DOI: 10.1111/j.1365-263X.2006.00801.x

Anomalies of tooth formation in hypohidrotic ectodermal dysplasia

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International Journal of Paediatric Dentistry 2007; 17: 10–18

Objective. The X-linked hypohidrotic ectodermal dysplasia (HED) is the most common type of ectodermal dysplasia. The clinical identification of possible heterozygous females can be difficult because of the varying degrees of clinical signs caused by X-chromosome inactivation. This study is the first to elaborate on anomalies of tooth formation found in a group of hemizygous males and heterozygous females with known *ED1* mutations. These tooth anomalies may be used as dental biomarkers for heterozygous females, enabling an earlier diagnosis, and therefore, better treatment and genetic counselling.

Methods. Anomalies of tooth formation were examined using panoramic radiographs, dental casts and oral photographs in hemizygous males and heterozygous females who were identified by molecular genetic analysis. The results were compared to existing controls and normative data.

Results. All affected males had multiple missing permanent teeth and tooth malformations. The heterozygous females had a significantly higher frequency of agenesis of permanent teeth compared to normative data. The heterozygous females had an increased prevalence of tooth malformations and reduced tooth size, especially in the mesiodistal dimension.

Conclusions. We conclude that observed anomalies of tooth formation may be used as dental biomarkers in the clinical identification of potentially heterozygous females.

Introduction

To date, more than 150 distinct conditions have been reported that involve ectodermal dysplasia[1]. Most of these are rare and manifest variable defects in the morphogenesis of ectodermal structures such as the hair, skin, nails, teeth and glands. The most common form of ectodermal dysplasia is X-linked hypohidrotic ectodermal dysplasia (HED; OMIM #305100), which affects males more severely, while heterozygous females show variable severity, ranging from mild to severe, because of inactivation of the X-chromosome[2,3].

The *ED1* gene is located at Xq12–q13.1 and encodes the transmembrane protein ectodysplasin-A, which is a member of the tumour necrosis factor (TNF) family. The gene is normally expressed in tissues derived from the ectoderm, and several splice forms are known. *ED1* mutations lead to the X-linked form of HED[4], while mutations in the gene encoding the receptor for ectodysplasin-A, *EDAR*, located at 2q11–q13, lead to the autosomal recessive and autosomal dominant forms of HED[5]. To date, more than 85 different mutations in *ED1* have been identified (The Human Gene Mutation Database, Cardiff, UK).

Teeth derive from the ectoderm, developing as an interaction between the oral epithelium and the underlying mesenchyme[6]. Therefore, both males and heterozygous females with HED are expected to have anomalies of tooth formation, including agenesis of teeth, malformation of teeth and reduced tooth size[7–9]. Generally, affected males have agenesis of most of the primary and permanent teeth, while heterozygous females have an increased frequency of agenesis of permanent teeth, but to a much lesser degree than the affected males. Tooth malformations such as conical incisors

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Table 1. Characteristics of the permanent teeth in males with hypohidrotic ectodermal dysplasia (HED), heterozygous females and female controls.*

Variable	Males with HED	Heterozygous females	Female controls	*P*-value‡
Number of subjects	23	36	73†	–
Mean age [years (range)]	20 (5–49)	33 (6–67)	29 (15–58)	–
Agenesis [*n* (%)]:				
at least one tooth (excluding M_3)	23/23 (100)	31/36 (86)	§	< 0.001
six or more teeth (excluding M_3)	23/23 (100)	10/36 (28)	§	< 0.001
Mean number of missing teeth (range)	22 (14–28)	4 (0–22)	–	–
Agenesis of at least one M_3 [*n* (%)]	23/23 (100)	9/26 (35)	§	0.179
Abnormal crown morphology (excluding M_3) [*n* (%)]	15/15 (100)	27/32 (84)	0/73 (0)†	< 0.001
Partly fused/pyramidal roots (excluding M_3) [*n* (%)]	5/11 (45)	19/36 (53)	18/73 (25)†	< 0.01
Taurodontism (excluding M_3) [*n* (%)]	9/11 (82)	24/36 (67)	11/73 (15)†	< 0.001

