplasia and hypomineralization. This represented a

Table I. The distribution of participants with primary, mixed and permanent teeth, their age and percentages of enamel disturbances.

	n	Median age* (range)	*n* (%) with enamel disturbances
Primary dentition	15	4.0 (1.5–6)	6 (40)
Mixed dentition	22	9.5 (6–16)	17 (77)
Permanent dentition	13	18.0 (11–44)	10 (77)
Total	50	10 (1.5–44)	33 (66)

*In years.

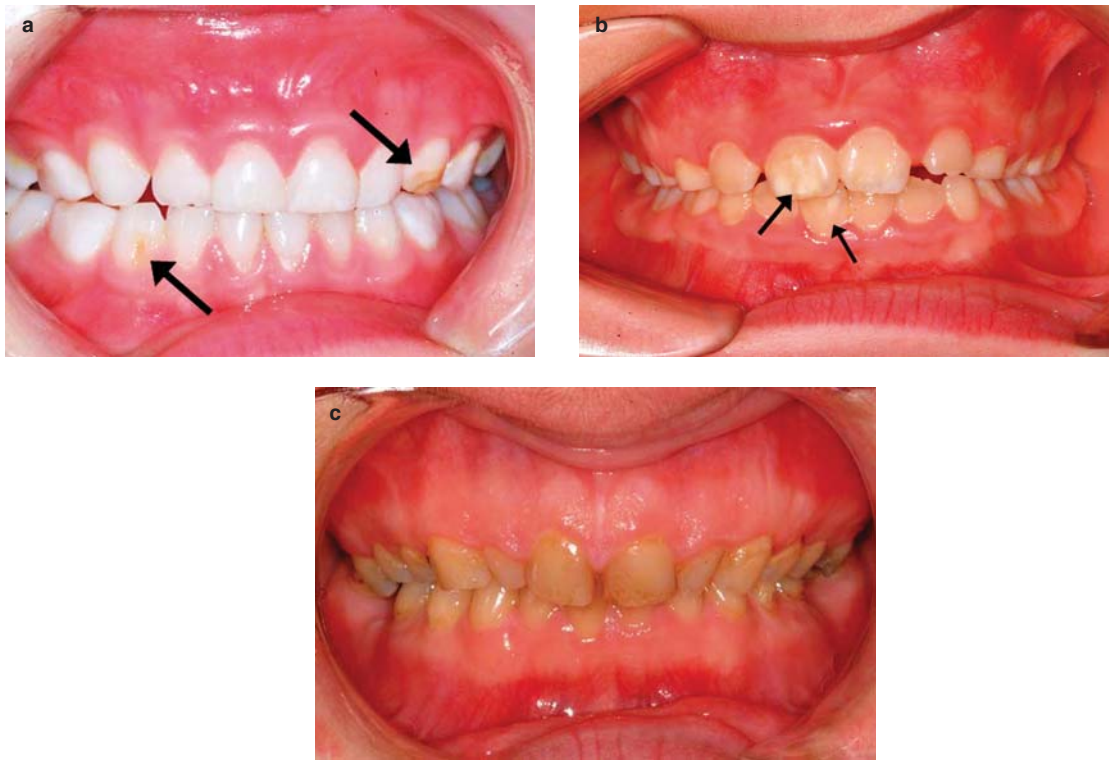

Figure 1. (a) Example of enamel hypoplasias (arrows) in primary teeth in a person with 22q11-deletion syndrome. (b) Example of enamel hypomineralizations (arrows) in permanent teeth in a person with 22q11-deletion syndrome. (c) Example of severe enamel disturbances affecting all permanent teeth in a person with 22q11.2-deletion syndrome.

significant difference ($p < 0.01$), as the expected number of teeth with both defects would be 16 if the two enamel disturbances were independently distributed.

