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Awadh, Wael

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Original article

Taurodontism in the first permanent molars in Van der Woude syndrome compared to isolated cleft palate

Wael Awadh^{1,2}, Marie Pegelow³, Arja Heliövaara⁴, and David P. Rice^{1,*}

¹Orthodontics, Department of Oral and Maxillofacial Diseases, University of Helsinki and Helsinki University Hospital, Helsinki, Finland ²Division of Orthodontics, Department of Preventive Dental Sciences, College of Dentistry, Jazan University, Jazan, Saudi Arabia ³Division of Orthodontics, Department of Dental Medicine, Karolinska Institutet, Stockholm, Sweden ⁴Cleft Palate and Craniofacial Center, Department of Plastic Surgery, Helsinki University Hospital, Helsinki, Finland

Correspondence to: David P. Rice, Orthodontics, Department of Oral and Maxillofacial Diseases, Biomedicum 1, PL 63 (Haartmaninkatu 8), 00014 University of Helsinki, Finland. E-mail: David.Rice@Helsinki.fi

Summary

Objectives: To analyse prevalence, pattern, and severity of taurodontism in individuals with Van der Woude syndrome (VWS) exhibiting cleft palate and compare with aged-matched non-syndromic cleft palate (NSCP) and non-cleft controls.

Materials and methods: One hundred and seventy-eight dental panoramic tomographs (DPTs) (105 girls and 73 boys) consisting of 42 VWS patients ($\bar{x} = 8.55 \pm 1.02$ years), 42 NSCP patients ($\bar{x} = 8.59 \pm 1.02$ years), and 94 normative non-cleft children ($\bar{x} = 8.79 \pm 1.16$ years) were assessed and their first permanent molars evaluated. Measurement 3 of the taurodontism index developed by Shifman and Chanannel with the Tulensalo modification was used. Prevalence, pattern, and severity were compared between groups. Statistical differences were determined by one-way analysis of variance and Fisher test. Repeatability was calculated by Cohens Kappa test.

Results: The prevalence of taurodontic molars was 59.5% in VWS, 45.2% in NSCP, and 26.6% in non-cleft controls. The prevalence and severity of taurodontism in VWS and NSCP were significantly higher than in non-cleft children in all first permanent molars. There was no significant difference in prevalence and severity between VWS and NSCP. The odds for having taurodontism in the VWS group was approximately double compared to the NSCP group. Most of the taurodontic molars showed hypotaurodontism and taurodontism occurred bilaterally more frequently than unilaterally.

Conclusion: This study shows a higher prevalence of taurodontism in VWS and NSCP. Most taurodontic molars are hypotaurodontic and most occur bilaterally.

Introduction

Taurodontism (Online Mendelian Inheritance in Man OMIM #272700) is a condition in which the pulp chambers of multi-rooted teeth are elongated occluso-apically and characterized by apical displacement of the root bi- or trifurcation (1). This is accompanied by

a reduced or absent constriction at the cemento-enamel junction (2). Taurodontism is seen in both permanent and primary teeth, although less commonly in the latter (2, 3). In the most extreme form, a molar tooth may, instead of having several roots, have only one root with an enlarged pulp chamber (4). Crown to root ratio was used to determine

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the taurodontism severity index, and the taurodontism divided into subgroups according to the index of severity (5). He introduced the terms hypotaurodont, mesotaurodont, and hypertaurodont (5). Taurodontic teeth are also classified as pyramidal, conical and fused in their morphology (4). The prevalence of taurodontism varies widely in normal populations from 0.3% in Sweden to 2–3% in Indian, Eskimos, and Native Americans to 46% in Chinese population (6, 7). The frequency of hypo-, meso-, and hypertaurodontism is 2.8%, 0.4%, and 0.57%, respectively, in Caucasian Americans (8). Inheritance as a dominant trait has been suggested (9). Taurodontism has been reported in both the primary and the permanent dentition, and in premolar as well as molar teeth (1). It can affect single or multiple teeth and occur either unilaterally or bilaterally (1). Maxillary second molars followed by mandibular second molars are the most commonly teeth affected, with maxillary third molars being the least affected in an Indian population (6). The diagnoses of taurodontism can be important when treating an individual for caries, particularly if endodontic therapy or extraction are being considered (10). Taurodontism may also complicate prosthetic and orthodontic treatment (10).