*The data are presented as the mean number (range) or the number of affected subjects/total number of subjects (percentage). †Denotes an orthopantomogram evaluated by the one of the authors. ‡*P*-values for the heterozygous females compared to female controls were obtained by chi-square test. §denotes normative data given in the results section under agenesis.

and canines, and taurodontism of the molars are common in affected males, and may also occur in heterozygous females to a less severe degree[9]. Finally, decreased tooth size has been reported in both affected males and heterozygous females[7,8]. The genotype, however, was unknown in all of the above studies. Two previous clinical studies of males with HED and heterozygous females who were identified by mutation analysis included only a brief comment on the dentition in terms of agenesis of the teeth[10,11].

In this study, which is part of a genotype–phenotype correlation study of Danish males with HED and heterozygous females, who were all identified by molecular genetic analysis, data on anomalies of tooth formation were analysed. We hypothesized that affected males and heterozygous females have significantly increased frequencies of anomalies of tooth formation, in the form of agenesis and malformation of the teeth, and reduced tooth size, when compared to normative data. The affected males have significantly more severe anomalies of tooth formation than heterozygous females.

A further hypothesis was that this study could contribute to the identification of dental biomarkers observed in males with HED and heterozygous females with a known mutation in the *ED1* gene, which could aid the clinical identification of females who were potentially heterozygous.

Subjects and methods

Study group

With the existence of a well-organized Danish community dentistry system covering all children in Denmark, it has been possible to include nearly all males with HED and heterozygous females in this study (see Table 1). Families with a proband clinically diagnosed with HED were contacted and invited to participate in the study. Informed consent was obtained in all instances. Probands and females who were possibly heterozygous were examined clinically and radiographically using panoramic radiographs and cephalometric radiographs, and blood samples were taken for DNA and chromosome analysis. Only hemizygous males and heterozygous females were included in this study. For data regarding the female controls, see Table 1. The study was approved by the Ethical Committee of Copenhagen and Frederiksberg, Denmark.

Agenesis of permanent teeth

Agenesis and malformations of permanent teeth in affected males and heterozygous females were assessed clinically using oral photographs and panoramic radiographs. Both the prevalence of agenesis and tooth-type agenesis were determined. In the affected male group, the tooth-type definition was often difficult because

of a marked deviation in tooth morphology. Here, the definition was based on the position of the tooth in the dental arch. Since the correct identification of missing mandibular incisors is problematic as a result of a very similar morphology, these teeth were pooled in the results. Oligodontia was defined as agenesis of six or more teeth[12]. Whenever the cause for the missing tooth was unknown (agenesis versus extraction), data were not included in the analyses. Data regarding agenesis of teeth were compared to normative data from Haavikoo[13], and Ravn and Nielsen[14].

Tooth malformation

The crown morphology of the incisors was classified as abnormal if it was either conical or tapered (Fig. 1). The dental roots of the molars were analysed from two aspects. One aspect was the root morphology (Fig. 2), which was classified into three types: separated, i.e. the usual variant with three separated root components in the maxillary molars and two separated root components in the mandibular molars; partly fused, i.e. the root components appeared to be more or less fused; and the pyramidal (cuneiform)

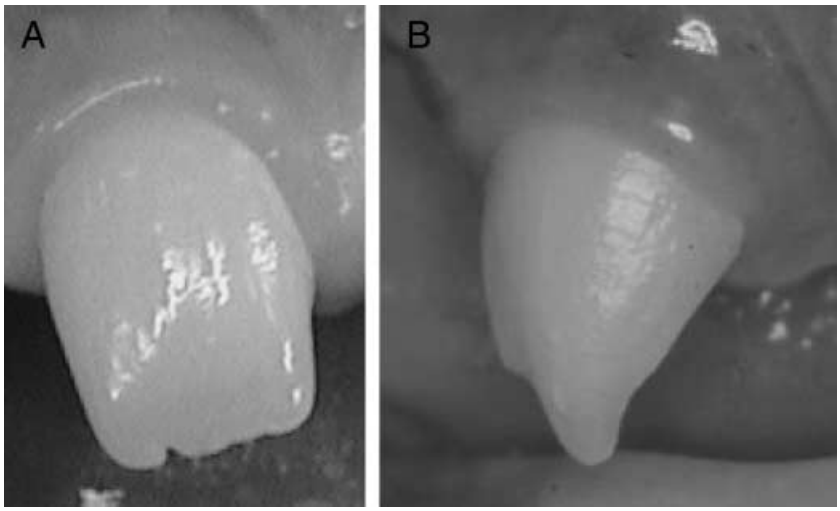

Fig. 1. (a) Tapered tooth crown of the maxillary incisor and (b) conical tooth crown of the maxillary incisor.