Association with medical conditions

Table III presents data regarding the main features of the syndrome that may influence enamel development, for example neonatal hypocalcaemia or later hypoparathyroidism, CCA, autoimmune diseases, frequent infections, VPI, premature birth and size for gestational age as compared to Norwegian standards [13]. Forty-six of the 49 participants tested by MLPA had the typical A-D deletion (3 Mb), two had the A-B deletion (1.5 Mb) and one the A-C deletion. A more thorough presentation is published elsewhere ([12], manuscript in preparation). An age of 12 years was chosen as a cut-off value when considering the possibility of hypoparathyroidism influencing enamel formation, because the second permanent molars erupt as the last teeth (third molars excluded) around this age. The first episode of hypoparathyroidism occurred at birth in 10 participants and before 4 years of age in all 12 affected individuals. Only two patients had permanent hypoparathyroidism from birth onwards and these two demonstrated differing forms of enamel disturbance: one presented with hypoplasias in 17 of 18 primary teeth and the other with hypomineralizations in six and hypoplasias in three out of 21 (one supernumerary) primary teeth. Three participants (aged 10, 4 and 2 years) with a diagnosis of early hypoparathyroidism had no enamel disturbances, whereas 25 individuals without a diagnosis of hypoparathyroidism did have enamel disturbances. In general, the majority of participants had PTH levels in

Table II. The distribution of enamel hypomineralizations and hypoplasias in the 1148 teeth examined.

Type of enamel disturbance	Primary teeth, *n* (%)	Permanent teeth, *n* (%)	Total, *n* (%)	*p*-value
Hypomineralization	56 (11.2)	159 (24.6)	215 (18.7)	< 0.01
No hypomineralizations	462 (88.8)	471 (75.4)	933 (81.3)	
Hypoplasia	47 (9.1)	39 (6.2)	86 (7.5)	0.06
No hypoplasia	471 (90.9)	591 (93.8)	1062 (92.5)	
Total	518 (100.0)	630 (100.0)	1148 (100.0)	

Number of teeth present in every individual varied between six and 28.

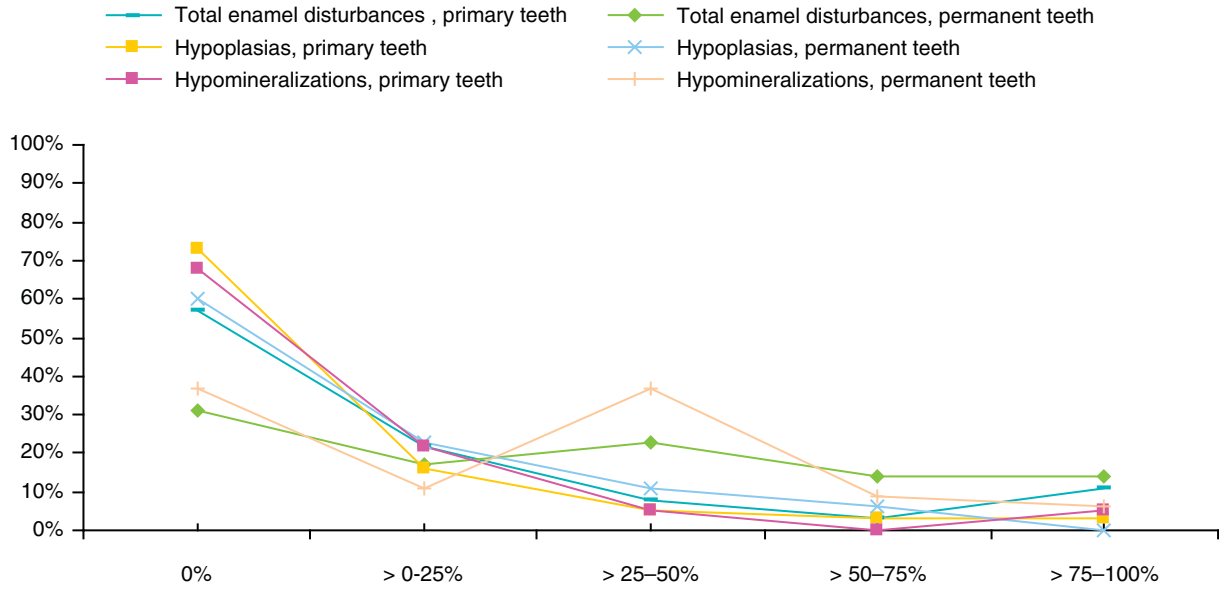

Figure 2. Percentage of participants (y-axis) demonstrating different severity grades of enamel developmental disturbances, defined as percentage of affected teeth (x-axis). The figure demonstrates that many individuals had disturbances in enamel development, although most persons had less than 50% of the teeth present affected.

the lower normal range or below (Figure 3) and most calcium levels were in the normal range as individuals with known hypoparathyroidism were treated with calcium and vitamin D.