An increased prevalence of taurodontism in non-syndromic cleft lip and/or palate (NSCL/P) has been reported (11, 12). Taurodontism has been recorded equally in twins discordant and concordant for clefts, 41% (11). In a relatively large sample (724) of non-syndromic cleft patients, they found taurodontism in 60.4% of cleft lip and palate patients, 62.4% of cleft lip only patients, and 67% in patients with cleft palate only, compared to 42.8% of a control population (13). In general individuals with cleft palate only seem to have a higher frequency of taurodontism than individuals with either cleft lip and palate or cleft lip only (11, 13).

Taurodontism is associated with several other craniofacial developmental conditions including Amelogenesis imperfecta (Types IA and IV) (OMIM #104530 and #104510) and Trichodontoosseous syndrome (OMIM #190320) (14). Taurodontism is also seen in individuals with X linked hypohidrotic ectodermal dysplasia (OMIM #305100). These individuals are characterized by sparse hair, sweaty anomalies as well as hypodontia (15). Other conditions with taurodontism as an associated feature include Down syndrome (OMIM #190685), Williams–Beuren syndrome (OMIM #194050), Klinefelter syndrome and 47,XXX karyotype (16–18).

Van der Woude syndrome (VWS) (OMIM #119300) is an autosomal dominant disorder affecting 1 in 35 000–100 000 people (19). VWS is the most common syndromic form of orofacial clefting accounting for 1–2% of all cleft cases (20). In addition to clefting, individuals with VWS commonly exhibit lower lip pits and or lip sinuses and hypodontia (21). CL/P is found in 50% and hypodontia in 25% of patients with VWS. Regarding hypodontia, the most frequent pattern of missing teeth are upper second premolars, lower second premolars, and upper lateral incisors (22). Mutations in *IRF6* and *GRHL3* have been shown to be the major genetic causes of VWS (23, 24).

Taurodontism has previously been reported in a cohort of 13 VWS patients, in which 6 exhibited taurodontism (25). The aim of this study was to analyse and compare the prevalence pattern and severity of taurodontic molars in a large cohort patients born with VWS, with aged-matched patients born with non-syndromic cleft palate (NSCP) and age-matched non-cleft controls.

Materials and methods

Study design, setting, and participants

This retrospective cross-sectional cohort study was performed on dental panoramic tomographs (DPTs) of 378 children consisting of

52 DPTs of patients born with VWS exhibiting cleft palate (taken 1971–2013), 52 DPTs of age-matched patients born with NSCP (isolated cleft palate) (taken 1990–2013), and 274 DPTs of non-cleft aged-matched children (taken 1965–8). The cleft palate type in both VWS and NSCP groups had equally subdivided types (70.5% hard palate cleft, 13.7% soft palate cleft, and 15.6% submucous cleft palate). Patients were diagnosed and treated at the Cleft Palate and Craniofacial Centre, Department of Plastic Surgery, Helsinki University Hospital and the research conducted at the Cleft Palate and Craniofacial Centre, Faculty of Medicine, University of Helsinki, Finland. For all the children with VWS a geneticist or an experienced specialist verified the diagnosis. DPTs of the NSCP group were randomly selected from patients aged 8 years from the archive of the cleft centre using the free-random selection program ‘Pick Me!’ (By Donation Coder forum, 2009). The examiners were blinded from the group identity when analysing the DPTs. DPTs of the non-cleft group were from the normative Finnish database. This collection consists of DPTs taken of 1017 children between 2 and 19 years of age. The material was collected from school children in Helsinki, Finland (26). To reduce the risk of selection bias it was decided to use the whole 6–10 years old cohort from the normative Finnish collection.