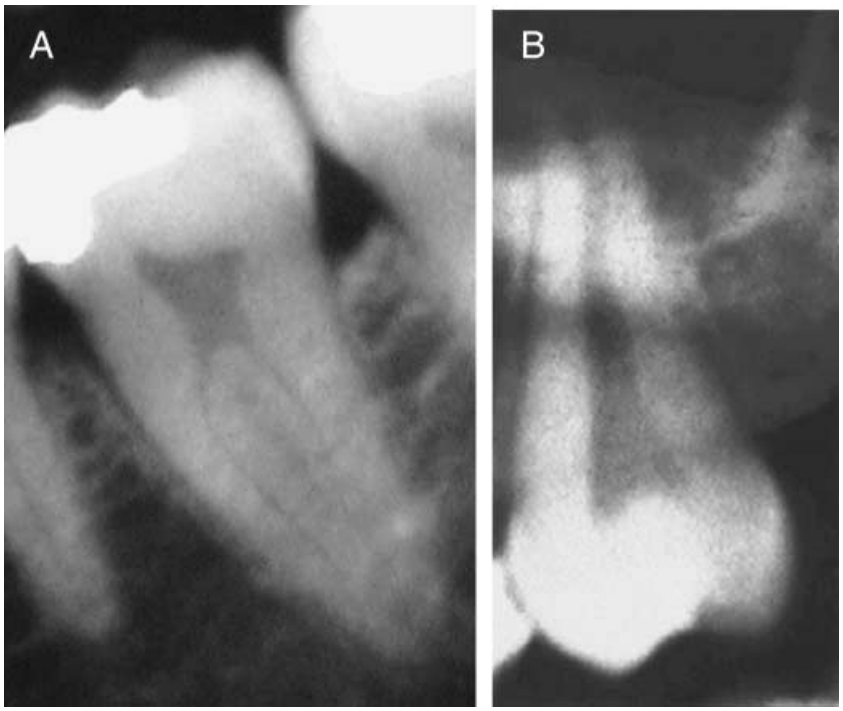

Fig. 2. (a) Partly fused mandibular molar root and (b) pyramidal (cuneiform) maxillary molar root.

type, i.e. the occlusal surface of the tooth forms the base of the pyramid and the tip of the root its apex[15,16]. In this study, the pyramidal (cuneiform) root variant was not classified as taurodontic since it is regarded as single rooted teeth[17]. Another aspect was taurodontism, which is a condition where the body of the tooth is enlarged at the expense of the root[18]. In this study, the tooth was defined as taurodontic if its root trunk extended below the alveolar margin[19]. This method was chosen because it could be used both in the mandible and the maxilla. If the diagnosis of crown morphology, root morphology or taurodontism was uncertain for some reason, the tooth was not included in the analyses.

The frequency of the defined deviations in crown and root morphology in the group of heterozygous females was compared to the frequency of these traits assessed in panoramic radiographs of healthy, age-matched women without agenesis of teeth (excluding M_3) or extensive dental work; the panoramic radiographs of these individuals were obtained from the Department of Radiology, School of Dentistry, Copenhagen, Denmark.

Tooth size

Tooth measurements were made on dental casts of high strength gypsum cement (HydroCal™, HydroCal Inc., Laguna Hills, CA, USA) made from alginate impressions of the heterozygous females.