Overall, individuals with a history of CCA ($n = 35$) had fewer teeth affected than those without such a history ($n = 15$, medians 15.4% vs 29.6%, $p = 0.05$). The difference was due to fewer hypomineralizations in those with CCA (medians 0.0% vs 25.0%, $p = 0.02$). In the group with permanent teeth only ($n = 13$), the same difference was found for enamel disturbances in total (median 21.4% vs 46.6%, $p = 0.01$) and for hypomineralizations (medians 0.0% vs 32.7%, $p < 0.01$). In the group with a mixed dentition the same results were obtained, as participants with CCA ($n = 17$) had lower frequencies of enamel disturbances (medians 13.6% vs 50.0%, $p = 0.01$) and hypomineralizations (medians 9.1% vs 50.0%, $p = 0.01$) than individuals without CCA ($n = 5$).

No clinically relevant correlations (data not shown) were found between the frequency of enamel disturbances and blood calcium and PTH levels, duration of pregnancy or birth weight. Frequent infections, autoimmune diseases, VPI or low birth weight were not associated with enamel disturbances.

Discussion

Only a few studies on dental developmental disturbances in 22q11.2 DS have been published. We present a descriptive study of all known and willing individuals with a genetically confirmed diagnosis in Norway, making it a nationwide study. Our data are

Table III. Clinical characteristics of participants.

	n	Median age when studied, years	Missing data
Number of participants	50	10 (range 1.5–44a)	none
Neonatal hypocalcemia/hypoparathyroidism[b]	12	6	none
CCA	35c	8	none
Autoimmune diseases	5	18	none
Frequent infections before 7 years	41	10	none
VPI	34	10	5
Premature birth (week 28–36)	8	8	2
SGA 5[d]	9	10	2

CCA, Congenital Cardiac Anomaly; VPI, Velopharyngeal Insufficiency; SGA 5, Small for gestational age.
[a]Age distribution: 1–4 years $n = 10$, 5–7 years $n = 11$, 8–11 years $n = 12$, 12–17 years $n = 10$, 18–44 years $n = 7$.
[b]Hypoparathyroidism diagnosed before 12 years of age.
[c]Only two of 35 patients with cardiac anomalies had no operation. Twenty-three were operated on within the first year of life.
[d]Birth weight below the 5th percentile according to gestational age using Norwegian standards.

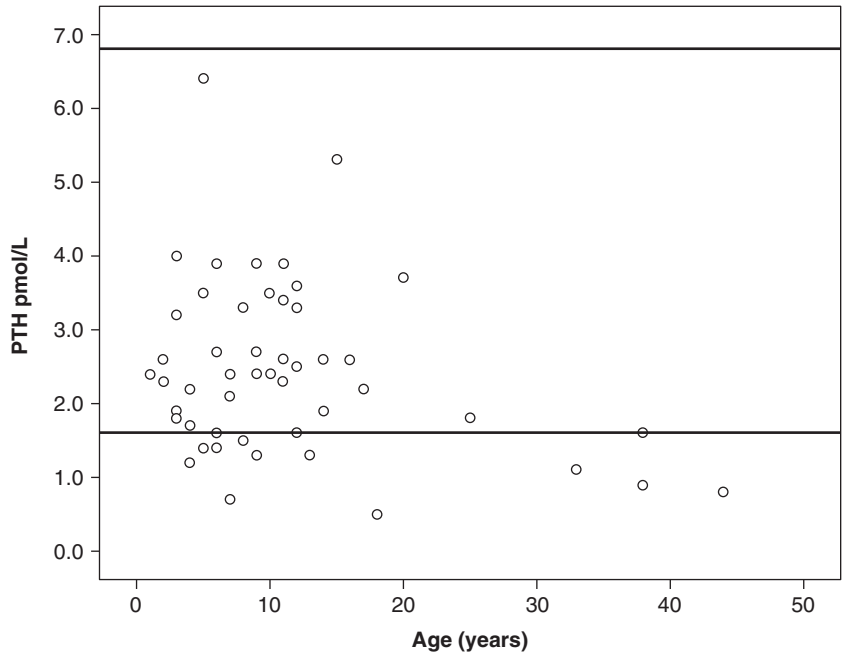

Figure 3. Individual PTH-blood levels (y-axis) in all participants according to age (x-axis). Upper and lower reference values for normal PTH levels are marked with lines.