The inclusion criteria were: All subjects in the syndrome group had VWS only. DPT was taken between the age of 6 and 10 years. DPT radiograph for diagnosis was of good quality. The exclusion criteria were: less than half of the roots were developed. One or more first permanent molars had been extracted or had a large restoration. Poor quality of radiographs. If the patient was diagnosed with another cleft type in addition to the cleft palate, submucous cleft; and if the patient had an additional syndrome combined with VWS.

After following the study criteria, 10 radiographs were excluded from the VWS sample, 10 from the NSCP sample, and 180 from the non-cleft sample. The reasons for exclusion were the poor quality of the radiograph, restored, decayed, or missing first molar teeth. This resulted in 42 radiographs in the VWS group for evaluation, 42 radiographs in the NSCP group, and 94 radiographs in the normative Finnish control group. For all groups the mean age and range were similar (Table 1). The Federation Dentaire Internationale (FDI) tooth identification system was used.

Ethical issues

Helsinki and Uusimaa Hospital District approved study protocol HUS/358/2018. The principles of the declaration of Helsinki were followed.

Measurements of dental features by DPT

Maxillary and mandibular first permanent molars were evaluated for taurodontism, assessing both the prevalence pattern and severity. Tooth outlines were drawn from radiographs using tracing paper and a pencil (0.5 mm). We evaluated the prevalence and severity of taurodontic molars by using ‘measurement 3’, the distance between the connecting line of the cemento-enamel junctions and the highest point of the floor of the pulp chamber from the taurodontism index described by Shifman and Chanannel (29) and modified by Tulensalo *et al.* (30). If the measurement 3 of the tooth was lower than 3.5 mm, the tooth was classified as a non-taurodontic molar. Taurodontic teeth were classified in to three subcategories. Hypotaurodontism was defined as a range of 3.5–5.0 mm, mesotaurodontism 5.5–7.0 mm, and hypertaurodontism 7.5 mm or over (30). Measurements were recorded to the

nearest 0.5 mm. Age, gender, and group were blinded during the examination.

Repeatability study

Forty five DPTs (15 DPTs from each group) were randomly selected using the free-random selection program 'Pick Me!' (By Donation Coder forum, 2009). The same investigator (WA) traced the radiographs twice with a 48 hours interval. Repeatability was calculated using Cohens Kappa test.

Statistics

Statistical analysis was performed using SPSS (version 22.0, SPSS Inc., Chicago, Illinois, USA). One-way analysis of variance was used to test the severity of taurodontism, to analyse differences between the groups. Fisher test was used to check the prevalence of taurodontism. Univariable logistic regression was used to analyse the interaction of variables 'group', 'age', and 'gender' effects for presence of taurodontism. A *P*-value <0.05 was considered to indicate a significant difference. The statistical analyses were performed by a statistician.

Table 1. Description of the cohort and subject groups.

Group	<i>n</i> (178)	Gender	<i>n</i>	Age range (years)	\bar{x}	SD
VWS	42	M	13	6.65–10.81	8.55	1.02
		F	29			
NSCP	42	M	14	6.24–10.83	8.59	1.02
		F	28			
Non-cleft control	94	M	46	6.35–10.67	8.79	1.16
		F	48			

n, sample size; \bar{x} , mean in years; M, male; F, female; SD, standard deviation.

Table 2. Prevalence and pattern of taurodontism in VWS and NSCP.