The mesiodistal and buccolingual dimensions of the teeth were measured to an accuracy of 100 μm with a digital calliper (Mitutoyo Digimatic Calliper, Mitutoyo, Tokyo, Japan) with sharpened beaks. The mesiodistal crown diameter was measured as the greatest distance between the contact points on the approximal surfaces. The calliper was positioned parallel to both the occlusal and vestibular surfaces[20]. The buccolingual crown diameter was defined as the greatest measurement at a right angle to the mesiodistal diameter[21]. Only fully erupted teeth without caries, restorations or other interfering factors were measured. Since tooth size was found to be similar on the left and right sides of the same dental arch, left and right measurements were collapsed into means. If only one measurement was available, this value was used. Our material was compared to normative data from Townsend[22].

Precision

Randomly selected orthopantomograms were used to examine the inter- and intra-examiner agreement regarding the tooth malformation parameters. The kappa values of all observations were higher than 0.81. To measure the inter- and intra-examiner agreement regarding tooth size, 83 randomly selected teeth were measured, revealing nearly complete agreement between examiners ($r = 0.99$) and within the same examiner ($r = 0.99$). The percentage difference between and within examiners in relation to the mean was $0.7 \pm 0.9\%$ between examiners, and $0.4 \pm 0.7\%$ within the main examiner.

Statistical analysis

The R 2.2.1 statistical computer software (R Development Core Team, Vienna, Austria) and Microsoft Excel were used to analyse the results. Data from the orthopantomographic radiographs were analysed as 2×2 tables with heterozygous females versus healthy controls by the chi-square test, while the two-sample *t*-test was used to test differences between the means of the tooth measurements. The level of significance was set at 5%.

Results

Data regarding agenesis, tooth malformations and tooth size were only compared statistically between the heterozygous females and female controls. For the affected males, no statistical analysis was attempted against male controls or the heterozygous females because of sparse dental material being available as a result of multiple missing permanent teeth in all affected males.

Agenesis of permanent teeth

The prevalence of agenesis of permanent teeth in the affected males and heterozygous females is given in Table 1. All affected males had

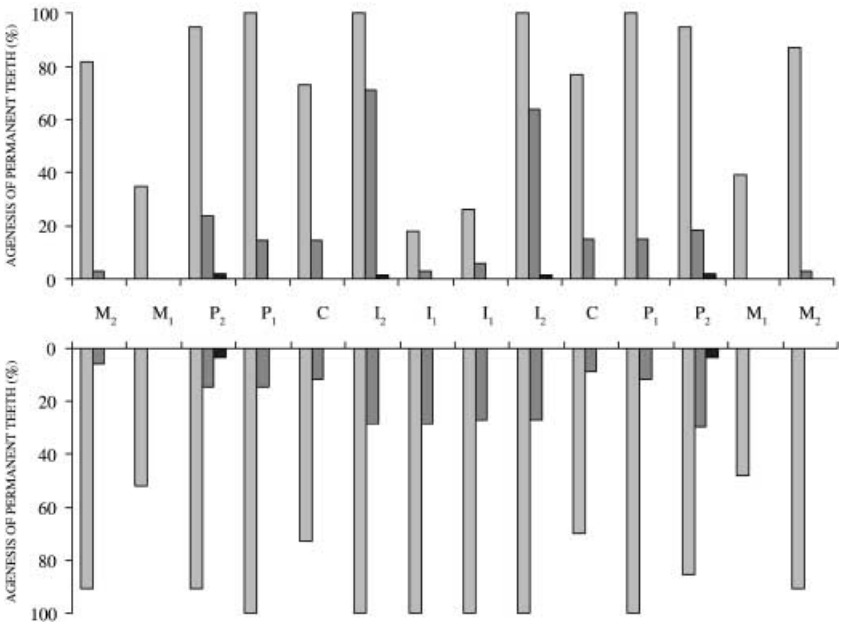

Fig. 3. Frequency of agenesis of individual permanent teeth in males affected by hypohidrotic ectodermal dysplasia and heterozygous females in comparison to normative data from Ravn and Nielsen[15]. Affected males ■, Heterozygous females ■, Normative data ■.

agenesis of the majority of their permanent teeth, and the mean number of missing teeth (excluding M_3) in this group was 22, with a range from 14 to 28 teeth; one boy showing anodontia. The mean number of teeth present was only five, with a range from 0 to 14 teeth (data not shown). It was observed that the most stable teeth in this group were the central incisors in the maxilla, the first molar in the maxilla and mandible, and the canines in the maxilla (Fig. 3). Within the affected male group, the total number of teeth affected by agenesis in the maxilla was 225 teeth with 84 teeth present (excluding the third molar), whereas the total number in the mandible was 274 teeth with 45 teeth present ($P < 0.001$). Thus, generally more teeth were missing in the mandible within the group of affected males.