probably representative for the diagnosed Norwegian 22q11DS patient population. However, with an estimated 22q11.2 DS incidence of 1:4000 a high number of persons with the diagnosis is undetected. Undiagnosed cases are expected to be milder. However, some of the seriously affected individuals included in the present study were diagnosed late, indicating that the phenotypic variation is great also among the undiagnosed individuals.

The present findings support a high prevalence of congenital tooth agenesis and enamel developmental disturbances similar to that described in Swedish patients [8]. However, contrary to the Swedish study no associations with other medical conditions were found.

The Swedish study identified agenesis of one or more teeth in seven of 53 individuals with 22q11.2 DS (13%) [8] and a recent study on Brazilian patients found a prevalence of tooth agenesis of 9% [14]. In our study, tooth agenesis was identified in six of 40 patients (15%), somewhat higher than the 4.5% found in the general population in Norway [15]. Recording tooth agenesis on radiographs from children under the age of 9 years may lead to an overestimation, as the second premolars may develop late and not be visible on the X-rays until later. However, only one of the individuals under the age of 9 years lacked second premolars and this participant's dental development was otherwise age-appropriate.

The exclusion of three patients with extensive tooth extractions or dental caries may indicate that the prevalence of enamel disturbances in the examined population is even higher than our finding of 66%. The study did not include a control group, but the frequency of enamel disturbances found is already much higher than the 5–33% reported in healthy populations [16,17]. Molar-incisor hypomineralization (MIH), an enamel developmental disturbance with unknown etiology, is probably prevalent in the Norwegian population, although no studies have been performed. In Sweden the reported prevalence of MIH vary between 4–18% [18], much lower than the 66% with enamel mineralization disturbances among our participants. Only 10 of our participants had affection of permanent first molars and/or incisors and in several of them the permanent premolars were unerupted and, therefore, no definitive MIH diagnosis could be made. The enamel disturbances in most individuals with 22q11.2 DS is different from MIH.

The Swedish group reported hypoplasias in 30% and hypomineralizations in 43% of patients, whilst the corresponding percentages in the present study are 42% and 58%, respectively. In the Swedish material the prevalence of hypomineralizations was equal in the primary and permanent dentitions, whereas hypoplasias were more frequent in the primary dentition. In the present study, however, hypomineralizations were found to be more prevalent in permanent than in primary teeth and this was also found on an individual level in the group with a mixed dentition. Analyzing a group with both primary and permanent teeth is useful, as individual factors such as genetic background, disease and nutrition which may affect dental development are partly excluded. Such influencing factors may, of course, vary with time and therefore affect the two dentitions differently. On the other

hand, in individuals with a mixed dentition different tooth groups will be over- and under-represented in the respective dentitions, possibly masking differences and/or similarities between them. Ideally the intra- and inter-observer agreement should have been examined, but this could not be achieved for practical reasons, as the participants traveled from all over Norway and underwent extensive examinations in a short time-frame. Many participants also presented with developmental delay and/or were anxious about the examinations. Although photographs were obtained, these were not sufficient to carry out all the necessary observations.

The different prevalences of hypomineralizations and hypoplasias in the primary and permanent dentitions may reflect different causative pathological mechanisms. Only two teeth in this material were shown to have both hypoplasia and hypomineralization defects, suggesting that the two types of enamel disturbances are close to mutually exclusive. Alternatively, the presence of hypoplasia may mask hypomineralized enamel and we may therefore have underdiagnosed the latter.