Category	No taurodontism	Taurodontism	Total	<i>P</i> -value
<i>n</i> (all samples)	109	69	178	
Groups, <i>n</i> (%)				
Non-cleft	69 (73.4)	25 (26.6)	94 (100.0)	
VWS	17 (40.4)	25 (59.5)	42 (100.0)	
NSCP	23 (54.7)	19 (45.2)	42 (100.0)	
Chronological age, mean (SD)	8.82 (1.16)	8.47 (0.97)	8.68 (1.10)	0.042
Mean taurodontism (measurement 3, mm) (SD)	2.44 (0.38)	3.61 (0.55)	2.90 (0.73)	<0.001
Pattern of taurodontism for all subjects, <i>n</i> (%)				
FDI tooth notation	109 (100.0)	0 (0.0)	109 (61.2)	
46	0 (0.0)	3 (4.3)	3 (1.7)	
36	0 (0.0)	1 (1.4)	1 (0.6)	
36, 46	0 (0.0)	10 (14.5)	10 (5.6)	
26	0 (0.0)	5 (7.2)	5 (2.8)	
26, 36	0 (0.0)	2 (2.9)	2 (1.1)	
26, 36, 46	0 (0.0)	1 (1.4)	1 (0.6)	
16	0 (0.0)	1 (1.4)	1 (0.6)	
16, 36	0 (0.0)	1 (1.4)	1 (0.6)	
16, 36, 46	0 (0.0)	1 (1.4)	1 (0.6)	
16, 26	0 (0.0)	15 (21.7)	15 (8.4)	
16, 26, 46	0 (0.0)	1 (1.4)	1 (0.6)	
16, 26, 36	0 (0.0)	5 (7.2)	5 (2.8)	
16, 26, 36, 46	0 (0.0)	23 (33.3)	23 (12.9)	

Taurodontism is more common in both VWS and NSCP compared to non-cleft controls. The most common pattern of taurodontism is that all maxillary and mandibular first permanent molars are affected followed by either both maxillary first permanent molars or both mandibular first permanent molars. *n*, sample size; SD, standard deviation.

Results

Patterns of taurodontism

The prevalence of taurodontic molars was (25 out of 42, 59.5%) in individuals with VWS, (19 out of 42, 45.2%) in individuals with NSCP, and (25 out of 94, 26.6%) in non-cleft controls. Younger children (mean age 8.47± 0.97 years) had significantly more taurodontism than older (mean age 8.82 ± 1.16 years) (*P* = 0.042). Taurodontism was found more frequently bilaterally (85.5%) than unilaterally (14.5%). Taurodontism was observed most commonly in all four first permanent molars (33%), thereafter both upper first molars (22%), and then both lower first molars (15%) (Table 2).

Prevalence of taurodontism by tooth and groups

The prevalence of taurodontism can either be calculated as the frequency of individuals with taurodontic teeth in the study population or as the ratio of taurodontic teeth to the total number of examined teeth (6, 12, 13, 31). In this study, we calculated the prevalence of taurodontism as the frequency of patients who had taurodontism in each first permanent molar. We did not evaluate the second

permanent molars, because in our patients the second permanent molar development was still immature.

Taurodontism was significantly more prevalent in individuals with either VWS (25 out of 42, 59.5%), or NSCP (19 out of 42, 45.2%) compared to non-cleft controls (25 out of 94, 26.6%) (Figure 1). When considering each molar, the prevalence of taurodontism in both the VWS and NSCP groups was significantly higher than in the non-cleft group for all first maxillary and mandibular permanent molars, (16, $P \leq 0.005$), (26, $P = 0.050$), (36, $P \leq 0.001$), and (46, $P \leq 0.001$) (Table 3 and Figure 2).

The highest prevalence of taurodontism in VWS was sequentially found in mandibular left first permanent molars (50%), then maxillary first permanent molars (42.9%), then mandibular right first permanent molars (40.5%) (Table 3 and Figure 2). The highest prevalence of taurodontism in NSCP was found in mandibular left first permanent molars (38.1%), then maxillary first permanent molars and mandibular right first permanent molar in same percentage (31%) (Table 3 and Figure 2). The prevalence of taurodontism in the NSCP group was not significantly different compared to VWS (Supplementary Table 1). The highest prevalence of taurodontism in non-cleft children was sequentially found in maxillary left first permanent molars (22.3%), then maxillary right first permanent molars (17%), mandibular right first permanent molars (9.6%), and mandibular left first permanent molars (7.4%) (Table 3 and Figure 2).