Table 1 shows that the overall prevalence of agenesis of at least one permanent tooth (excluding M_3) in the heterozygous females was nine times higher than in the normative data, where it was 9% for females. Likewise, agenesis of six or more permanent teeth was found in more than one-quarter of this group compared to a prevalence of only 0·4% in the normative data. The mean number of missing teeth in this group was four, and thus, only about one-fifth of that observed in the affected male group. The range of missing teeth, however, was extreme, with five females missing no permanent teeth and a single female missing 22 teeth (which equals the mean number of missing teeth in the affected male group). The teeth most frequently missing in this group were the lateral incisors in the maxilla, the central and lateral incisors in the mandible, and the premolars in both the maxilla and the mandible, particularly the second premolars (Fig. 3). Within the heterozygous females, the prevalence of agenesis in the mandible and maxilla was almost the same, with no statistical difference (data not shown).

It was noteworthy that, in the heterozygous female group, the prevalence of agenesis of at least one third molar was not significantly higher compared to the normative data, where 20% of the females lacked one or more third molars. Ten heterozygous females, however, were not included in this analysis either because the cause of one or more missing third molars was unknown (i.e. agenesis or extraction), or these females were too young to correctly estimate the presence/agenesis of the third molar.

Tooth malformations

All affected males with formation of incisors in the maxilla had abnormal crown morphology of these teeth. Both tapered and conical morphology was observed (data not shown).

In affected males with molar formation, it was observed that the root morphology was frequently abnormal, with close to half of the cases showing either partly fused or pyramidal (cuneiform) type roots. With regard to taurodontism, 21 out of 23 affected males had taurodontic molars.

Heterozygous females showed a significantly higher frequency of tooth malformations than observed in the controls ($P < 0.01$) (Table 1). In this group, the crown morphology of the maxillary incisors was more tapered, while the mandibular incisors were more often conical (data not shown). Four females in this group were not included in this analysis because of agenesis/dental restoration of the incisors or because the teeth examined were not fully developed. When examining the root morphology of the molars, it was observed that the heterozygous female group showed a significantly increased frequency of either partly fused or pyramidal (cuneiform) type of roots (Table 1). In contrast, the pyramidal (cuneiform) root variant was very rare in the female controls. With regard to taurodontism, the heterozygous females also showed a higher frequency than the controls.

Tooth size

The tooth-size measurements of the heterozygous females are listed in Table 2. It was generally observed that the heterozygous females had significantly smaller teeth than seen in the normative data. This was particularly the case in the mesiodistal tooth dimension, especially so in the mandible. The mesiodistal overall proportional differences between the heterozygous females and the normative data were 9.73 ± 3.48% smaller for the maxilla and 11.03 ± 4.02% smaller for the mandible. The buccolingual