Contrary to reports from some authors [19], the present data show that enamel disturbances were less prevalent among individuals with CCA. This was seen for both enamel disturbances in general and for hypomineralizations in total as well as in the groups with permanent and mixed dentitions. In the youngest participants with a primary dentition, the prevalences of the different enamel disturbances were comparable in individuals with and without CCA. Little is known about CCA as a factor in the development of enamel, but it has been postulated that hypoxia may disturb normal ameloblast function during amelogenesis [20]. Poor nutrition may also play a role in normal dental development [21]. The heart defects among children with 22q11.2 DS are usually severe conotruncal defects, often diagnosed immediately after birth, and this was the case amongst the participants in the present study. It is possible that a CCA immediately taken care of in a modern hospital facility may lead to both better oxygenation and nutrition in infants with 22q11.2 DS. In fact, a recent study found that children with non-syndromic congenital heart disease had as low levels of dental enamel defects as healthy children [20].

One of the medical traits in 22q11.2 DS is neonatal or later appearing hypoparathyroidism due to reduced parathyroid hormone (PTH) production with a decrease in blood calcium levels and an increase in phosphorus levels. Previous studies have demonstrated an association between hypoparathyroidism *per se* and enamel disturbances [22,23]. However, these studies have not discriminated between isolated hypoparathyroidism and hypoparathyroidism as part of genetically diagnosed syndromes. Hypoparathyroidism due to autoimmune destruction of the parathyroid glands is one of the major components of autoimmune polyendocrine syndrome, type 1 (APS1) [24], and enamel disturbances are prevalent in this condition. The clinical outcome is, however, different and more severe in APS1 than in 22q11.2 DS, as the enamel in permanent teeth usually is severely hypoplastic or totally absent in parts of the permanent crowns [own unpublished data]. Furthermore, the enamel disturbances in APS1 are chronologically distributed in the permanent teeth only [own unpublished data]. In the present study we did not observe a clear chronological distribution of enamel defects in individuals with 22q11.2 DS. A diagnosed hypoparathyroidism at an early age did not affect the prevalence of enamel disturbances, either in primary or in permanent teeth. Furthermore, no association could be found between the blood values of PTH or calcium and enamel disturbances. There is limited knowledge about the pathogenesis and natural course of hypoparathyroidism in 22q11.2 DS, but a developmental defect may explain why the parathyroid glands are small and have limited capacity of PTH production. Alternatively, an autoimmune destruction or inhibition of function could also be operational, since individuals with the 22q11.2 DS are prone to autoimmune diseases. However, we found no association between enamel disturbances and autoimmune diseases supporting that it could be an autoimmune etiology of the enamel defects, due to autoimmune destruction of the ameloblasts or the proteins secreted into the enamel matrix, as suggested in APS1 [25].

Enamel defects may be caused by changes in expression of one or more genes of the deleted area on chromosome 22. It is a challenge to match the clinical observations with the molecular characterization in 22q11.2 DS to determine if the anomalies are primarily related to single gene defects or more complex interactions. A candidate gene is *TBX1* which is included in the deletions associated with 22q11.2 DS. The gene is expressed in the murine epithelial cells that give rise to ameloblasts during tooth development [10]. Furthermore, mice lacking a functional Tbx1 gene exhibit hypoplastic maxillary incisors [26] and enamel formation in teeth from Tbx−/− fetuses is arrested [11]. This gene is included in all common deletions. In the present material no genotype-phenotype analyses were possible, as 46 of 49 participants examined with MLPA had the most common 3000 bp deletion.

The prevalence of enamel disturbances in the examined group is very much higher than reported in the general population. However, many have only mild disturbances and in most participants the defective enamel has been formed at different times of development. Hypoparathyroidism and/or hypocalcaemia are not clear etiological factors for the enamel disturbances. Both direct and indirect effects

of the chromosomal deletion may play a role in the enamel developmental disturbances observed in 22q11.2 DS.

From a clinical viewpoint, it is important that individuals with 22q11.2 DS have regular contact with a dental team. In addition to the high prevalence of enamel developmental disturbances and tooth agenesis, it has been demonstrated that patients with the syndrome have low salivary secretion and buffer capacity in addition to elevated levels of cariogenic bacteria in saliva [27]. Many also experience anxiety regarding dental examinations and treatment. It is therefore advisable for these individuals and their carers to establish routines in order to promote and maintain good oral health.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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