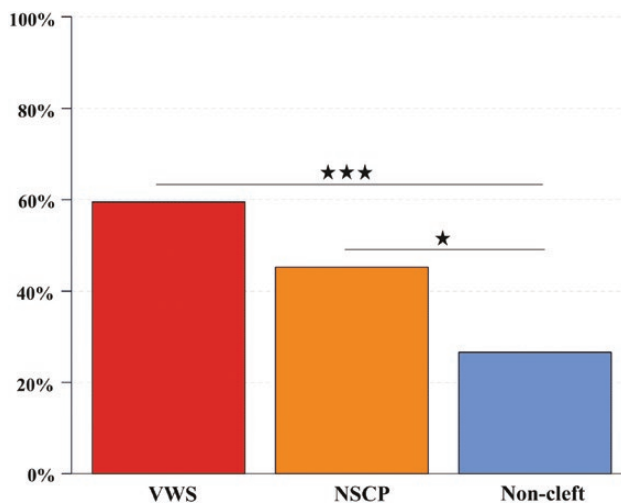


Figure 1. Taurodontism is significantly more prevalent in individuals with either VWS or NSCP compared to non-cleft controls. * $P < 0.05$, *** $P < 0.001$.

Table 3. Comparisons of the prevalence of taurodontism between groups in each studied tooth.

Tooth FDI notation	Non-cleft (Ref.) ($n = 94$) n (%)	VWS ($n = 42$) n (%)	NSCP ($n = 42$) n (%)	P -value	Test
16	16 (17.0)	18 (42.9)	13 (31.0)	0.005**	Fishers
26	21 (22.3)	18 (42.9)	13 (31.0)	0.050*	Fishers
36	7 (7.4)	21 (50.0)	16 (38.1)	<0.001***	Fishers
46	9 (9.6)	17 (40.5)	13 (31.0)	<0.001***	Fishers

A higher prevalence of taurodontism in both VWS and NSCP compared to non-cleft controls for every tooth assayed (16, 26, 36, and 46). n , sample size.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

Effects variable to presence taurodontism using univariable logistic regression

Both VWS and NSCP groups had significantly higher odds ratio for taurodontism compared to the non-cleft group. The VWS group had 4.06 times higher odds for having taurodontism compared to the non-cleft group ($P = 0.000$). The NSCP group had 2.28 times higher odds of having taurodontism compared to the non-cleft group ($P = 0.030$). There was no significant difference between genders. However, males had slight higher odds ratio than females (not significant) (Supplementary Table 1).

The severity of taurodontism by tooth and groups

Both VWS and NSCP groups had more severe taurodontism compared to the non-cleft as a reference control group in all first maxillary and mandibular permanent molars, (16, $P \leq 0.001$), (26, $P = 0.024$), (36, $P \leq 0.001$), and (46, $P \leq 0.001$) (Table 4). However, there was no difference in severity between VWS and NSCP groups for each of the first permanent molars (Supplementary Table 2). Four of the taurodontic molars from the groups were mesotaurodontic, all the other were hypotaurodontic (Table 4).

Repeatability study

Inter-observer repeatability by Cohens Kappa test between two measurements showed excellent agreement for all molars. The range of Kappa values was 0.81–0.93.

Discussion

Taurodontism in VWS and NSCP

Our data demonstrate a high prevalence of taurodontism in both the VWS and NSCP cohorts. Taurodontism has been reported in VWS previously (25). They documented 6 subjects with at least 1 taurodontic tooth in a cohort of 13 VWS patients (46%). In our larger sample, the prevalence of taurodontism was 59.5%. We also documented the pattern of taurodontism in the first permanent molars and found taurodontism to be more commonly bilateral than unilateral. Most of the taurodontic molars were hypotaurodontic in form.