Table 2. Tooth size in heterozygous females compared to normative data.*

Tooth	Number of teeth	Heterozygous females		Female controls		Proportional difference (%)	*P*-value
		Mean	SD	Mean	SD		
Mesiodistal size							
Maxilla I_1	9	7.8	0.5	8.69	0.52	10.43	< 0.001
Maxilla I_2	7	5.9	0.5	6.70	0.54	11.51	< 0.001
Maxilla C	10	7.0	0.3	7.71	0.35	9.66	< 0.01
Maxilla P_1	7	5.9	0.6	6.94	0.35	14.37	< 0.001
Maxilla P_2	4	5.8	0.3	6.61	0.36	11.88	< 0.001
Maxilla M_1	4	9.9	0.3	10.37	0.51	4.65	< 0.01
Maxilla M_2	6	9.5	0.8	10.02	0.64	5.61	NS
Mandible I_1	19	4.7	0.3	5.42	0.31	14.11	< 0.001
Mandible I_2	19	4.9	0.6	5.99	0.36	18.59	< 0.001
Mandible C	20	6.1	0.4	6.64	0.32	8.73	< 0.001
Mandible P_1	17	6.3	0.4	7.03	0.37	10.59	< 0.001
Mandible P_2	8	6.5	0.4	7.03	0.39	8.25	< 0.001
Mandible M_1	10	9.9	1.0	10.95	0.64	9.82	< 0.01
Mandible M_2	10	9.8	0.6	10.52	0.69	7.10	< 0.01
Buccolingual size							
Maxilla I_1	10	6.8	0.4	7.21	0.50	3.03	NS
Maxilla I_2	6	6.2	0.4	6.30	0.49	2.38	NS
Maxilla C	10	7.3	0.6	8.11	0.44	10.48	< 0.001
Maxilla P_1	10	8.4	0.7	9.15	0.48	8.52	< 0.001
Maxilla P_2	8	8.7	0.7	9.16	0.56	4.89	NS
Maxilla M_1	10	11.0	0.5	11.35	0.53	3.30	< 0.05
Maxilla M_2	10	10.9	0.5	11.35	0.70	3.79	< 0.05
Mandible I_1	20	5.4	0.4	5.94	0.41	9.39	< 0.001
Mandible I_2	19	5.7	0.6	6.24	0.41	9.24	< 0.001
Mandible C	19	6.7	0.6	7.43	0.52	9.72	< 0·001
Mandible P_1	18	7.3	0.3	7.77	0.54	6.08	< 0·001
Mandible P_2	15	7.9	0.6	8.39	0.55	5.84	< 0·01
Mandible M_1	18	10.0	0.4	10.46	0.49	4.37	< 0·001
Mandible M_2	10	9.8	0.5	10.31	0.57	5.07	< 0·01

*Key: (SD) standard deviation; and (NS) not significant. *P*-values obtained by *t*-test. Normative data obtained from Townsend[23].

proportional differences between the heterozygous females and the normative data were 5.20 ± 3.09% smaller for the maxilla and 7.10 ± 2.27% smaller for the mandible.

Discussion

Because of the varying clinical picture of HED in the heterozygous females, there is a need to utilize available methods (e.g. panoramic radiograph and dental casts) to aid the clinical identification of possibly heterozygous females. Therefore, this study elaborates on anomalies of tooth formation (observed from ortopantomographic radiographs and dental casts) in affected males and heterozygous females, in whom the mutation in the *ED1* gene was confirmed by mutation analysis. It is the first study to report in detail on these anomalies in a group with a known mutation of the *ED1* gene. Furthermore, the sample size of the heterozygous females in particular was relatively large compared to previous studies.

The finding in this study of agenesis of multiple permanent teeth in affected males is in agreement with previous reports[7–9]. The mean number of 22 missing permanent teeth observed in affected males in this study is almost identical to the finding of Crawford *et al.*[9], studying 22 affected males. The finding of the central incisor in the maxilla, the first molar in the maxilla and mandible, and the maxillary canines being the most stable teeth in affected males is in agreement with previous reports[7,9].

The increased prevalence of hypodontia in heterozygous females observed in this study is also in agreement with previous studies[7–9]. The mean number of four missing permanent teeth in this group is similar to the observations from the study by Crawford *et al.*[9] of 23 heterozygous females, whereas the maximum number of missing teeth among 15 obligate heterozygotes was two in Airenne's[8] study. No previous study has described the extreme variability in the number of missing teeth that was observed in this study (range = 0–22). This is noteworthy since it represents the degree of variability in heterozygous females. The finding that the most frequently missing teeth in the heterozygous females were the lateral incisors in the maxilla is in agreement with the observations of Airenne[8]. Furthermore, this study documents for the first time that the prevalence of agenesis of at least one third molar was not significantly increased in heterozygous females. This observation is somewhat surprising since the prevalence of agenesis of the third molar is significantly higher than normal in other syndromes with hypodontia (e.g. Down syndrome)[23]. The finding could indicate that the development of the third molar is not as badly affected by HED as it is in other syndromes. In this study, we used the general definition of agenesis of the third molar as being agenesis of at least one third molar; however, if we had used the criterion of at least one molar present, 83% (26 of 31) of the heterozygous females would fulfil that criterion, as compared to the study by Shapiro *et al.*[23] of Down syndrome, where only 59% (16 of 27) fulfilled it.

Since the panoramic radiographs of affected males and heterozygous females often show characteristic traits, it was important to define and illustrate these characteristics in order to use them in the clinical diagnoses of the affected males and heterozygous females. Therefore, we evaluated the molar roots with regard to both root morphology and taurodontism. No previous study has reported on the root morphology in HED before. In this study, it was observed that both affected males and heterozygous females showed a high prevalence of deviations in root morphology. The definitions of crown morphology in this study were different from previous works, and therefore, could not be compared with other studies. Both the affected males and heterozygous females, however, showed a high prevalence of deviated crown morphology. These findings support the experimental studies that have shown an association between changed tooth morphology and agenesis[6].

There are different metrical analysis methods of taurodontism available (e.g. Holt and Brook[24], and Seow and Lai[25]), but none of these methods are universal, and all of them measure only one or both mandibular molars. In this study, where the affected males showed marked agenesis of multiple permanent teeth, especially in the mandible, it was important to choose a method that could be used in both dental arches. It is generally accepted that the pyramidal (cuneiform) type of molar root is not taurodontic

since it is defined as single rooted molar[17,26]. Therefore, the pyramidal variants were not classified as taurodontic teeth in this study. The higher frequency of taurodontism in affected males that was observed correlates with the study by Crawford *et al*.[9] In this study, however, it was also shown that heterozygous females have a higher frequency of taurodontism compared with female controls.

In our study, tooth size was only measured in heterozygous females because of a pronounced agenesis of the permanent teeth and a deviated morphology of the teeth present in the affected male group. Because there is no difference in the tooth size between Australians of Caucasoid ancestry and Danes[27], our results were compared to Townsend's material[22]. The reduced mesiodistal and buccolingual dimensions that were found correlate with earlier work[7,8]. In previous studies of otherwise healthy people with hypodontia, however, it was observed that tooth size was reduced in both affected individuals and the relatives of those with oligodontia[28,29].

As mentioned above, it was not statistically possible to compare the affected males to a male control group or to the heterozygous females because of pronounced agenesis in the affected male group. Therefore, it was not possible to statistically reject or accept our hypothesis that affected males suffer from more dental anomalies than heterozygous females. From another perspective, however, the number of normal teeth in the affected male group was much lower than in all the other groups.

In conclusion, we found that both the affected males and heterozygous females had a higher prevalence of agenesis of permanent teeth and the mean number of missing teeth seen in affected males was more than five times higher than in heterozygous females. The frequency of tooth malformation, taurodontism and reduced tooth size was high in the HED groups. These findings correspond with our hypothesis and emphasize the importance of a thorough examination of the panoramic radiographs for dental anomalies like agenesis, changes in the crown and root morphology, and taurodontism. In combination with the clinical picture, such measurements can be used as part of a comprehensive clinical examination and clinical identification of possible heterozygous females.

What this paper adds

- This is the first study that reports in detail on anomalies of tooth formation in males with hypohidrotic ectodermal dysplasia and heterozygous females who were identified by molecular genetic analysis.
- This paper demonstrates the importance of panoramic radiographs and dental casts in the identification of heterozygous females.

Why this paper is important to paediatric dentists

- Paediatric dentists are often the first medical personnel to identify females who are potentially heterozygous. Therefore, it is important to establish which clinical markers these clinicians can use to clinically diagnose these females at an early age. Early diagnosis can maximize treatment by ensuring prompt referral to a specialist unit, thereby enabling long-term treatment planning and genetic counselling.

Acknowledgements

We wish to thank all those who participated in this study. The skilful clinical assistance of Mrs Bente Trangeled is gratefully acknowledged. We also wish to thank the Centres for Rare Oral Diseases in Copenhagen and Århus, Denmark, the Royal Dental Collage, Århus, Denmark, and the Community Dentistry clinics in Denmark for helping us to contact the participants. The study was supported by the Association of Public Health Dentists in Denmark and Kgl. Hofbundtmager Aage Bangs Fond.

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