We found that 45.2% of our NSCP cohort exhibited taurodontism. In a cohort of 224 adult patients with NSCP, they found a taurodontic frequency of 67.0% (13). They also found taurodontism in 60.4% of subjects with unilateral cleft lip and palate, and 62.4% in unilateral cleft lip patients, and 42.8% in a non-cleft control group. In the whole cleft population they found that the upper second permanent molar teeth were most often affected (13). In a case-control study of 88 subjects with NSCLP, 36 patients (40.9%) exhibited

taurodontism compared to 23.3% of control group (12). Most teeth were classified as hypotaurodontic, followed by mesotaurodontic then hypertaurodontic in form (12). These wide variations in taurodontic frequency may reflect the populations sampled, and the method used to determine taurodontism. However, they also may be a reflection of the teeth evaluated and of the age patients sampled. For both non-cleft and all cleft types, taurodontism is more frequent in second molars than in first molars (32). So as the second molars develop after the first, the older the patient, the more likely they are to have a taurodontic molar. In our study, we only investigated first molars as at the age of the participants, 8 years, as the second molar is still at an early stage of development.

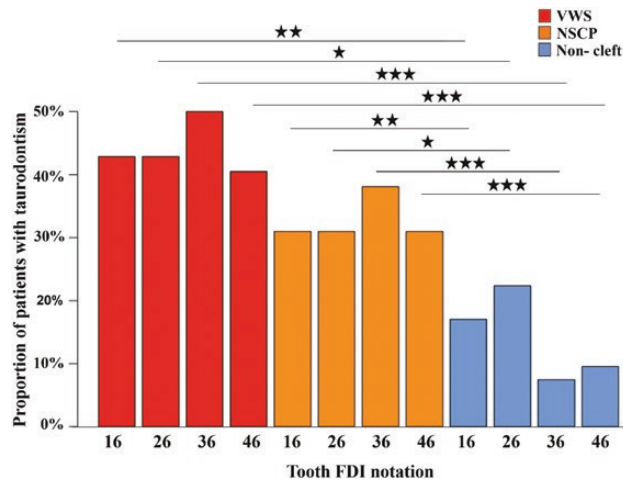


Figure 2. Comparison of the prevalence of taurodontism between groups for each tooth. For every tooth assayed (16, 26, 36, and 46) there is a higher prevalence of taurodontism in both VWS and NSCP compared to non-cleft controls. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

Table 4. Comparison of the severity of taurodontism between groups.

FDI tooth notation	Severity of taurodontism	Non-cleft ($n = 94$) (Ref.)	VWS ($n = 42$)	NSCP ($n = 42$)	Total ($n = 178$)	P -value	Test
16	Mean (SD) mm	2.63(0.72)	3.17 (0.76)	2.98 (0.85)		<0.001***	t -test
	n (%)						
	Hypo	16 (17)	18 (42.9)	13 (31)	47 (26.4)		
26	Mean (SD) mm	2.74 (0.71)	3.11 (0.84)	3.02 (0.93)		0.024*	t -test
	n (%)						
	Hypo	21 (22.3)	18 (42.9)	13 (31.0)	52(29.2)		
36	Mean (SD) mm	2.59 (0.52)	3.32 (0.97)	3.31 (1.02)		<0.001***	t -test
	n (%)						
	Hypo	7 (7.4)	21 (50.0)	15 (15.9)	43 (24.1)		
46	Mean (SD) mm	2.63 (0.57)	3.29 (0.92)	3.24 (0.96)		<0.001***	t -test
	n (%)						
	Hypo	9 (9.6)	16 (38)	11(11.7)	36 (20.2)		
	Meso	—	1 (2.3)	2(2.1)	3 (1.6)		
	Hyper	—	—	—	—		

All taurodontic teeth found exhibit hypotaurodontism in all groups, except four mandibular first molars were mesotaurodontism in both VWS and NSCP groups. * $P < 0.05$. ** $P < 0.01$. *** $P < 0.001$. n , sample size; SD, standard deviation.

In our study material symmetric bilateral taurodontism was more common than unilateral. Most other studies have found a similar correlation, that most taurodontism cases are bilateral (29, 32). However, in other study they found that nearly half of their cases were unilateral (33). Furthermore, we found that most of the cases of taurodontism were hypotaurodontic in morphology. And this also correlates with previous findings (34).

There is conflicting literature on the influence of gender of taurodontism. Some studies have found a significantly higher prevalence in females (4, 35). However our study and many other studies contrast this, with no significant difference noted between genders (31, 36, 37). It should be noted however, that taurodontism has been associated with X linked hypohidrotic ectodermal dysplasia and the additional X chromosome in 47,XXY and 47,XXX karyotypes (15, 17, 18).

The method of assessing taurodontism

In this study, we used a method originally described by Blumberg *et al.* and adapted by Shifman and Chanannel (27, 29) and Tulensalo *et al.* (30). The Tulensalo modification compensated for the different magnification of DPT radiographs compared to intraoral radiographs. This method has been shown to be reliable in assessing taurodontism in the developing dentition (30). Many other methods for assessing taurodontism have been developed (6, 35, 38–40). Notably measuring the ratio of the crown height to the total tooth length. However, for this method to be used, the root needs to be fully developed and this was therefore not applicable to our sample, aged 8 years (33, 41).

The aetiology of taurodontism in VWS

The features of VWS include both orofacial clefting and hypodontia. Both these phenotypes are independently associated with taurodontism (33). Moreover, taurodontism has been described in patients with incisor–pre-molar hypodontia and oligodontia (42, 43).

Loss of function mutations in *IRF6* are important causes of VWS (23). Mutant mice carrying a homolog of the gene mutated in the human VWS which die perinatally, exhibit disrupted palate development and widespread epithelial abnormalities including intraoral adhesions, which are also observed in VWS patients (44). *IRF6* is needed for proper periderm development and function. The periderm, the outermost layer of the oral epithelium, has a key role in stopping inappropriate pathological adhesions as well as controlling palatal adhesion and fusion competence (45). To obviate the perinatal death of *IRF6* mutant mice and allow the study of the later stages of tooth development, mice carrying mutant *IRF6* under that control of a different promoter (*Pitx2Cre*) have been generated (46). These mice have been reported to have dental morphological defects including severe taurodontism, as well as peg-shaped teeth, C-shaped molars and loss of separate mesial and distal first molar canals with transverse mid-root region of the mandibular molar. In addition, *Pitx2Cre/+; Irf6fl/+* mice also exhibit hypodontia, supplemental incisors. *IRF6* is expressed in the developing oral/palatal epithelium, the dental epithelium and in the ameloblasts, and clearly has a functional role during palate and tooth morphogenesis and dental hard tissue formation and can go some way to explaining the multiple craniofacial phenotypes seen in patients with VWS (28,46,47).

Strengths and limitations

The main strength of this research is the large cohort of the rare condition, VWS. The data with standardized records were collected over a 42-year period. Also of merit are appropriate control groups, which are taken from the same general population and geographical region as the test sample and are well matched for age and gender.

One limitation concerning the non-cleft control sample was the large 'drop out' rate of the radiographs. Another limitation was that while there was overlap in the historical time periods over which the radiographs were taken, there were still differences in the time periods between the groups.

Conclusion

The prevalence and severity of taurodontism in VWS and NSCP were significantly higher than in non-cleft children of all first permanent molars. Most of the taurodontic molars showed hypotaurodontism and taurodontism occurred more frequently bilateral than unilateral.

Supplementary material

Supplementary data are available at *European Journal of Orthodontics* online.

Supplementary Table 1. The presence of taurodontism in VWS and NSCP compared to non-cleft individuals using univariable logistic regression. There is an increased odds ratio for both VWS and NSCP compared to the non-cleft group. There is no statistical difference in the odds ratio between genders. *n*, sample size.

Supplementary Table 2. Comparison of severity of taurodontism between VWS and NSCP groups. There is no statistical difference in severity of taurodontism between VWS and NSCP groups for every tooth assayed (16, 26, 36, and 46). **P* < 0.05, ***P* < 0.01, ****P* < 0.001.

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Conflicts of interest

The authors have no conflict of interest.

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